

Relationship Between Gestational Diabetes Mellitus and Low Maternal Birth Weight

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OBJECTIVE— To study the relationship between low birth weight and the presence of gestational diabetes mellitus (GDM) or peripheral insulin resistance during pregnancy.

RESEARCH DESIGN AND METHODS— We studied the relationship between peripheral insulin sensitivity (calculated by Matsuda and DeFronzo's oral glucose tolerance test (OGTT)-derived insulin sensitivity index [ISI_{OGTT}]) or GDM prevalence and birth weight in 604 pregnant women, classified as normally glucose tolerant ($n = 462$) or affected with GDM ($n = 142$) after a 100-g 3-h oral glucose tolerance test. We then categorized these subjects into two groups: individuals with birth weight in the <10th percentile (<2,600 g; $n = 68$) and individuals with birth weight in the >10th percentile ($n = 536$).

RESULTS— GDM prevalence was higher in the group in the lowest birth weight decile (<2,600 g; 24/68; 35%) than in the group with normal/high birth weight (118/536; 22%; $\chi^2 = 5.917$; $P = 0.01$). Relative risk for GDM adjusted for age, parity, family history of diabetes, and prepregnancy body weight was about twofold in the group with low birth weight (odds ratio = 1.89 [95% CI 1.088–3.285; $P = 0.023$]), and the prevalence of low birth weight was about threefold higher in the first ISI_{OGTT} decile. In 450 women whose newborn's weight was known, the delivery of macrosomic babies was associated with a twofold higher relative risk for GDM in women who themselves had low birth weight. In the latter, the relationships between their newborn's weight and either maternal glucose tolerance (positive) or ISI_{OGTT} (negative) were amplified.

CONCLUSIONS— Low maternal birth weight was associated with a twofold higher risk for GDM, independent of major confounders. Such a risk was highest in women with low birth weight who delivered macrosomic babies, and in the group with low birth weight, the relationship between maternal glucose tolerance or insulin resistance and offspring's neonatal weight was much more evident.

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According to the hypothesis of the thrifty phenotype, low neonatal weight is related to a higher peripheral insulin resistance as well as to the appearance, during adult life, of the clinical correlates of the insulin resistance syndrome, including type 2 diabetes (1–3). Low birth weight would thus mirror a

retardation of the intrauterine programming process that leads to reduced organ maturation (4,5).

Pregnancy is characterized by a physiological state of insulin resistance, which is further magnified in women affected by gestational diabetes mellitus (GDM) (6,7). Furthermore, pregnant women

with GDM have many features of the metabolic syndrome (8) and have a high risk of developing type 2 diabetes (9). Maternal insulin sensitivity is inversely related to offspring's neonatal weight (10,11), and a small maternal birth weight could therefore hypothetically modify the risk of giving birth to macrosomic babies. It is still unknown whether insulin resistance and a woman's own birth weight are linked during pregnancy, and there are conflicting results regarding the relationship between GDM and maternal birth weight (12,13).

We therefore designed our study to evaluate whether there is a relationship between maternal birth weight and peripheral insulin resistance or the presence of GDM in a group of pregnant women. A second purpose of this study was to verify whether low maternal birth weight modifies the relationship between insulin resistance or GDM and the neonatal offspring's weight.

RESEARCH DESIGN AND METHODS

This study included 604 pregnant women who, during the last 2 years, consecutively performed a 100-g 3-h oral glucose tolerance test (OGTT) between the 24th and 28th gestational week. The test was performed at the Outpatients Clinic of the Diabetes Unit of the Hospital of Pistoia, Italy, according to a standardized program of the Regional Health Service, in essential agreement with the recommendations of the American Diabetes Association (14). According to this protocol, a full 100-g 3-h OGTT should be performed in all women who are classified as glucose intolerant to a previous 1-h 50-g OGTT, who show a 1-h plasma glucose level >7.8 mmol/l, or who have other risk factors for GDM (history of glucose intolerance, of macrosomic deliveries during previous pregnancies, or of diabetes in first-degree relatives). We chose this "high-risk" population because it represents a sample of women who are the common target of screening, and therefore we can expect a higher ratio of GDM cases per screened

