Phenotype of Infants of Mothers with Gestational Diabetes

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The phenotype of the infant of the diabetic mother is generally perceived as being macrosomic or large for gestational age. However, not all infants of women with gestational diabetes mellitus (GDM) are macrosomic and, under certain circumstances, because of the interaction of genes and environment, can present as small for gestational age at birth. In contrast, the macrosomic infant presenting with hypoglycemia may not necessarily be the infant of a woman with GDM, but have an underlying metabolic or genetic dysregulation accounting for a similar phenotype. In this review, we will attempt to review the increasing prevalence of obesity in adults, adolescents, and possibly neonates as well. In an effort to better define macrosomia in the infant of the GDM mother, we will review the body composition analyses of infants of GDM mothers. Last, in addition to well-known factors such as maternal glucose control and overall nutrient availability, we will discuss the independent effect of maternal pregravid obesity on fetal adiposity in the infant of the GDM mother. We will be able to develop rational treatment modalities only if we have a better understanding of the various maternal components and factors relating to growth in these infants.

PHENOTYPE — The word "phenotype" has its origins in the Greek language: *phainein*, to show or appear, and *typos*, a type or mark. In reviewing the definition of phenotype, it became apparent that the meaning of the word has changed over the past few decades. In the 1960s, the standard definition in a medical dictionary was "the outward visible expression of the hereditary constitution of an organism" (1). This definition appeared well suited to descriptions of the fetus of a diabetic mother at that time. For example, in Pedersen's text, the external appearance of the infant of the mother with diabetes is described as, "Most conspicuous is obesity, the round cherub's cheeks, buried eyes, and short neck. Many infants have a plethoric appearance, reddened skin, and an abundance of head hair" (2).

However, more recent definitions of phenotype recognize the scientific advances beyond that of simple description of outward appearances. Currently, phenotype is defined as "the complete observable characteristics of an organism or group, including anatomic, physiological, biochemical, and behavioral traits, as determined by the interaction of both genetic makeup and environmental factors" (3). The interaction between genes and environment can result in a variety of phenotypic expressions of infants of mothers with GDM.

In 1998, Hattersley et al. (4) reported on the various phenotypic permutations associated with the single gene mutations in the glucokinase gene (Fig. 1). Glucokinase phosphorylates glucose to glucose-6-phosphate in the pancreas and liver. A heterozygous glucokinase mutation results in hyperglycemia, usually with a mildly elevated fasting glucose and abnormal oral glucose tolerance test. This is due to both a defect in the sensing of glucose by the β-cell, resulting in decreased insulin release, and to a lesser degree from reduced hepatic glycogen synthesis. If the heterozygous mutation is present in the fetus, then the altered glucose sensing by the fetal pancreas will result in a decrease in insulin secretion. Because in the fetus insulin is a primary stimulus for growth, any defect in fetal insulin secretion will result in decreased fetal growth and possible growth restriction. Hence, depending on if mother, fetus, or both have this gene defect in the glucokinase gene, the phenotype of the infant can vary from intrauterine growth restriction, through normal fetal growth and on to macrosomia.

In contrast, genetic imprinting may result in the offspring having the phenotype of an infant of a GDM mother, but the mother has normal glucose tolerance. Genetic imprinting is defined as the expression of either a maternal or paternal gene, the parent of origin of which determines the expression of a single allele of a gene. An example of genetic imprinting that results in the offspring having the phenotype of a GDM mother is the Beckwith-Wiedemann syndrome (5). At birth, these infants present with macrosomia, defined as an average birth weight of 4 kg with increased subcutaneous tissue and muscle mass. Other findings include neonatal polycythemia and hypoglycemia. The hypoglycemia may be related to increased IGF-II expression, resulting in neonatal hyperinsulinemia. The most common situation is when the maternal copy of the gene (11p15.5) is inactivated. The only active copy of the gene is then the paternal copy. Hence, at birth, the infant with Beckwith-Wiedemann syndrome may have the phenotype of an infant of a GDM mother based on macrosomia, hypoglycemia, and polycythemia, whereas the mother may have completely normal glucose tolerance. The interaction of genes and the environment then has the

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Received for publication 28 March 2006 and accepted in revised form 5 May 2006.

