Lipid Profile, Glucose Homeostasis, Blood Pressure, and Obesity-Anthropometric Markers in Macrosomic Offspring of Nondiabetic Mothers

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OBJECTIVE — The study was to determine whether being the macrosomic offspring of a mother without detected glucose intolerance during pregnancy has an impact on lipid profile, glucose homeostasis, and blood pressure during childhood.

RESEARCH DESIGN AND METHODS — Plasma total, HDL, and LDL cholesterol; triglycerides; apolipoprotein (Apo) A-1, -B, and -E; lipoprotein (a); fasting glucose and insulin; homeostasis model assessment of insulin resistance (HOMA-IR) index; blood pressure; BMI; and detailed anthropometry were evaluated in 85 children aged 3–10 years old, born appropriate for gestational age (AGA; $n = 48$) and large for gestational age (LGA; $n = 37$) of healthy mothers.

RESULTS — At the time of the assessment, body weight, height, skinfold thickness, BMI, waist circumference, and blood pressure did not differ between the LGA and AGA groups with the exception of head circumference ($P < 0.01$). There were no significant differences in plasma total or LDL cholesterol; triglycerides; Apo A-1, -B, or -E; lipoprotein (a); Apo B–to–Apo A-1 ratio; or glucose levels between the groups. The LGA group had significantly higher HDL cholesterol levels ($P < 0.01$), fasting insulin levels ($P < 0.01$), and HOMA-IR index ($P < 0.01$) but lower values of the glucose-to-insulin ratio ($P < 0.01$) as compared with the AGA group.

CONCLUSIONS — Children born LGA of mothers without confirmed impaired glucose tolerance during pregnancy show higher insulin concentrations than AGAs.

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Fetal growth is a complex process involving the interaction of mother, placenta, and fetus (1). Growth and development of the fetus depends upon nutrients such as glucose, lipids, and amino acids (1). Genetic factors, in addition to the maternal and fetal status, are reported to play a role (1,2). Epidemiological, clinical, and experimental findings indicate that gestational diabetes mellitus (GDM), as well as maternal obesity or excessive weight gain during pregnancy, are significant risk factors for fetal overnutrition and macrosomia (1,2). Maternal hyperglycemia leads to fetal hyperglycemia, which in turn stimulates pancreatic islet cells and causes hyperinsulinemia (2,3). This intrauterine hyperinsulinemic state results in increased amounts of fat tissue, liver glycogen content, and total body size (2,3). Macrosomic infants of diabetic mothers are prone to glucose intolerance, obesity, and diabetes during childhood and adulthood (2,4–6). Disturbances not only in the metabolism of carbohydrates but also in lipids observed at birth in newborns of diabetic mothers may influence the metabolic profile later in life (2,5,7–10).

There is limited data regarding the metabolic profile of macrosomic offspring of healthy mothers. Moreover, these studies refer to neonatal or infantile age-groups and pay only restricted attention to childhood (8,11,12). It is important to determine whether being the macrosomic offspring of a mother without detected glucose intolerance during pregnancy has an impact on the lipid profile, insulin secretion, and glucose homeostasis during childhood. A possible association with the development of atherosclerosis, cardiovascular disease, and metabolic syndrome in advanced age should also be explored in this group of children (13).

The purpose of this study was to investigate the effect of fetal macrosomia in apparently healthy pregnancies on lipid profile, glucose homeostasis, blood pressure, BMI, and other anthropometric variables during childhood.

RESEARCH DESIGN AND METHODS

— The study included 85 children aged 3–10 years that were born at the University Hospital of Ioannina, Ioannina, Greece, 1 January 1992 to 31 December 1997. These children were full-term offspring (gestational age 37–42 weeks) of nonobese (BMI< 30 kg/m^2) and nondiabetic mothers with absence of chronic hypertension or GDM in previous pregnancies and not receiving drugs known to affect glucose metabolism throughout gestation. All pregnant women of the study were tested with a 100-g oral glucose tolerance test at 24–28 weeks of gestation.