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Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; OR, odd ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Main characteristics of women with GDM and normal glucose tolerance

| | Normal glucose tolerance | GDM | P |
|--|--------------------------|-------------|--------|
| n | 462 | 142 | — |
| Age (years) | 31.3 ± 4 | 32.9 ± 4.4 | 0.0001 |
| Prepregnancy BMI (kg/m ²) | 23.1 ± 4.3 | 23.8 ± 3.8 | NS |
| Actual BMI (kg/m ²) | 25.9 ± 4 | 26.6 ± 3.9 | NS |
| Family history of diabetes (%) | 32.1 | 42.2 | 0.01 |
| Systolic blood pressure (mmHg) | 114.7 ± 9.5 | 115.4 ± 8 | NS |
| Diastolic blood pressure (mmHg) | 71.3 ± 7.5 | 72.2 ± 8.1 | NS |
| Parity (n) | 1.8 ± 1 | 1.8 ± 1 | NS |
| 2-h glucose area under the curve (mol · l ⁻¹ · 2 h ⁻¹) | 0.8 ± 0.1 | 1.1 ± 0.1 | 0.0001 |
| 2-h insulin area under the curve (nmol · l ⁻¹ · 2 h ⁻¹) | 58.7 ± 30.8 | 67.9 ± 40.7 | 0.005 |
| ISI _{OGTT} (mg · dl ⁻¹ · min ⁻¹) | 5.7 ± 3.7 | 3.9 ± 2 | 0.0001 |
| Maternal birth weight (g) | 3,282 ± 555 | 3,221 ± 555 | NS |

Data are means ± SD.

individuals. The 1-h 50-g OGTT was performed in 470 cases and was positive in 427 cases. GDM was diagnosed by a full 100-g 3-h OGTT in 112 women whose 1-h 50-g OGTT was >7.8 mmol/l (23.8%), in 2 of 43 with a negative test, and in 28 of 134 without a previous 1-h 50-g test (19.7%). In all these cases, the women were treated with diet only. In 154 cases, women or their mothers remembered their birth weight. Birth weight was known by means of written record in 450 women, but, nevertheless, these records were largely incomplete as to gestational age of pregnancies. Age, birth weight, parity, and prepregnancy BMI were, on average, similar in these two groups, and in this young population (<40 years of age), the birth weights ascertained through family's memories and through legal or medical documents should be in agreement because, as previously described, in this case, the younger the population, the more birth weights correspond to reality (15).

Plasma glucose (Glucose GOD-PAP; Roche Diagnostic, Mannheim, Germany) and insulin (Immunometric Assay; DPC, Los Angeles, CA) were measured at baseline and at 60, 120, and 180 min after 100-g glucose oral load in all women. The areas under time multiplied by concentration curves of glucose and insulin were computed by trapezoidal integration and expressed as moles per liter per 2 h and as nanomoles per liter per 2 h, respectively. Peripheral insulin sensitivity was graded by using the insulin sensitivity index of

Matsuda and DeFronzo (16) as follows: ISI_{OGTT} = 10,000/square root [fasting plasma glucose (mg/dl) × fasting plasma insulin (mU/l)] × (mean glucose value during the OGTT × mean basal insulin value during the OGTT). This index was recently validated in pregnant women with or without GDM (17). Blood pressure was measured before the test in the supine position and was expressed as the mean value of three consecutive measurements. GDM was diagnosed in a total of 142 women using the criteria suggested by the American Diabetes Association (14). The women were further categorized into two groups: individuals with

birth weights in the <10th percentile (<2,600 g; n = 68) and individuals with birth weights in the >10th percentile (n = 536). The study was approved by the ethical committee of our hospital.

Statistical analysis

Data are expressed as means ± SD. Differences between means were tested by two-tailed Student's *t* test. Comparisons between slopes of regression lines were calculated by ANOVA (18). Differences between frequencies were evaluated by the χ^2 method. Logistic analysis regression was used to estimate odds ratio (OR) associated with risk of GDM after adjusting for main confounders. Significance level was set at *P* < 0.05. All data were analyzed by a SAS statistical package for personal computers (19).

RESULTS

As shown in Table 1, diabetic women were older and were characterized by higher 2-h areas under the curve for glucose and insulin, as well as by a reduced mean value of ISI_{OGTT}. When the women were stratified according to their birth weight, all studied parameters did not present significant differences (Table 2). Nevertheless, although the pregnant women's birth weight was, on average, not different in the group with GDM (Table 1), the prevalence of GDM was significantly higher (24/68; 35%) in the group in the first birth weight decile (<2,600 g) compared with the prevalence in the other deciles (118/536; 22%; $\chi^2 = 5.917$; *P* = 0.01, as shown in Fig. 1).

