Metabolic Syndrome in Childhood: Association With Birth Weight, Maternal Obesity, and Gestational Diabetes Mellitus

Charlotte M. Boney, MD*; Anila Verma, MBBS, PhD‡; Richard Tucker, BS§; and Betty R. Vohr, MD§

ABSTRACT. Objective. Childhood obesity has contributed to an increased incidence of type 2 diabetes mellitus and metabolic syndrome (MS) among children. Intrauterine exposure to diabetes and size at birth are risk factors for type 2 diabetes mellitus, but their association with MS in childhood has not been demonstrated. We examined the development of MS among large-for-gestational-age (LGA) and appropriate-for-gestational age (AGA) children.

Study Design. The major components of MS (obesity, hypertension, dyslipidemia, and glucose intolerance) were evaluated in a longitudinal cohort study of children at age 6, 7, 9, and 11 years who were LGA (n = 84) or AGA (n = 95) offspring of mothers with or without gestational diabetes mellitus (GDM). The cohort consisted of 4 groups, ie, LGA offspring of control mothers, LGA offspring of mothers with GDM, AGA offspring of control mothers, and AGA offspring of mothers with GDM. Biometric and anthropometric measurements were obtained at 6, 7, 9, and 11 years. Biochemical testing included measurements of postprandial glucose and insulin levels and high-density lipoprotein (HDL) cholesterol levels at 6 and 7 years and of fasting glucose, insulin, triglyceride, and HDL cholesterol levels at 9 and 11 years. We defined the components of MS as (1) obesity (BMI >85th percentile for age), (2) diastolic or systolic blood pressure >95th percentile for age, (3) postprandial glucose level >140 mg/dL or fasting glucose level >110 mg/dL, (4) triglyceride level >95th percentile for age, and (5) HDL level <5th percentile for age.

Results. There were no differences in baseline characteristics (gender, race, socioeconomic status, and maternal weight gain during pregnancy) for the 4 groups except for birth weight, but there was a trend toward a higher prevalence of maternal obesity before pregnancy in the LGA/GDM group. Obesity (BMI >85th percentile) at 11 years was present in 25% to 35% of the children, but rates were not different between LGA and AGA offspring. There was a trend toward a higher incidence of insulin resistance, defined as a fasting glucose/insulin ratio of <7, in the LGA/GDM group at 11 years. Analysis of insulin resistance at 11 years in a multivariate logistic regression revealed that childhood obesity and the combination of LGA status and maternal GDM were associated with insulin resistance, with odds ratios of 4.3 (95% confidence interval [CI]: 1.5–11.9) and 10.4 (95% CI: 1.5–74.4), respectively. The prevalence at any time of ≥2 components of MS was 50% for the LGA/GDM group, which was significantly higher than values for the LGA/AGA group (29%), AGA/GDM group (21%), and AGA/AGA control group (18%). The prevalence of ≥3 components of MS at age 11 was 15% for the LGA/GDM group, compared with 3.0% to 5.3% for the other groups. Cox regression analysis was performed to determine the independent hazard (risk) of developing MS attributable to birth weight, gender, maternal prepregnancy obesity, and GDM. For Cox analyses, we defined MS as ≥2 of the following 4 components: obesity, hypertension (systolic or diastolic), glucose intolerance, and dyslipidemia (elevated triglyceride levels or low HDL levels). LGA status and maternal obesity increased the risk of MS approximately twofold, with hazard ratios of 2.19 (95% CI: 1.25–3.82) and 1.81 (95% CI: 1.03–3.19), respectively. GDM and gender were not independently significant. To determine the cumulative hazard of developing MS with time, we plotted the risk according to LGA or AGA category for the control and GDM groups from 6 years to 11 years, with Cox regression analyses. The risk of developing MS with time was not significantly different between LGA and AGA offspring in the control group but was significantly different between LGA and AGA offspring in the GDM group, with a 3.6-fold greater risk among LGA children by 11 years.