During the above-mentioned period, 42 large-for-gestational-age (LGA) offspring of nondiabetic and nonobese mothers were born in this hospital and planed to be enrolled in the study. Thirty-seven of the 42 (88%) children agreed to

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Abbreviations: AGA, appropriate for gestational age; Apo, apolipoprotein; GDM, gestational diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; LGA, large for gestational age.

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

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participate in the study. The control group consisted of 48 children born appropriate for gestational age (AGA) at the same period by nondiabetic and nonobese mothers matched for pregestational BMI, height, age, parity, and socioeconomic status to mothers of LGA children. At the time of the study this hospital hosted the majority of deliveries (85%) in a well-defined geographical area in which all study mothers were living.

The gestational ages of the children were assessed according to the mothers' menstrual histories and ultrasonography and then confirmed by the neonatologists' assessment of the babies' maturity within 24 h of delivery. Birth weight, crown-heel length, and birth head circumference were also recorded immediately after delivery (14). Macrosomia was defined as a birth weight of ≥4,000 g or >90th percentile for their gestational ages (1). The macrosomic group was divided in two subgroups according to the birth weight: *1*) LGA ≥97th percentile ($n = 12$) and *2*) LGA between 90th and 97th percentile ($n = 25$) and compared with AGA group. AGA was defined as birth weight, crown-heel length, and head circumference between the 10th and 90th percentile for their gestational ages. Written parental consent was obtained, and the experimental protocol was approved by the research ethics committee of Ioannina University Hospital.

The study groups were evaluated between 3 and 10 years of age. Body weight was determined to the nearest 0.1 kg, with the child dressed only in underwear and wearing no shoes, using a digital electronic scale (SECA, Hamburg, Germany). Head circumference was measured with a measuring tape as the maximum circumference between the supraorbital ridge and the occiput. Body height was measured to the nearest 0.1 cm by a Harpenden stadiometer. Waist circumference was also measured at umbilicus level to the nearest 0.5 cm. BMI was calculated according to the formula weight (in kilograms) divided by the square of height (in meters). Skinfold thickness measurements (in millimeters) of the biceps, triceps, subscapular, and suprailiac muscles were used to assess central and peripheral adiposity (15). They were determined according to World Health Organization standards on the left side to the nearest 0.2 mm using a Harpenden skinfold mechanical caliper. All skinfold measurements were carried out in triplicate, and the mean values were used for analysis. Blood pressure (Korotkoff sounds phase I and IV were used for systolic and diastolic pressure, respectively) (16) was measured in triplicate using a mercury sphygmomanometer on the right arm in the recumbent position after a 5-min rest. Techniques recommended by the fourth report on blood pressure control for children were followed (16). All children of the study were in Tanner stage 1 to exclude any possible effects of pubertal development on insulin, glucose-to-insulin ratio, and homeostasis model assessment of insulin resistance (HOMA-IR) index.

Venous blood samples for laboratory analysis were also taken on these children after a 12-h overnight fast. Serum total cholesterol, triglycerides, HDL cholesterol, lipoprotein (a), and apolipoprotein (Apo) A-1,- B, and -E were determined with techniques previously described (17). Serum LDL cholesterol was calculated using the Friedewald formula (provided that triglycerides levels were <400 mg/dl) (18). Fasting plasma insulin levels were determined using an immunoenzymatic method (analyzer AXSYM; Abbott, Abbott Park, IL) and fasting glucose concentrations by the glucose oxidase method. The HOMA index suggested by Mathews et al. (19) for simple assessment of insulin sensitivity was calculated by the formula (glucose [mmol/l] × insulin [mU/l]/22.5).

Statistical analysis

An unequal sample size of 85 children for each comparison was calculated to be adequate for detecting a difference of 15% in blood parameters between the two groups with a power >80% on a significance level of 5%. The calculation of the sample size was based on estimations of the SDs of the above parameters in data from the control group (20). Data were analyzed by one-way ANOVA, using Fisher's protected least significant difference test for comparing the means of the study groups pairwise. Spearman's rank correlation coefficient was used to assess any possible interdependency between the examined parameters. Mann-Whitney *U* tests were used for the comparison between abnormally distributed data. Analyses were performed using the Stat View software package of SAS Institute. Differences were considered statistically significant at *P* value <0.05.

