Determinants of Fetal Growth at Different Periods of Pregnancies Complicated by Gestational Diabetes Mellitus or Impaired Glucose Tolerance

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OBJECTIVE — To determine maternal parameters with the strongest influence on fetal growth in different periods of pregnancies complicated by an abnormal glucose tolerance test (GTT).

RESEARCH DESIGN AND METHODS — Retrospective study of 368 women with gestational diabetes mellitus (GDM; ≥2 abnormal GTT values, $n = 280$) and impaired glucose tolerance (IGT; one abnormal value, $n = 88$) with 869 ultrasound examinations at entry to and during diabetic care. Both groups were managed comparably. Abdominal circumference (AC) ≥90th percentile defined fetal macrosomia. Maternal historical and clinical parameters, and diagnostic and glycemic values of glucose profiles divided into five categories of 4 weeks of gestational age (GA; <24 weeks, 24 weeks/0 days to 27 weeks/6 days, 28/0–31/6, 32/0–35/6, and 36/0–40/0 [referred to as <24 GA, 24 GA, 28 GA, 32 GA, and 36 GA categories, respectively]) were tested by univariate and multiple logistic regression analysis for their ability to predict an AC ≥90th percentile at each GA group and large-for-gestational-age (LGA) newborn. Data obtained at entry were also analyzed separately irrespective of the GA.

RESULTS — Maternal weight, glycemia after therapy, rates of fetal macrosomia, and LGA were not significantly different between GDM and IGT; thus, both groups were analyzed together. LGA in a previous pregnancy, (odds ratio [OR] 3.6; 95% CI 1.8–7.3) and prepregnancy obesity (BMI ≥30 kg/m^2; 2.1; 1.2–3.7) independently predicted AC ≥90th percentile at entry. When data for each GA category were analyzed, no predictors were found for <24 GA. Independent predictors for each subsequent GA category were as follows: at 24 GA, LGA history (OR 9.8); at 28 GA, LGA history (OR 4.2), and obesity (OR 3.3); at 32 GA, fasting glucose of 32 GA (OR 1.6 per 5-mg/dl increase); at 36 GA, fasting glucose of 32 GA (OR 1.6); and for LGA at birth, LGA history (OR 2.7), and obesity (OR 2.4).

CONCLUSIONS — In the late second and early third trimester, maternal BMI and LGA in a previous pregnancy appear to have the strongest influence on fetal growth, while later in the third trimester coincident with the period of maximum growth described in diabetic pregnancies, maternal glycemia predominates.

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Abbreviations: AC, abdominal circumference; GA, gestational age; GDM, gestational diabetes mellitus; GTT, glucose tolerance test; IGT, impaired glucose tolerance; LGA, large for gestational age; OGTT, oral glucose tolerance test; OR, odds ratio.

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

Normalizing the macrosomia rate is a primary goal in treating women with pregnancies complicated by gestational diabetes mellitus (GDM). Macrosomia is not only associated with a higher rate of birth injury for the mother and newborn (1), it is also associated with higher weight and accumulation of fat in childhood (2) and with a higher rate of obesity in adults (3). While normalizing maternal glucose levels has reduced neonatal morbidity in GDM, the macrosomia rate still has remained elevated compared with the normal obstetrical population (4). Existing studies have concentrated on risk factors for macrosomia at birth. The aim of our study was to determine the maternal parameters with the strongest influence on fetal growth at different periods of pregnancies complicated by both GDM and impaired glucose tolerance (IGT). We used the fetal abdominal circumference (AC) to describe fetal growth because accelerated growth of the fetal AC in the early third trimester has been shown to be a good predictor for macrosomia at birth and reflects the asymmetric growth in diabetic pregnancies (5,6).