Conclusions. We showed that LGA offspring of diabetic mothers were at significant risk of developing MS in childhood. The prevalence of MS in the other groups was similar to the prevalence (4.8%) among white adolescents in the 1988–1994 National Health and Nutrition Examination Survey. This effect of LGA with maternal GDM on childhood MS was previously demonstrated for Pima Indian children but not the general population. We also found that children exposed to maternal obesity were at increased risk of developing MS, which suggests that obese mothers who do not fulfill the clinical criteria for GDM may still have metabolic factors that affect fetal growth and postnatal outcomes. Children who are LGA at birth and exposed to an intrauterine environment of either diabetes or maternal obesity are at increased risk of developing MS. Given the increased obesity prevalence, these findings have implications for perpetuating the cycle of obesity, insulin resistance, and their consequences in subsequent generations.

ABBREVIATIONS. T2DM, type 2 diabetes mellitus; LGA, large for gestational age; AGA, appropriate for gestational age; MS, metabolic syndrome; GDM, gestational diabetes mellitus; NCEP, Na-
The epidemic of childhood obesity that has occurred in the past 20 years is associated with an increase in the prevalence of type 2 diabetes mellitus (T2DM) among children and adolescents. By 1994, ~14% of children and 12% of adolescents were overweight, as defined by a BMI of >85th percentile for age, and recent data indicate that the prevalence of obesity has continued to increase. The increased obesity was accompanied by an increase in T2DM among adolescents, from ~5% of new cases of diabetes in 1982 to ~45% (depending on geographic location) in 1999. There are a number of risk factors for T2DM among children and adults in addition to obesity. A well-recognized risk factor among adults is the metabolic syndrome (MS), also called syndrome X, which was first described in the 1950s and predisposes individuals to diabetes and cardiovascular disease. MS is defined as the association of obesity, insulin resistance, glucose intolerance, hypertension, and a characteristic dyslipidemia.

There is a growing body of literature on the prevalence of components of the MS among obese children and adolescents. This raises great concern about the potential development of not only T2DM but also early stages of cardiovascular disease in childhood. Longitudinal studies of Pima Indian children demonstrated that birth weight, ie, either small for gestational age (SGA) or large for gestational age (LGA), exposure to diabetes in utero, and obesity are the major factors in the development of childhood T2DM and hypertension.

We have been monitoring a cohort of children born either appropriate for gestational age (AGA) or LGA, to mothers with or without gestational diabetes mellitus (GDM). The purpose of this study was to determine whether children who were LGA at birth and offspring of mothers with or without GDM are at increased risk for developing the MS in childhood. Therefore, we present data on LGA and AGA children of mothers with and without GDM who were monitored prospectively from 6 to 11 years of age, to determine the effects of LGA status and maternal GDM on the development of MS.

METHODS

Subjects

Mothers with documented GDM who fulfilled the modification of the National Diabetes Data Group criteria described by Carpenter and Coustan and control mothers who passed the 1-hour, 50-g, screening, blood glucose test were contacted 4 years after the delivery of a term healthy infant born LGA or AGA. Premature, postterm, and SGA infants were excluded. Frequency matching was used to achieve balanced samples within the groups of GDM and control mothers. Children were matched for LGA (birth weight >90th percentile for gestational age) or AGA (birth weight between the 10th and 90th percentiles for gestational age) status. Birth weight was obtained from the medical records. Of 252 mothers with GDM who were contacted, 96 (38%) agreed to have their children participate in a longitudinal cohort study; 101 control mothers (~10% of those contacted) agreed to have their children participate. Biochemical testing was begun at 6 years of age; therefore, this report is based on the 94 children of GDM mothers and the 85 children of control mothers who were evaluated at 6, 7, 9, and 11 years. During the 5-year follow-up period, 62% of the children were retained in the study. There were no statistical differences between the 6- and 11-year samples with respect to baseline anthropometric measurements, biochemical measures, or group composition. The institutional review board of Women and Infants’ Hospital of Rhode Island approved the study, and informed consent to enroll the children in a longitudinal study was obtained. Information on family history of cardiovascular disease and T2DM among first-degree relatives was obtained, and the socioeconomic status score for each family was determined with the Hollingshead index.