This article is based on a presentation at a symposium. The symposium and the publication of this article were made possible by an unrestricted educational grant from LifeScan, Inc., a Johnson & Johnson company.

Abbreviations: AGA, average-for-gestational-age; GDM, gestational diabetes mellitus; LGA, large-for-gestational-age; NGT, normal glucose tolerance; SGA, small-for-gestational-age.

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

DOI: 10.2337/dc07-s209

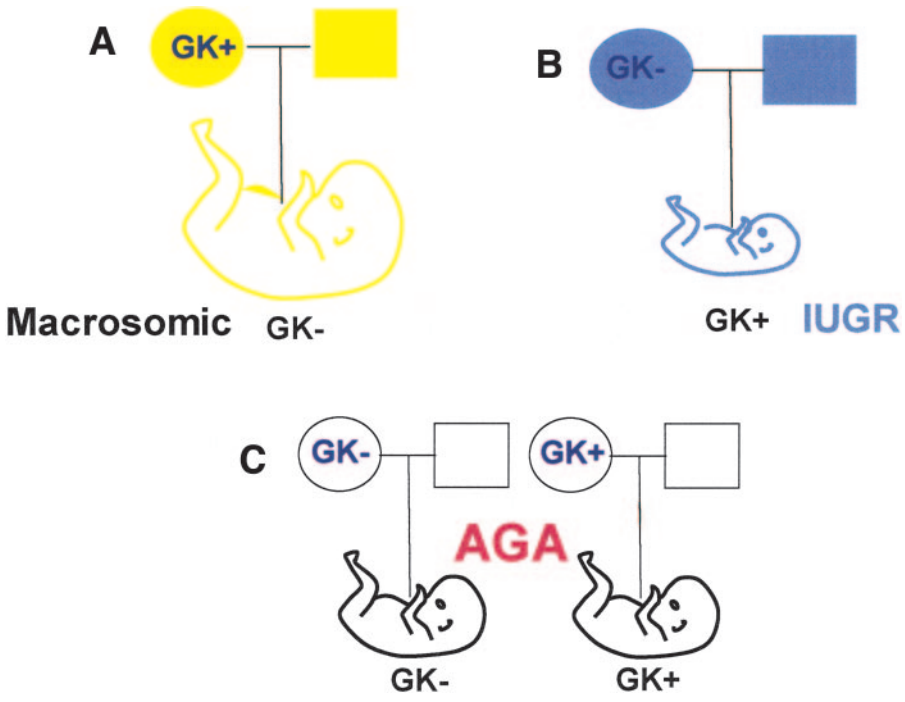

Figure 1—*The glucokinase (GK) mutations: variation in fetal growth. If the heterozygous GK mutation is in the mother and not the fetus* (A)*, then the fetus is at risk for being macrosomic based on excess maternal nutrient availability* (B)*. If only the fetus has the GK mutation, then the fetus is at risk for being intrauterine growth restricted (IUGR) because of the altered glucose sensing by the fetal pancreas, with resultant decreased fetal insulin secretion. C: If the mother and the fetus either both have or do not have the GK mutation, then there is decreased risk of the fetus being macrosomic or IUGR. Adapted from Hattersley et al. (4).*

potential to produce a myriad of phenotypes in the infant of the GDM mother, though fetal macrosomia still represents the most common phenotype.

HOW TO DEFINE MACROSOMIA — In contrast to the definition of phenotype, the definition of macrosomia, i.e., excessive body size, has not changed much in the past decades. In reference to fetal growth, macrosomia is commonly defined as either birth weight greater than the 90th centile for gestational age or >4,000 g, independent of gestational age or sex. However, both of these definitions fail to take into account other factors that may be significant variables relating to fetal growth, such as sex, socioeconomic status, ethnicity, parity, and geographic variables such as altitude.