RESEARCH DESIGN AND METHODS

Study population

In this retrospective study, subjects were selected from the population of pregnant women with glucose intolerance who attended the diabetes clinic of the Vivantes Medical Center Neukoelln in Berlin, Germany, between 1994 and 1998 and had been retrospectively entered into an ongoing database. Study inclusion criteria were as follows: *1*) documented presence of glucose intolerance first diagnosed in pregnancy; *2*) accurate gestational age (GA), confirmed by an ultrasound examination before 20 weeks of gestation; *3*) singleton pregnancy; *4*) complete fetal biometry determined by ultrasound at entry to diabetic therapy and a concurrent glu-

cose profile measured within 3 days of the ultrasound examination; 5) absence of identified fetal anomalies; and 6) absence of maternal vascular disease including preexisting hypertension. The maternal parameters assessed included age, parity, history of prior large-for-gestational-age (LGA) newborn (birth weight ≥90th percentile [7]) or GDM; prepregnancy BMI and weight gain during current pregnancy; and smoking and hypertension in pregnancy. Glycemic parameters included GA at time of diagnosis of GDM or IGT, HbA_{1c} levels at diagnosis, glucose levels determined by the diagnostic oral glucose tolerance test (OGTT) and daily glucose profiles, and insulin use. Fetal parameters were the AC percentiles (8) at the entry and the monthly follow-up ultrasound examinations. Newborn parameters included sex, birth weight, and length and classification of the infants as LGA or non-LGA. LGA was defined according the 90th percentile for GA using current German growth curves (7).

Diabetes management

Reflecting obstetrical standards in Germany, testing for GDM in our study subjects was performed selectively in women with risk factors as determined by their community physicians. The diagnosis of GDM was established by a 75-g OGTT with measurement of capillary blood glucose levels by glucose oxidase (Glucose Analyzer; Beckman, Brea, CA). Diagnostic criteria for GDM used in Germany at the time of study were a fasting plasma glucose ≥90 mg/dl, 1-h postprandial glucose ≥165 mg/dl, and 2-h postprandial glucose ≥145 mg/dl (adopted from O'Sullivan and Mahan [9]). Diagnosis of GDM required at least two abnormal values, and IGT required one abnormal value. After the diagnosis, community physicians referred the women to the Diabetes Obstetrical Clinic of the Vivantes Medical Center for diabetic management and delivery. Primary ambulatory obstetrical care continued to be provided by the community physician.

Women with GDM and IGT were educated regarding an individualized diabetic diet based on prepregnancy weight (30 kcal · kg^{-1} · day^{-1}) with caloric restriction for obese women (25 kcal · kg^{-1} · day^{-1}). All women were instructed to self-monitor their blood glucose by performing a daily glucose profile (three preprandial and three 1-h postprandial measurements) twice a week using a reflectance with electronic memory (Advantage Glucose meter; Roche Diagnostics, Mannheim, Germany). Accuracy of the glucose meters was tested biweekly by comparison with a laboratory glucose measurement (glucose oxidase). Insulin therapy was recommended when the mean of all glucose values of a profile exceeded 100 mg/dl after a 2-week trial of diet. When insulin therapy was initiated, glucose profiles were performed daily and insulin dose was adjusted to achieve fasting glucose values ≤90 mg/dl and 2-h postprandial values ≤120 mg/dl.

An initial ultrasound examination with complete fetal biometry was scheduled at the entry visit with follow-up examinations scheduled monthly in conjunction with Diabetes Clinic visits. Ultrasound examinations were scheduled monthly for each patient without regards to suspected maternal risk factors for macrosomia. All ultrasound examinations were performed by senior physicians trained in obstetrical ultrasound. The fetal AC was measured in the standard cross-section view of the abdomen at the level of the stomach and portal sinus of the liver.

Statistical analysis

All ultrasound examinations performed during the study were divided into five categories according to GA at the time of examination, i.e., <24 weeks, 24 weeks/0 days to 27 weeks/6 days, 28/0–31/6, 32/0–35/6, and 36/0–40/0, and are referred to as <24 GA, 24 GA, 28 GA, 32 GA, and 36 GA categories, respectively. Ultrasound data from the entry visit irrespective of the GA was also analyzed separately. Each AC measurement was classified as either AC <90th percentile or AC ≥90th percentile according to the standards published by Hadlock et al. (8). Subjects were not excluded from the analysis if they missed an ultrasound appointment.