Body Composition and Metabolic Assessment

Biochemical and anthropometric measurements of blood pressure (BP), height, and weight were made at 6, 7, 9, and 11 years. Height was measured with a stadiometer affixed to a wall and weight was calculated as weight (in kilograms) divided by height squared (in square meters) and were compared with age and sex standards from the Centers for Disease Control and Prevention (www.cdc.gov/growthcharts). Tanner staging to evaluate puberty was not performed by a skilled examiner; however, self-reporting of pubertal signs, as described by Duke et al, was performed at age 11, and there were no differences among the groups. A Dinamap (Welch Allyn) vital-signs monitor was used to measure systolic and diastolic BP. The mean of ≥2 measurements obtained under relaxed conditions was used.

The biochemical testing included measurements of plasma glucose, insulin, and lipid levels. Postprandial glucose and insulin levels were determined by standard methods at 1 hour postprandial in the first 4 years. Fasting glucose, insulin, and triglyceride levels were measured at 9 and 11 years. Random serum cholesterol and high-density lipoprotein (HDL) levels were measured at 6, 7, 9, and 11 years. These analyses were described previously. At each of the 4 visits, however, a small number of children refused to have blood samples drawn or the specimens were inadequate for all tests; therefore, complete biochemical data were not available for all children at each visit.

We assessed insulin resistance on the basis of fasting insulin and glucose levels, using 2 methods. Fasting glucose/insulin ratios of <7 are correlated strongly with insulin resistance determined with the clamp technique among children. However, this ratio underestimates insulin resistance if glucose levels are abnormal; therefore, we also used homeostasis model assessment, which involves the product of glucose and insulin. Both methods are correlated strongly with insulin resistance measured with the euglycemic clamp technique among children.

Definitions

Identification of MS among children is often based on the adult criteria defined by the National Cholesterol Education Program (NCEP). In the adult definition, a minimum of 3 of 5 major criteria (obesity determined by waist circumference, hypertension, low HDL levels, elevated triglyceride levels, and glucose intolerance) should be fulfilled. Modifications to these criteria for children in our cohort were obesity defined as BMI >85th percentile for age, elevated BP defined as systolic or diastolic BP >95th percentile for age, HDL concentration <5th percentile for age, and triglyceride concentration >95th percentile for age. As for adults, glucose intolerance was defined as a fasting blood glucose level of >110 mg/dL or a 2-hour postprandial glucose level of >140 mg/dL after a standard mixed meal. A limitation of our study was that fasting blood tests were performed only at 9 and 11 years but HDL levels were measured at 6, 7, 9, and 11 years, and thus it was not feasible to define MS for all years between 6 and 11 years with the NCEP criteria of 3 of 5 variables. Therefore, we defined MS as ≥2 of the following 4 criteria: obesity, hypertension, evidence of dyslipidemia (low HDL levels or elevated triglyceride levels), and glucose intolerance.

Statistical Analyses

Bivariate analyses were performed to detect differences among the 4 groups constituting the cohort, with analysis of variance for continuous variables and χ² tests for proportion differences. Multivariate logistic regression analyses of the entire cohort at 11 years were performed with insulin resistance (glucose/insulin ratio of
<7) as a dependent variable and maternal obesity, gender, child-
hood obesity at 11 years, LGA status, GDM, and LGA-GDM
interaction as independent variables. The logistic regression
model was validated with the method described by Hosmer and
Lemeshow.29 Cox regression analysis30 of the entire cohort was
used to compute hazard ratios for MS development from 6 to 11
years, with adjustment for the covariates of GDM, maternal obe-
sity, LGA versus AGA, and LGA-GDM interaction. In addition,
the cumulative hazard (risk) of developing MS from 6 to 11 years
in the cohort was plotted for LGA and AGA categories within the
GDM group and within the control group. For Cox modeling, the
assumptions that the observations were independent and that the
hazard ratio was proportional across groups over time were both
met. For verification, plots of the cumulative hazard obtained with
the Kaplan-Meier technique were compared with the plots ob-
tained with Cox regression analysis. SAS (version 6.12; SAS Insti-
tute, Cary, NC) and SPSS for Windows (version 11.0; SPSS, Chi-
cago, IL) statistical packages were used for analysis and plotting
of graphs.