RESULTS — The mean (±SD) anthropometric indexes of the 37 LGA and 48 AGA subjects at birth and during the study period, as well the maternal characteristics during the pregnancy period, are depicted in Table 1. The characteristics of the five nonparticipant LGA offspring at birth as well as the characteristics of their mothers did not differ from the rest of the LGA group. The mothers did not differ regarding BMI before pregnancy, age, height, weight gain during pregnancy, parity (first parity 33 and 37% and second parity 48 and 51% for AGAs and LGAs, respectively), and socioeconomic status (Table 1). Overweight (BMI 25–29.9 kg/m^2) was recorded in six (16.2%) and eight (16.6%) mothers of the AGAs and LGAs, respectively, (P = NS). At the time of the children's examination, the mean age and the basic anthropometric indexes (body weight and body height) did not differ between the LGA and AGA groups with the exception of head circumference ($P < 0.01$) (Table 1). In addition, no statistical differences were found in skinfold thickness for different parts of the body or for BMI, waist circumference (Tables 1 and 2), and blood pressure. Positive correlation between blood pressure (systolic and diastolic) and BMI at the time of the examination ($P < 0.01$) was found in all groups. No significant differences were observed in the plasma glucose; total or LDL cholesterol; triglycerides, Apo A-1, -B, and -E; lipoprotein (a); and Apo B–to–Apo A-1 ratio between the two groups (Table 3). Children born as LGA had significantly higher HDL cholesterol levels compared with those born as AGA (1.37 ± 0.24 vs. 1.24 ± 0.20) ($P < 0.01$) (Table 3). The fasting insulin levels and HOMA-IR index were higher in the LGA compared with the AGA group ($P < 0.01$) (Table 4). The glucose-to-insulin ratio was significantly lower in the LGAs ($P < 0.01$) (Table 4). Comparisons of the same parameters between the subgroups of children born LGA ≥97th percentile or LGA between 90th and 97th percentile and the AGA group were also conducted. The mean (±SD) age of the two subgroups was comparable (6.8 ± 1.6 and 6.72 ± 1.7 years, respectively) and did not differ from the mean age of the control AGA group. Children born as LGA ≥97th percentile had higher HDL cholesterol and insulin levels ($P < 0.01$ and $P < 0.001$, respectively) as well as HOMA-IR index values ($P < 0.001$) but had lower glucose-to-insulin ratio ($P < 0.01$) than the control group (Tables 3 and 4). Moreover LGA between the 90th and 97th percentile tended to have higher HDL cholesterol ($P = 0.075$), insulin ($P =$

Table 1—*Basic anthropometric indices at birth and at the time of study of 3- to 10-year-old children born LGA or AGA and characteristics of their mothers*

	AGA group (n = 48)	LGA group (n = 37)	P value
Characteristics of the children			
At birth			
Gestational age (weeks)	39.4 ± 1.4 (37–42)	39.8 ± 1.1 (37–42)	0.23
Body weight (g)	3,470 ± 387 (2,500–3,980)	4,261 ± 182 (4,000–4,600)	<0.0001*
Body length (cm)	51.9 ± 1.9 (47–57)	54.4 ± 2.2 (51–59)	<0.0001*
Head circumference (cm)	35 ± 1.1 (33–37)	36.7 ± 1.1 (34–38.5)	<0.0001*
At the time of study			
Age (years)	6.7 ± 1.7 (3–10)	6.7 ± 1.6 (3–10)	0.92
Body weight (kg)	30.1 ± 8.4 (15–50)	30.9 ± 9.7 (15–59)	0.69
Body height (cm)	126.5 ± 12.4 (96–155)	127.9 ± 12.2 (96–150)	0.61
Head circumference (cm)	52.6 ± 1.1 (50–54.5)	53.4 ± 1.5 (50–56)	0.0065*
Waist circumference (cm)	61 ± 8 (45–79)	61.5 ± 8.2 (48–89)	0.69
BMI (kg/m^2)	18.5 ± 2.7 (12.4–24.3)	18.6 ± 3.4 (12–26)	0.86
Characteristics of the mothers			
Age (years)	26.7 ± 4 (21–33)	25.3 ± 4 (21–37)	0.46
Body height (cm)	164 ± 6 (155–175)	165 ± 5 (153–180)	0.29
Initial BMI (kg/m^2)	23 ± 3 (18–29.8)	23.1 ± 2.2 (20.2–28.6)	0.49
Weight gain during pregnancy	13.3 ± 4 (8–26)	14.8 ± 4 (8–25)	0.16