We are all aware of the recent trends for increases in the prevalence of adult overweight and obesity (6). However, there have also been significant increases in overweight in children, defined as ≥95th centile of BMI for age over the last decade, particularly in minority groups. In children as young as 2–5 years old, the prevalence of obesity has increased from 5 to 10.4% over the last 15–20 years (7). Do these trends in increasing weight of the population apply to birth weight as well? Based on recent reports from Scandinavia (8,9) and North America (10), the answer is yes. In Denmark from 1990 through 1999, the percent of babies weighing >4,000 g at birth has increased from 16.7 to 20% (8). In Sweden, there has been a 23% increase in birth weight of large-for-gestational-age (LGA) babies, defined as >2 SDs birth weight for gestational age, over the same time period (9). In North America, although average birth weights have increased only modestly, the percent of term small-for-gestational-age (SGA) babies (both white and black) has decreased in the U.S. by 11–12%, whereas in Canada, there has been a 27% decrease in SGA babies over the period from 1985 to 1998. In contrast, the percent LGA babies has increased during the same time period in the U.S. by 5% (white) and 9% (black) and by 24% in Canada (10). Hence, not only are the adult and adolescent populations experiencing an increase in the prevalence of obesity, but the same may be occurring at the time of birth.

BODY COMPOSITION ANALYSIS OF INFANTS OF WOMEN WITH NORMAL GLUCOSE TOLERANCE AND GDM — In our studies of fetal growth/macrosomia, we have elected to concentrate on measures of body composition, i.e., fat and fat-free or lean body mass. The rationale for this approach stems from work done in the previous century. As far back as 1923, research by Moulton (11) described that the variability in weight within mammalian species was explained by the amount of adipose tissue, whereas the amount of lean body mass was relatively constant and changed in a consistent manner over time. In the fetus, Sparks (12), using autopsy data and chemical analysis in 169 fetuses, described a relatively comparable rate of accretion of lean body mass in SGA, average-for-gestational-age (AGA), and LGA fetuses, but considerable variation in the accretion of fetal fat. Fat accretion in the SGA fetus was considerably less than in the AGA fetus, which in turn was less than that of the LGA fetus. Last, the term human fetus at birth has the greatest percent body fat (~12%) compared with other mammals (13). For these reasons, we have elected to assess fetal growth in our studies using estimates of body composition. The methodologies we have used include anthropometric, stable isotope, and total-body electrical conductivity. Space considerations do not allow us to go into methodological detail, but references are provided (14–16).

We have recently published a series of studies comparing the body composition analysis of infants of women with normal glucose tolerance (NGT) and GDM (Table 1) within 48 h of birth (17,18). These studies used both total-body electrical conductivity and anthropometric methodologies. Although there was no significant difference in birth weight or fat-free mass between the groups, there was a significant increase in fat mass and percent body fat in the infants of the GDM mothers. The body composition analyses were confirmed by the anthropometric/skinfold measures. These data were adjusted for potential confounding variables such as parity and gestational age without any significant change in results.

We further analyzed these data by examining a subset of AGA neonates (17). In Table 2, there are no significant differences in birth weights between the AGA infants of the GDM and NGT groups. However, there was again a significant in-

Table 1—*Neonatal body composition and anthropometrics in infants of women with GDM and NGT*

	GDM	NGT	*P*
n	195	220	—
Weight (g)	3,398 ± 550	3,337 ± 549	0.26
Fat-free mass (g)	2,962 ± 405	2,975 ± 408	0.74
Fat mass (g)	436 ± 206	362 ± 198	0.0002
Body fat (%)	12.4 ± 4.6	10.4 ± 4.6	0.0001
Tricep (mm)	4.7 ± 1.1	4.2 ± 1.0	0.0001
Subscapular (mm)	5.4 ± 1.4	4.6 ± 1.2	0.0001
Flank (mm)	4.2 ± 1.2	3.8 ± 1.0	0.0001
Thigh (mm)	6.0 ± 1.4	5.4 ± 1.5	0.0001
Abdomen (mm)	3.5 ± 0.9	3.0 ± 0.8	0.0001

Data are means ± SD. From Catalano et al. (17).

crease in fat mass, percent body fat, and skinfold measures in the infants of the GDM mothers compared with the NGT. Interestingly, the fat-free mass in the infants of the GDM mothers was significantly less compared with the infants in the NGT group. Similar results were obtained when we performed another independent analysis of only LGA neonates (18) (Table 3). Based on these results, we conclude that birth weight alone may not be a sensitive enough measure to recognize subtle differences in fetal growth in the infants of the GDM mother.