Table 2—Main characteristics of pregnant women stratified by birth weight

| | Birth weight ≥2,600 g | Birth weight <2,600 g | P |
|--|-----------------------|-----------------------|--------|
| n | 536 | 68 | — |
| Age (years) | 31.6 ± 4.1 | 32.1 ± 4.7 | NS |
| Prepregnancy BMI (kg/m ²) | 23.3 ± 4.2 | 22.8 ± 4.7 | NS |
| Actual BMI (kg/m ²) | 26.1 ± 4 | 25.6 ± 3.5 | NS |
| Family history of diabetes (%) | 35.3 | 36.9 | NS |
| Systolic blood pressure (mmHg) | 114.9 ± 9.2 | 114.8 ± 8.9 | NS |
| Diastolic blood pressure (mmHg) | 71.5 ± 7.5 | 71.8 ± 7.9 | NS |
| Parity (n) | 1.8 ± 1 | 1.8 ± 1 | NS |
| 2-h glucose area under the curve (mol · l ⁻¹ · 2 h ⁻¹) | 0.9 ± 0.1 | 0.9 ± 0.1 | NS |
| 2-h insulin area under the curve (nmol · l ⁻¹ · 2 h ⁻¹) | 60.1 ± 33.9 | 64.7 ± 29.8 | NS |
| ISI _{OGTT} (mg · dl ⁻¹ · min ⁻¹) | 5.3 ± 3.3 | 5.1 ± 4.7 | NS |
| Maternal birth weight (g) | 3,390 ± 449 | 2,305 ± 320 | 0.0001 |

Data are means ± SD.

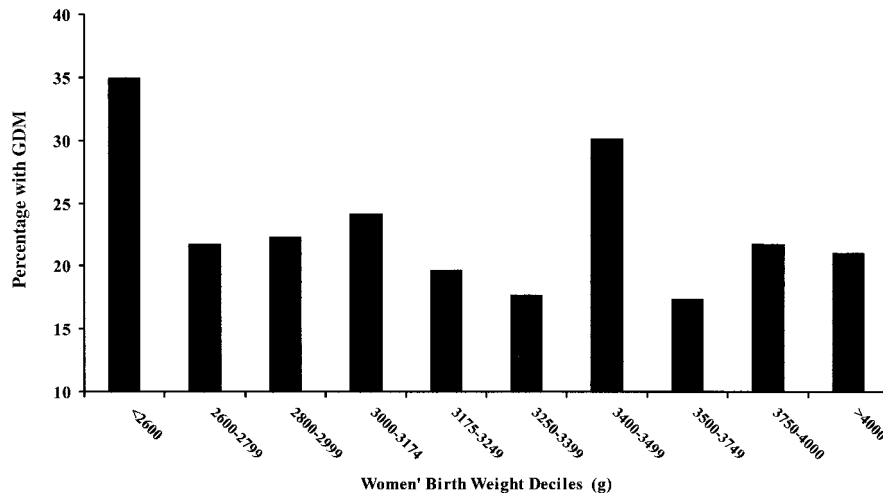


Figure 1—Prevalence of GDM in women stratified by deciles of their birth weight.

After adjusting for age, parity, family history of diabetes, and prepregnancy BMI, the relative risk of having GDM was about twofold in women with birth weights <2,600 g (OR: 1.89; 95% CI 1.088–3.285; $P = 0.023$).

In the subgroup of 450 women whose delivery records were precisely known, the maternal birth weights were evaluated across tertiles of their newborn's weight adjusted for sex and gestational age. This analysis shows that, within each tertile, the prevalence of GDM was higher in the group of mothers with a small birth weight. The highest prevalence of GDM (43%) was, however, observed in individuals with a small birth weight who deliv-

ered the heaviest babies (in the upper tertile) (Fig. 2). The OR of being affected with GDM in mothers whose birth weight was <2,600 g, compared with individuals with a birth weight $\geq 2,600$ g, was 1.38 (95% CI 0.65–2.95, NS) in the first tertile of offspring's neonatal weight; 2.40 (95% CI 1–5.77; NS) in the second tertile; and 2.27 (95% CI 1.12–4.55; $P = 0.03$) in the third tertile. Maternal birth weight was unrelated to age, glucose/insulin 2-h areas under the curve, ISI_{OGTT}, and blood pressure and was directly related to both actual and prepregnancy BMI ($r = 0.11$, $P = 0.005$ and $r = 0.12$, $P = 0.005$, respectively) and to offspring's neonatal weight ($r = 0.12$, $P = 0.007$), although

these relationships appear very weak and explain a negligible percentage of these variables' variance. The percentage of women with low birth weight was about threefold higher in the first ISI_{OGTT} decile than in the upper ISI_{OGTT} decile (14 vs. 5%; $P = 0.04$).