Data are means ± SD (range). *P < 0. 0001, 0.0065 refers to LGA vs. AGA.

0.068), and HOMA-IR index (P = 0.06) values compared with control subjects (Tables 3 and 4).

When children born macrosomic were divided in two subgroups according to whether their mother's first-degree relatives had diabetes or not (n = 17 and n = 20, respectively), we observed significantly lower glucose-to-insulin ratio in children of the former group (15 ± 6 vs. 26.6 ± 22, P < 0.05).

To evaluate whether the observed differences were associated with a ponderal index (weight at birth [g] × 100/length at birth [cm^3]) variation, we classified LGA children as proportional (ponderal index between 10th and 90th percentile, n = 34) and disproportional (ponderal index >90th percentile, n = 3) (21). Only 3 of 37 (8%) LGAs were >90th percentile, so this subgroup was too small for statistical evaluation. No significant differences were also observed in the examined metabolic parameters within the LGA group when LGA children were reclassified in three subgroups according to ponderal index tertiles.

CONCLUSIONS — Even though fetal macrosomia occurs more often in diabetic mother pregnancies, there are considerable numbers of macrosomic infants born of nondiabetic mothers (8–14%) (1). Factors thought to be implicated are maternal multiparity, obesity, and excessive weight gain during pregnancy (1,2). These same factors are considered to affect the newborn's metabolism (1,2). Several studies have investigated the relationship between macrosomia and abnormalities of carbohydrate or lipid metabolism in diabetic, prediabetic, or obese mothers and their offspring (2,4–9,22). In addition, most of the studies dealing with the metabolic state of macrosomic offspring of nondiabetic mothers include only the neonatal or infantile ages (11,12,22). The present study examines the metabolic state of children born as LGA of mothers with a normal glucose tolerance test to investigate whether maternal glucose levels in the nondiabetic range may have an impact on the metabolic outcome of these children.

The higher insulin and HOMA-IR index values found in the children born macrosomic in this study as compared with the AGA ones are consistent with the report of Hoegsberg et al. (22) even though that study was of infants. Hyperinsulinemia in fetuses whose mothers do not have GDM or confirmed impaired glucose tolerance might be attributed to mild maternal hyperglycemia below the threshold of diagnosis (5,13). The possibility of developing a late impaired glucose metabolism after the screening time in some of the mothers of this study could not be excluded (23). These disturbances might affect the fetal growth (22).

As reported by Kurishita et al. (24) even in nondiabetic, normoglycemic pregnancies, undetected hyperglycemic episodes during pregnancy have been shown to influence the neonatal state.

Table 2—*Skinfold thickness from different body sites in all study groups*

Study groups	n	Biceps (mm)	Triceps (mm)	Subscapular (mm)	Suprailiac (mm)
AGA	48	6.9 ± 2.7 (3–14)	9.7 ± 3.5 (5–18)	8.5 ± 3.7 (4–18)	9.6 ± 4.6 (4–19)
LGA	37	7.3 ± 3.4 (4–18)	9.1 ± 3.9 (3–20)	8.8 ± 4.1 (5–19)	9.8 ± 5.3 (4–22)
LGA ≥97th percentile	12	8.7 ± 3.8 (4–18)	11.2 ± 4.4 (5–20)	9.9 ± 4 (5–19)	12 ± 5.3 (4–22)
LGA 90th–97th percentile	25	6.7 ± 3.1 (4–14)	8.1 ± 3.4 (4–17)	8.3 ± 4.2 (5–19)	8.8 ± 5 (4–19)

Data are means ± SD (range).