Difference between pregnancies with and without fetal macrosomia or LGA at birth and differences between women with GDM and IGT were tested for statistical significance by *t* tests or ANOVA (continuous variables) or by χ^2 analysis (categorical variables). Normally distributed data are presented as mean ± 1 SD.

Univariate logistic regression analysis was performed to determine parameters with significant correlation to the fetal macrosomia status at entry and at each GA category. Tested parameters included maternal age, parity and BMI, weight gain during pregnancy, prior LGA newborn, glycemic parameters at entry (OGTT, HbA_{1c}, and fasting and postprandial values of the profile), and the mean of the fasting, the postprandial (three measurements), and all glucose levels (six measurements) from the profiles performed within 3 days before and after the ultrasound examination in each given GA category. The influence of the glucose values measured during the proceeding GA category on the subsequent further fetal growth was also evaluated. LGA status at birth was similarly correlated with the maternal parameters, and the entry and subsequent glycemic parameters by univariate analysis.

Finally, multiple logistic regression analysis was performed to determine independent predictors for the fetal macrosomia status at entry, at each GA category, and for LGA newborns.

All statistical analyses were performed with the statistical program SPSS 9.0 (SPSS, Chicago, IL).

RESULTS

Study population

Of 406 women meeting the study criteria, 38 were excluded because of missing maternal anthropometric data, thus leaving 368 women for the final analysis. Of the final study population, 76% of the women (n = 280) were diagnosed with GDM and 24% (88) with IGT. Women with GDM compared with women with IGT had significantly higher OGTT values (fasting 97.1 vs. 82.1 mg/dl; 1 h 205.7 vs. 181.5 mg/dl; 2 h 161.9 vs. 117. 5 mg/dl; $P < 0.05$ for all comparisons) and entry HbA_{1c} levels (6.2 vs. 5.6%, $P = 0.04$), and more frequently required insulin therapy (9.2 vs 0.9%, $P = 0.0006$); however, third trimester glycemic control was not different after initiation of therapy. No other maternal entry parameters were significantly different between subjects with GDM and IGT, nor were the rates of entry AC ≥90th percentile (17.6 vs. 16.4%) or LGA at birth (18.2 vs. 17.5%). Therefore, women with GDM and IGT were analyzed as one group. Throughout the study, strict therapeutic thresholds, i.e., a fasting glucose ≤95 mg/dl and mean daily glucose levels <100 mg/dl, were met in 90.3–93.5% and 85.2–93.5% of the profiles of both groups, respectively.

A total of 869 ultrasound examinations with matching maternal glucose profiles within 3 days of examination were analyzed. Not all subjects could be included in each GA category due to different GAs at entry and varying compliance with scheduled ultrasound appointments. Of the 368 subjects, 99 (26.9%) had one ultrasound examination, 105 (28.5%) had two, and 180 (48%) had three or more examinations. Of the entry ultrasound examinations, 95% were distributed almost equally between those performed before 28 weeks, in the 28 GA and in the 32 GA categories. The rate of fetal macrosomia at entry was 18.5% and was not significantly different from the rate of LGA at birth (17.6%).

Characteristics of women with pregnancies with and without an entry AC ≥90th are displayed in Table 1. Women whose fetuses had a fetal AC ≥90th at entry were significantly more likely to have had a prior pregnancy with LGA, were of higher parity, had a higher prepregnacy weight and BMI, and more frequently gave birth to a LGA newborn.