No a priori sample size or power calculations were performed
for the Cox regression analysis. Of the 179 children who were
assessed during the 5-year period, 4 had a missing value for
maternal prepregnancy BMI and were therefore excluded from the
Cox proportional-hazards analysis, leaving 175 children (83 LGA
subjects and 92 AGA subjects) for Cox modeling. To determine
posthoc the power to detect differences in the hazard for devel-
oping MS by 11 years, we assumed a twofold hazard for the LGA
group, compared with the AGA group, for developing MS. Of the
175 children assessed at 6 years, 69 were lost to follow-up moni-
toring by 11 years of age. Therefore, taking into account 39% (69 of
175 subjects) attrition by age 11, the power (1 - β) to detect a
twofold increase in the hazard ratio with a 2-sided
α = .05 was 77%, as determined with Power and Precision software (Bisot,
New York, NY).31

RESULTS

Table 1 presents the baseline characteristics of the
children at birth. Four groups were identified, ie,
LGA offspring of mothers with GDM (LGA/GDM),
AGA offspring of mothers with GDM (AGA/GDM),
LGA offspring of control mothers who did not meet
the criteria for a diagnosis of GDM (LGA/control),
and AGA offspring of control mothers (AGA/control).
Approximately one half of the children were
girls. The majority (>94%) of children were white,
reflecting the general population from which the
children were recruited. As designed, the only sig-
nificant difference among the children was birth
weight (LGA versus AGA, P = .0001). There was a
trend toward a higher prevalence of prepregnancy
obesity among the mothers of the LGA/GDM group
(P = .08). Maternal age, socioeconomic status, and
weight gain during pregnancy were comparable be-
tween GDM and control mothers, and rates of family
history of T2DM or cardiovascular disease were simi-
lar among the 4 groups of children.

For this cohort, we previously reported that obe-
sity rates at age 7 were higher among the former
LGA infants of GDM mothers.32 In this follow-up
study at age 9 and 11 years, there were no significant
differences in the prevalence of obesity (Table 2). In
the LGA/GDM group, 44% at 9 years and 35% at 11
years had a >85th percentile BMI. The prevalence of
obesity (BMI >85th percentile) at ages 9 and 11 years
in the other 3 groups ranged from 24% to 31%.

There were no significant differences among the
groups at 9 and 11 years with respect to BP, lipid
levels, glucose levels, and insulin resistance calcul-
ated with the homeostasis model (Table 2). Al-
though there were no significant differences in the
mean glucose/insulin ratios among the 4 groups
(Table 2), there was a trend (P = .08) toward in-
creased insulin resistance, defined as a glucose/insu-
lin ratio of <7, in the LGA/GDM group at 11
years. Given this trend, we analyzed insulin resis-
tance (glucose/insulin ratio: <7) in a multivariate
logistic regression analysis of the available sample of
11-year-old children for whom insulin and glucose
levels were measured (n = 88). Childhood obesity
and the interaction of LGA status and maternal GDM
were significantly associated with insulin resistance,
with odds ratios of 4.3 (95% confidence interval [CI]:
1.5–11.9; P = .008) and 10.4 (95% CI: 1.5–74.4; P = .019), respectively. Maternal GDM and LGA at birth
were not independently associated with insulin res-
istance. Maternal obesity and gender were not sig-
nificant; therefore, they were omitted from the final
model, to prevent overspecification.