Table 3—*Plasma lipids and Apo concentrations in the study groups*

Study group	*n*	Total cholesterol (mmol/l)	HDL cholesterol (mmol/l)	LDL cholesterol (mmol/l)	Triglycerides (mmol/l)	Apo A-1 (g/l)	Apo B (g/l)	Apo E (g/l)	Lipoprotein (a) (μmol/l)	Apo B–to–Apo A-1 ratio
AGA	48	4.29 ± 0.68 (2.20–5.56)	1.24 ± 0.20 (0.82–1.89)	2.74 ± 0.57 (1.14–3.96)	0.66 ± 0.29 (0.26–1.84)	1.51 ± 0.19 (1.10–1.94)	0.72 ± 0.14 (0.40–1.07)	0.04 ± 0.01 (0.003–0.06)	0.20 ± 0.24 (0.03–1.38)	0.48 ± 0.094 (0.29–0.71)
LGA	37	4.52 ± 0.75 (3.03–6.19)	1.37 ± 0.23 (0.98–1.91)*	2.86 ± 0.68 (1.56–4.36)	0.65 ± 0.16 (0.37–1.03)	1.57 ± 0.18 (1.28–1.96)	0.70 ± 0.17 (0.41–1.05)	0.04 ± 0.01 (0.02–0.06)	0.12 ± 0.11 (0.03–0.48)	0.45 ± 0.13 (0.33–0.76)
LGA 90th–97th percentile	25	4.49 ± 0.87 (3.03–6.19)	1.33 ± 0.23 (0.99–1.86)	2.86 ± 0.75 (1.56–4.36)	0.64 ± 0.15 (0.37–1.01)	1.55 ± 0.18 (1.28–1.96)	0.70 ± 0.18 (0.41–1.05)	0.04 ± 0.01 (0.02–0.05)	0.14 ± 0.12 (0.03–0.48)	0.46 ± 0.13 (0.25–0.75)
LGA ≥97th percentile	12	4.60 ± 0.42 (3.83–5.25)	1.44 ± 0.24 (1.14–1.91)*	2.86 ± 0.53 (1.97–3.86)	0.65 ± 0.16 (0.46–1.02)	1.62 ± 0.17 (1.48–1.92)	0.70 ± 0.17 (0.46–1.00)	0.04 ± 0.008 (0.03–0.06)	0.05 ± 0.04 (0.03–0.14)	0.4 ± 1.42 (0.25–0.66)

Data are mean ±SD (range). *$P < 0.01$ LGA vs. AGA and LGA ≥97th vs. AGA.

Even a limited degree of maternal hyperglycemia, considered to be in the normal range, may affect fetal weight (22,25). The question that remains is how fetal macrosomia may have an impact on glucose metabolism later in life. It has been speculated that in the case of children of diabetic mothers, this abnormality may be due to a persistent dysregulation of insulin secretion and a permanent derangement in metabolic or neuroendocrine systems (5). In LGA children of nonobese and nondiabetic mothers, one can hypothesize a similar mechanism related either to undetected derangements in glucose metabolism during pregnancy or to an unknown common denominator leading in both intrauterine macrosomia and metabolic disturbances later in life. Furthermore it is likely that environmental or unknown genetic factors may also play a role (2,24,25).

Since skinfold thickness and BMI were similar in the LGA and AGA groups that we examined, the difference in the abovementioned metabolic variables between them cannot be attributed to differences in adipose tissue content of the body. It is known that during childhood there is a physiological increase in plasma insulin levels until puberty (26). The fact that the study and the control groups were of similar age and prepubertal development indicates that these parameters did not have an impact on metabolic differences observed during statistical analysis.