METABOLIC FACTORS RELATED TO MACROSOMIA IN INFANTS OF GDM MOTHERS

— Fetal macrosomia, however defined, has been used as a primary outcome measure in the management of women with GDM. The primary modes of treatment of women with GDM have been aimed at optimizing glucose control. Although there are proponents for the importance of individual measures of fasting (19) compared with postprandial glucose control (20), primary emphasis has been placed on overall mean glucose control (21). The control of circulating glucose has used measures such as diet, exercise, and pharmacological therapy, including insulin and/or oral hypoglycemic agents. Additionally, ultrasound has been used as a tool to direct therapy of women with GDM. Using increased abdominal circumference in late second/early third trimester as a specific measure of macrosomia, one may be able to avoid pharmacological therapy in those women who have evidence of appropriate fetal growth (e.g., abdominal circumference less than the 75th centile for gestational age) and institute insulin therapy for those women with GDM whose fetuses have ultrasound evidence of increased abdominal circumference, regardless of maternal glucose concentration (22). The use of amniocentesis to measure amniotic fluid insulin in the third trimester has also been used to guide therapy (23). In addition to glucose control in the management of GDM, Freinkel (24) raised the issue in his Banting Lecture of the importance of nutrients other than glucose that are related to fetal macrosomia, i.e., fuel-mediated teratogenesis. As an example, Knoop et al. (25) demonstrated the importance of circulating maternal lipid concentrations in relationship to fetal growth.

MATERNAL OBESITY AND FETAL MACROSOMIA IN INFANTS OF GDM MOTHERS

— As noted previously, there has been a significant increase in the prevalence of obesity in women of reproductive age. Because many women diagnosed with GDM in the U.S. and in Europe are overweight or obese, recent studies have evaluated the impact of maternal obesity on fetal growth in women with GDM. In 2003, Schaeffer-Graf et al. (26) reported on independent predictors of fetal macrosomia both in utero (ultrasound abdominal circumference >90%) and at delivery (birth weight >90% based on the local German population standard). The independent predictors that were examined included maternal age, parity, history of previous LGA neonate or GDM, prepregnancy BMI, weight gain during the index pregnancy, smoking,

Table 2—*Neonatal body composition and anthropometrics in AGA infants of women with GDM and NGT*

	GDM	NGT	*P*
n	132	175	—
Weight (g)	3,202 ± 357	3,249 ± 372	0.27
Fat-free mass (g)	2,832 ± 286	2,919 ± 287	0.008
Fat mass (g)	371 ± 163	329 ± 150	0.02
Body fat (%)	11.4 ± 4.6	9.9 ± 4.0	0.002
Tricep (mm)	4.5 ± 0.9	4.1 ± 0.8	0.0002
Subscapular (mm)	5.1 ± 1.1	4.5 ± 1.0	0.0001
Flank (mm)	4.0 ± 1.2	3.7 ± 0.8	0.007
Thigh (mm)	5.7 ± 1.2	5.2 ± 1.3	0.002
Abdomen (mm)	3.3 ± 0.9	3.0 ± 0.8	0.002

Data are means ± SD. From Catalano et al. (17).

Table 3—*Neonatal body composition in LGA infants of women with GDM and NGT*

	GDM	NGT	*P*
n	50	52	—
Weight (g)	4,060 ± 380	4,120 ± 351	0.13
Fat-free mass (g)	3,400 ± 312	3,564 ± 310	0.0009
Fat mass (g)	662 ± 163	563 ± 206	0.02
Body fat (%)	16.2 ± 3.3	13.5 ± 4.5	0.002

Data are means ± SD. From Durnwald et al. (18).

hypertension, glucose values from the diagnostic oral glucose tolerance test, A1C, daily glucose profiles, and use of insulin. Using successive multivariate logistic regression, the results were as follows: *1*) at entry, only history of an LGA baby in a previous pregnancy and maternal BMI ≥30 kg/m^2 were predictive of an abdominal circumference >90%; *2*) at 24 weeks' gestational age, only a history of a previous LGA baby was predictive of an abdominal circumference >90%; and *3*) at 28 weeks, only maternal BMI ≥30 kg/m^2 and history of an LGA baby were predictive of an abdominal circumference >90%. Interestingly, only at 32 and 36 weeks was the fasting glucose a better predictor than a history of a prior LGA neonate and maternal obesity. Finally, at birth, only a maternal pregravid BMI ≥30 kg/m^2 and history of an LGA baby were predictive of having an LGA baby.