Figure 1 shows the percentage of children at any
age between 6 and 11 years in each of the 4 groups
who fulfilled our modified definition of MS, ie, at
least 2 of the following 4 components: obesity, hy-
pertension, evidence of dyslipidemia, and glucose
intolerance. In the LGA/GDM group, 50% of the
children met our minimal definition of MS, and this
was significantly higher than values for all other
groups (overall χ², P = .008). The AGA/GDM group
had 21% who met the criteria, whereas the LGA/
control and AGA/control groups had prevalences of
29% and 18%, respectively. A limitation of the study
is that fasting biochemical data were not obtained at
years 6 and 7; therefore, our condensed definition of

| TABLE 1. Baseline Characteristics of the Study Groups |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variables       | LGA/GDM (n = 42) | AGA/GDM (n = 52) | LGA/Control (n = 43) | AGA/Control (n = 42) | P Value |
| Birth weight, g, mean (SD) | 4107 (386)*† | 3316 (310) | 4132 (285)*† | 3370 (282) | .0001 |
| Female, %       | 45             | 50             | 52             | 44             | .85   |
| White, %        | 95             | 94             | 98             | 100            | .73   |
| Maternal obesity, %‡ | 35             | 20             | 26             | 12             | .08   |
| Maternal weight gain, kg, mean (SD) | 14.3 (7) | 13.4 (7) | 15.8 (6) | 14.6 (5) | .30   |
| Hollingshead socioeconomic status index, mean (SD) | 45.2 (11) | 43.1 (12) | 40.9 (12) | 42.6 (10) | .36   |

Analyses of means were by analysis of variance; analyses of proportions were by χ² test.
* Posthoc test for analysis of variance results, P < .05, compared with AGA/control group.
† Posthoc test for analysis of variance results, P < .05, compared with AGA/GDM group.
‡ Prepregnancy BMI of >27.3 mg/m².
MS is unconventional. To evaluate the prevalence of MS in the cohort on the basis of the conventional criteria established by NCEP, we examined the proportion of subjects 6 to 11 years of age in each of the 4 groups with ≥1 component (obesity, systolic or diastolic hypertension, high triglyceride levels, low HDL levels, glucose intolerance) of the MS (Table 3). If the standard NCEP definition of MS as 3 of 5 components during the 5-year study period is applied, then 15% of children in the LGA/GDM group at age 11 had 3 components meeting the conventional definition of MS, whereas only 3% to 5.3% of children in the other groups had 3 components and therefore evidence of MS.

To determine the independent hazard (risk) of developing MS attributable to birth weight category, gender, maternal prepregnancy obesity, and GDM, we analyzed the data for the entire cohort with Cox regression analysis (Table 4). Children who were LGA at birth had a twofold increased hazard of MS by 11 years of age (hazard ratio: 2.19; 95% CI: 1.25–3.82; \( P = .01 \)), and children who were offspring of mothers with obesity also had approximately a two-fold increased hazard (hazard ratio: 1.81; 95% CI: 1.03–3.19; \( P = .039 \)). GDM and gender were not independently significant. An interaction term for LGA and GDM was tested and was not significant (hazard ratio: 1.44; 95% CI: 0.47–4.66; \( P = .52 \)); therefore, it was deleted from the final model.

To illustrate the cumulative hazard of developing MS over time for the control and GDM groups, we plotted hazards according to age in LGA versus AGA categories in each group (Fig 2). In the control group, the cumulative hazard was similar over time for LGA and AGA children (0.35 vs 0.23; \( P = .56 \)). In the GDM group, the cumulative hazard for LGA children diverged from that for AGA children at 7 years and by 11 years was 3.6-fold greater than the value for AGA children (0.99 vs 0.27; \( P = .004 \)).