Finally, the relationship between worsening of glucose tolerance and offspring's neonatal weight was amplified in mothers with low birth weight, as shown by the significantly steeper slope of the regression line joining the 2-h area under the curve for glucose with the offspring's neonatal weight adjusted for sex and gestational age in women with birth weights <2,600 g {neonatal weight = $0.7139 + 0.2897 \times 2\text{-h glucose area under curve}$ [$R^2 = 0.104$, $P = 0.03$, for women with small birth weight ($n = 48$)], and neonatal weight = $0.9222 + 0.0890 \times 2\text{-h glucose area under curve}$ [$R^2 = 0.012$, $P = 0.03$, for women with birth weights $\geq 2,600$ g ($n = 402$)] ($P = 0.006$ by ANOVA for difference in slopes; Fig. 3). Likewise, offspring's relative neonatal weight was inversely related to ISI_{OGTT} ($r = -0.13$, $P = 0.009$), and this result was significantly more marked in the group with a low birth weight [neonatal weight = $1.0185 - 0.0068 \times \text{ISI}_{\text{OGTT}}$ ($R^2 = 0.078$, $P = 0.04$ for women with low birth weight), and neonatal weight = $1.0251 - 0.00383 \times \text{ISI}_{\text{OGTT}}$ ($R^2 = 0.012$, $P = 0.03$ for women with birth weights $\geq 2,600$ g)] (the slopes being significantly different, $P = 0.009$ by ANOVA; Fig. 3).

CONCLUSIONS— Our data suggest that, although the association between insulin resistance and pregnant women's birth weight is nonlinear, the risk of GDM is about twofold in pregnant women who themselves had low birth weight.

ISI_{OGTT} was, as expected, reduced in women with GDM, and, moreover, no linear relationship was observed between maternal birth weight and insulin resistance. Despite a similarity in the means of women's birth weight between groups with normal glucose tolerance and GDM, there was a significant increase in the prevalence of GDM, according to a "threshold effect" in women with birth weights in the lowest decile. This latter observation can explain the absence of significant variations in mean glucose/insulin areas under the curve and ISI_{OGTT} observed in the group of women with low

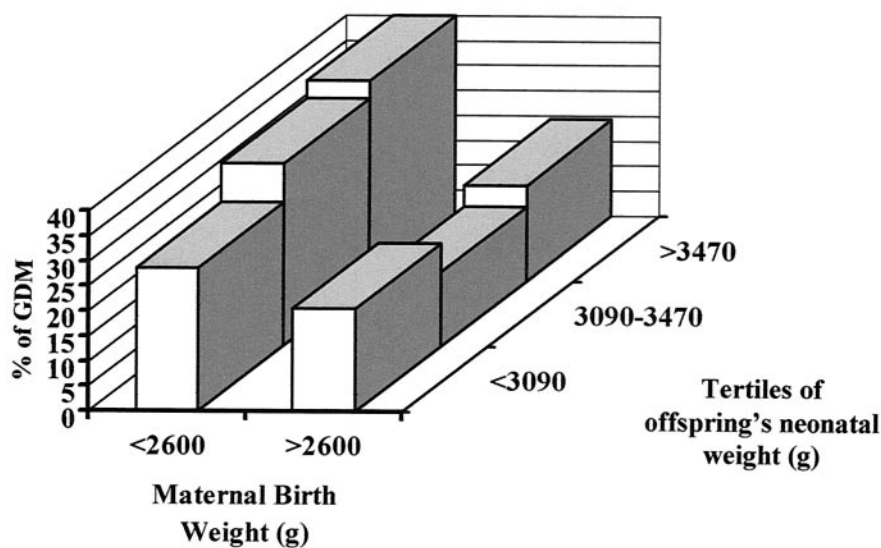


Figure 2—Prevalence of GDM in pregnant women stratified by their birth weight as well as by their offspring's birth weight.