In a recently published study (13), the authors examined the development of metabolic syndrome in a population of LGA and AGA children at the ages of 6, 7, 9, and 11 years. According to their findings, the prevalence at any given time of ≥2 components of metabolic syndrome was significantly higher in the LGA offspring of diabetic mothers than in those of nondiabetic mothers (50 and 29%, respectively) (13). They did not observe any significant difference in the mean glucose, insulin, or insulin resistance between children born macrosomic of mothers with or without GDM (13). However, the prevalence of children born macrosomic of nondiabetic mothers having two or more components of metabolic syndrome cannot be ignored.

The results also indicate that children born macrosomic of nondiabetic mothers had significantly higher HDL cholesterol levels than children born AGA ($P < 0.01$). This difference became greater with increasing birth weight. Studies of macrosomic newborns of diabetic or obese mothers have shown higher serum lipids and apolipoproteins compared with AGA newborns of healthy mothers (8,9). These data suggest that the synthesis of fat and protein might be increased in these fetuses (8,9). However, in macrosomic newborns of nondiabetic and nonobese mothers, serum lipid and apolipoprotein values did not differ significantly from those in AGA newborns (8,11). A population study in Uppsala, Sweden, of adult men showed a significantly positive correlation between birth weight and HDL cholesterol levels when adjusted for BMI (27). A study in 8-year-old Indian children also demonstrated a trend for rising HDL cholesterol concentrations with increasing birth weight, which was not, however, statistically significant (28). Although the present study showed higher levels of HDL cholesterol in children born LGA compared with those born AGA, we cannot define an underlying mechanism to explain these observations. Longitudinal studies are needed to delineate whether the observed differences may represent a lifelong condition.

According to Williams and Poulton (29) the increase in weight or height after birth and not the birth size is a determinant for elevated blood pressure later in life. In this study, in agreement with others, the difference in blood pressure between children born LGA and AGA was insignificant (13,29). The positive correlation between blood pressure and BMI found in all groups indicates that BMI contributes to elevated blood pressure levels and represents a good predictor of cardiovascular disease (30).

Although the distinction between AGA and LGA children is somehow artificial and arbitrary as intrauterine growth is a continuous process, it seems that the children at the upper end of the weight range may need more careful attention for possible development of metabolic aberrations during childhood.

Findings of this study indicate that even LGA offspring of mothers with no detected disturbances in glucose-insulin homeostasis during pregnancy (tested at 24–28 weeks gestational age) may be at risk for insulin resistance during childhood. Further studies are required to elucidate the possible mechanisms by which genetic factors as well as the intrauterine environment affect the metabolic profile of these children during life.

Table 4—*Glucose, insulin levels, and HOMA-IR index by birth weight in Greek children 3–10 years old*

Study group	*n*	Glucose (mmol/l)	Insulin (pmol/l)	Glucose-to-insulin ratio	HOMA-IR index
AGA	48	4.65 ± 0.47 (2.94–5.49)	29.6 ± 13.4 (6.94–59)	25.8 ± 16.9 (10.4–79.1)	0.91 ± 0.45 (0.13–2.09)
LGA	37	4.79 ± 0.30 (4.21–5.60)	40.9 ± 22.2 (5.55–88)*	21.5 ± 17.4 (7.1–95)*	1.3 ± 0.7 (0.15–2.9)*
LGA 90th–97th percentile	25	4.77 ± 0.32 (4.21–5.60)	36.8 ± 17.3 (5.55–73)	22.7 ± 18 (8.2–95)	1.14 ± 0.57 (0.15–2.33)
LGA ≥97th percentile	12	4.83 ± 0.26 (4.44–5.21)	49.3 ± 27.8 (9.02–88)†	18.9 ± 16.6 (7.1–66.9)*	1.6 ± 0.9 (0.3–2.9)†

Data are means ± SD (range). *$P < 0.01$ LGA vs. AGA, LGA ≥97th vs. AGA; †$P < 0.001$ LGA ≥97th vs. AGA.

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