DISCUSSION

The prevalence of obesity in this cohort of children at 11 years is very similar to the alarming and increasing rate of obesity among children in the United States. The prevalence of obesity in this cohort of children at 11 years is very similar to the alarming and increasing rate of obesity among children in the United States. The prevalence of obesity in this cohort of children at 11 years is very similar to the alarming and increasing rate of obesity among children in the United States.
States. National Health and Nutrition Examination Survey data from a survey of 4722 children in 1999–2000 revealed that 30.3% of children 6 to 11 years of age had a 85th percentile BMI. Obesity among children is a significant risk factor for the development of insulin resistance, and the degree of obesity is correlated with the degree of insulin resistance. We observed that obesity among the 11-year-old children was a strong predictor of insulin resistance, and the combination of LGA status and a mother with GDM might increase the risk. The consequences of insulin resistance, such as MS, are well known, and we found that children who were LGA and exposed to GDM also had a significantly higher risk of MS.

Birth weight (LGA or SGA) and in utero exposure to diabetes are important risk factors for childhood-onset T2DM among Pima Indian children. There is a large body of literature, mostly cross-sectional studies, that demonstrates an effect of low birth weight on the development of T2DM and MS in adulthood. In addition, there is an emerging body of literature indicating that GDM is a risk factor for insulin resistance and MS in childhood. A limitation of our study was not including SGA offspring of GDM and control mothers and comparing the risk of developing MS among AGA, LGA, and SGA children. However, given the increasing incidence of adult obesity, LGA is a more common outcome of pregnancy. Therefore, we chose to study LGA offspring, because LGA status might be more relevant for the risk of MS in the present generation of children.

We showed that LGA offspring of diabetic mothers (LGA/GDM group) are at significant risk for the development of MS, in a population of children not previously identified as being at high risk. In this group, 50% were at risk for MS and 15% met the NCEP definition (≥3 risk factors) of MS. The prevalence of the MS in the other 3 groups was similar to the prevalence (4.8%) among white adolescents in the 1988–1994 National Health and Nutrition Examination Survey. To our knowledge, this effect of LGA status with maternal GDM on childhood MS has not been previously demonstrated in the general population. However, exposure to diabetes in utero has been established as a significant risk factor for some of the components of MS (obesity, glucose intolerance, and hypertension) among Pima Indian children. An Australian study of risk factors for MS among 8-year-old children found no association with birth weight; however, that study did not include analysis of prenatal maternal factors. In contrast, our data indicate that the effect of birth weight on the risk of MS becomes evident by age 9 among children of mothers with previous GDM (Fig 2).

Interestingly, we found that exposure of children to maternal obesity was as strong a predictor of risk for MS as LGA status. This independent effect of maternal obesity on the risk of MS among children has not been shown previously. This suggests that, among obese mothers without clinical GDM, fetal hyperinsulinemia might develop because of mild maternal hyperglycemia that is below the threshold for a diagnosis of GDM or occurs later in the pregnancy, after screening. This is consistent with other studies showing that maternal obesity is a risk factor for LGA birth in the absence of frank GDM. However, unknown genetic factors and environmental influences may also contribute to obesity and subsequent MS risk.

<table>
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<th>Variable</th>
<th>Hazard Ratio</th>
<th>P Value</th>
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<td>1.25–3.82</td>
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<td>1.81</td>
<td>.039</td>
<td>1.03–3.19</td>
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<td>GDM versus control</td>
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<td>.191</td>
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<td>Male versus female</td>
<td>1.52</td>
<td>.133</td>
<td>0.88–2.61</td>
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* Prepregnancy BMI of >27.3 kg/m².

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<th>Group, n</th>
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<th>3 Components, %</th>
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Table 3. Prevalence of ≥1 Component of the MS at Each Year According to Group

Table 4. Hazard Ratio for the Risk of MS (n = 175)
We found that children who were LGA at birth and were exposed to an intrauterine environment of either diabetes or maternal obesity were at increased risk of MS during childhood. Given the increase in obesity prevalence among children and adults, these findings have implications for perpetuating the cycle of obesity, insulin resistance, and their consequences (GDM, T2DM, MS, and cardiovascular disease) in subsequent generations. Public health strategies are urgently needed to prevent obesity and to treat it effectively. We strongly encourage primary care providers to discuss lifestyle choices and the consequences of obesity as part of routine anticipatory guidance early in the care of children.

CONCLUSIONS

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