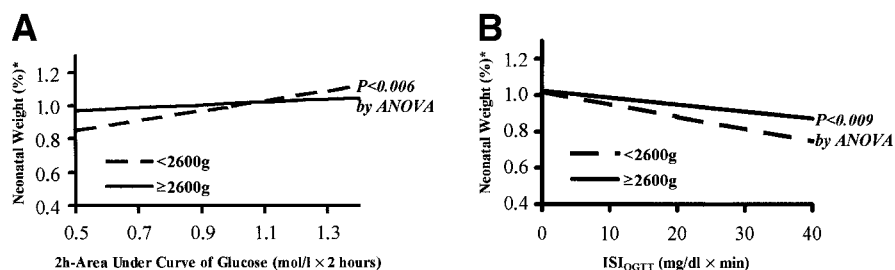


Figure 3—Regression lines relating glucose tolerance (A) and ISI_{OGTT} (B) to offspring's neonatal weight in mothers with birth weight $\geq 2,600$ or $< 2,600$ g. *Relative offspring's neonatal weight adjusted for sex and gestational age.

birth weight due to a dilution effect on the mean exerted by the large majority of nondiabetic subjects (about two-thirds). These results are in agreement with the data of Moses et al. (13), who did not find any linear relation between grade of glucose tolerance and birth weight in a group of pregnant women. Nevertheless, the different design of this latter study does not allow us to reach any conclusion on the hypothesis that birth weight categorization may be linked to GDM by a threshold effect. Our study has, in fact, some features that do not allow any true comparison with the data of Moses et al.: first, ours is not a population-based study because it involves a selected high-risk population. Second, the women's birth weight in our database is not adjusted by gestational weight, and, third, diagnosis criteria for GDM are different.

Although we studied a high-risk population, we did not observe a U-shaped distribution curve of GDM prevalence across deciles of pregnant women's birth weight, which is a characteristic of populations at high risk for diabetes such as, for instance, Pima Indians (20). A further difference is represented by the fact that mean body weight of the women studied either with or without diabetes was, on average, much leaner than that of the Pima Indians. This is a further demonstration that genetic factors, differences in perinatal life expectancy, or perhaps some other unknown factors may play a major role in determining the distribution shape of risk for diabetes and of GDM in adult Caucasian women with larger neonatal weights. Nevertheless, our data are in full agreement with the findings of a Norwegian population study including 138,714 women that reports a very similar OR (1.8; 95% CI 1.1–3) of having diabetes during pregnancy in women whose birth weight was $< 2,500$ g (12). Besides this

similarity, whether our study can be extrapolated to the whole population remains doubtful. Moreover, it is noteworthy that, according to the Norwegian study, adjusting for gestational age does not provide any additional predictive information on GDM risk.

A further aspect of our study is the relationship linking maternal birth weight with the offspring's neonatal weight. We confirm a previous observation that these two weights are linearly related (21), although this relationship appears very weak and explains a negligible 1% of offspring's weight variance. Our findings suggest that women with low birth weight who give birth to larger babies are at the highest risk for GDM. In other words, our results lead to the conclusion that maternal diabetes is more related to offspring macrosomia in women with low birth weight. This is also disclosed by the magnifying effect exerted by the mother's low birth weight on the direct relationship that links either maternal glucose tolerance (directly) or insulin sensitivity (inversely) to offspring fetal growth. All this suggests that a low birth weight, considered a proxy for low fetal growth rate in utero, may be acting as an amplifier of risk (in this case, fetal macrosomia associated with GDM) rather than a risk factor per se. The concept that reduced maturation in utero may act as a risk amplifier during adult life is, moreover, suggested by the findings of a previous study describing a stronger relationship between obesity and blood pressure in females whose mothers were exposed to poor nutrition during pregnancy (22).

In conclusion, low maternal birth weight seems to be associated with a two-fold higher risk for GDM, independent of major confounders. Such a risk is highest in women with small birth weight who

deliver macrosomic babies, and a small birth weight acts as an “amplifier” of the relationship between maternal glucose tolerance or insulin resistance and the newborn's weight. Our study suggests that knowledge of a woman's birth weight during the pregnancy may be useful from an epidemiological point of view, first, to assess the global risk of being affected with GDM and, second, to better predict a higher risk of giving birth to larger (macrosomic) babies in diabetic pregnant women.

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