In the U.S., Langer et al. (27) reported similar findings. In obese women with GDM whose glucose was well controlled on diet alone, the odds ratio (OR) for fetal macrosomia, defined as birth weight >4,000 g, was significantly increased (OR 2.12) compared with well-controlled (diet only) GDM subjects whose BMI was between 18.5 and 24.9 kg/m^2. Similar results, relating to the risk of fetal macrosomia in obese GDM, were reported in GDM subjects who were poorly controlled on diet or insulin. Only in those GDM subjects whose glucose was well controlled with insulin, was there no significant increased risk of macrosomia regardless of the women's pregravid BMI. We speculate that there may be independent effects of insulin in addition to glucose control affecting fetal growth, for example, insulin's effect on maternal lipid metabolism. Additionally, the criteria for optimal glucose management vary considerably among practitioners, as does the utilization of insulin and oral agents in the treatment of GDM. This may explain to a certain extent variation in outcome in the literature.

In an effort to better understand the potential independent effect of maternal obesity on growth of NGT and GDM mothers, we performed a stepwise logistic

Table 4—*Stepwise aggression analysis of factors relating to fetal growth and body composition in infants of women with GDM* (n = *195*) *and NGT* (n = *220*)

	R^2	Δr^2	
Birth weight			
Estimated gestational age	0.114	—	
Pregravid weight	0.162	0.048	
Weight gain	0.210	0.048	
Smoking (−)	0.227	0.017	
Parity	0.239	0.012	*P*=0.0001
Lean body mass			
Estimated gestational age	0.122	—	
Smoking (−)	0.153	0.031	
Pregravid weight	0.179	0.026	
Weight gain	0.212	0.033	
Parity	0.225	0.013	
Maternal height	0.241	0.016	
Paternal weight	0.250	0.009	*P*=0.0001
Fat mass			
Pregravid BMI	0.066	—	
Estimated gestational age	0.136	0.070	
Weight gain	0.171	0.035	
Group (GDM)	0.187	0.016	*P*=0.0001
Percent body fat			
Pregravid BMI	0.072	—	
Estimated gestational age	0.116	0.044	
Weight gain	0.147	0.031	
Group (GDM)	0.166	0.019	*P*=0.0001

The left column represents total cumulative r^2 value and the right column the incremental r^2 value associated with a given factor. Adapted from Catalano and Ehrenberg (28).

regression analysis on the 220 infants of NGT mothers and 195 term infants of GDM mothers previously described in Table 1. The results are given in Table 4 (28). Not surprisingly, gestational age at term was the independent variable with the strongest correlation with both birth weight and lean body mass. Maternal smoking had a negative correlation with both birth weight and lean body mass, and paternal weight had a weak correlation with only lean body mass. In contrast, maternal pregravid BMI had the strongest correlation with fat mass and percent body fat, explaining ~7% of the variance in both fat mass and percent body fat. Although ~50% of the subjects had GDM, only 2% of the variance in fat mass in this population was explained by a mother having GDM.

In summary, the infant of a GDM mother may have a variable phenotype based on the interaction of genes and the in utero environment. Additionally, the macrosomic fetus who presents much like the infant of a GDM mother may have the possibility, albeit small, of other genetic or metabolic dysfunctions mimicking GDM. Birth weight alone may not be a sensitive enough measure of fetal growth to assess the effects of GDM on the developing offspring. Consideration should be given to estimation of fetal adiposity, including such simple measures as Ponderal Index (weight/length^3). Last, given the increased prevalence of overweight and obesity in the population, and the independent effect of maternal pregravid obesity on fetal growth/adiposity, maternal obesity in and of itself needs to be addressed if the short- and long-term effects of fetal macrosomia in women with GDM are to be prevented.

Acknowledgments— This work was supported by National Institutes of Health Grant HD-22965 and General Clinical Research Center Grant M-1-RR-80.

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