Table 1 —*Maternal characteristics, glycemic values, and rate of LGA newborns in pregnancies with a fetal AC < or ≥90th percentile*

	AC <90th percentile	AC ≥90th percentile	*P*
n	300	68	
Maternal history			
Age (years)	30.2 ± 5.4	31.5 ± 5.4	0.08
Parity	1.9 ± 1.2	2.4 ± 2.0	0.013
Prepregnancy weight (kg)	71.5 ± 15.9	80.4 ± 20.0	0.0001
Prepregnancy BMI (kg/m^2)	26.8 ± 5.9	29.8 ± 5.1	0.03
Prepregnancy BMI >30 kg/m^2 (%)	25.7	44.1	0.002
Prior GDM (%)	10.0	11.8	0.6
Prior LGA (%)	8.0	25.0	<0.0001
Maternal glycemic values			
GA at diagnosis	27.1 ± 5.5	27.1 ± 5.8	0.6
OGTT			
fasting (mg/dl)	93.4 ± 23.7	98.3 ± 39.8	0.2
1-h (mg/dl)	198.7 ± 38.6	202.2 ± 38.0	0.5
2-h (mg/dl)	151.5 ± 41.5	150.0 ± 40.1	0.8
GDM (%)	74.8	75.4	0.7
IGT (%)	25.2	24.6	0.8
Study entry			
Gestational age at entry	28.8 ± 5.3	26.8 ± 5.9	0.6
Mean capillary glucose of the profile (mg/dl)	86.1	88.2 ± 12.5	0.3
HbA_{1c} (%)	6.1 ± 1.3	6.3 ± 1.1	0.3
Weight gain (kg)	11.5 ± 6.5	12.1 ± 5.2	0.4
Insulin use (%)	7.0	10.3	0.5
Neonatal parameter			
LGA (%)	12.6	43.1	<0.0001

Continuous variables are means ± SD.

Parameters influencing fetal growth

The univariate regression analysis found the following variables to be significant predictors for an AC ≥90th percentile at entry: a positive history of LGA, parity, and the maternal prepregnancy BMI (Table 2). BMI was also evaluated categorically using the World Health Organization's definition of obesity (BMI ≥30 kg/m^2) (10). Entry glycemic variables or GA at entry were not correlated with an entry AC ≥90th percentile.

When univariate analyses were performed in each GA category and at birth, different parameters were significantly correlated with an AC ≥90th percentile in different categories (Table 2). The 1- and 2-h glucose value of the OGTT and the mean of the postprandial glucose values (three measurements per profile) and the mean of all glucose values of the profiles were not significantly associated with AC ≥90th percentile in each GA category.

There was an unexpected lack of correlation between a history of LGA and an AC ≥90th percentile at 32 GA and 36 GA in contrast to a strong association between these variables in the earlier pregnancy. We looked more closely at the subjects in the 28-, 32- and 36-GA categories to see if the drop out in correlation was due to the fact that we did not have

Table 2 —*Significant univariate predictors for fetal AC ≥90th percentile at entry to diabetic care, at different gestational ages, and for LGA at birth in pregnancies with GDM and IGT*

	At entry	<24 GA	24 GA	28 GA	32 GA	36 GA	At birth
AC ≥90th percentile	68/368 (18.5)	21/138 (15.2)	20/121 (16.5)	32/212 (15.0)	52/255 (20.4)	25/143 (17.5)	69*/368 (17.6)
Historical	LGA		LGA	LGA			
	BMI			BMI	BMI	BMI	BMI
	Obesity†			Obesity	Obesity	Obesity	Obesity
	GDM						
	Parity			Parity			
Glycemic parameter			OGTT-FCG‡	OGTT-FCG			
					Profile-FCG§ 32 GA	Profile-FCG 32 GA	Profile-FCG 32 GA‖

Parameters tested without significant correlation are not shown. Data are *n*/total ultrasounds in category (%). *LGA; †BMI ≥30 kg/m^2; ‡fasting capillary glucose (FCG) of the OGTT; §fasting capillary glucose of the profile at 32–35 weeks; ‖borderline significance, $P = 0.06$.

Table 3 —*Independent predictors for an AC of the 90th percentile at entry, at different GA categories, and for LGA birth weight*

	At entry	24 GA	28 GA	32 GA	36 GA	At birth
Prior history of macrosomia	3.6 (1.8–7.3)	9.8 (3.0–32)	4.2 (1.5–11)			2.7 (1.3–5.6)
Prepregnancy BMI						1.04 (1.01–1.08)
Prepregnancy obesity (BMI >30 kg/m^2)	2.1 (1.2–3.7)	3.3 (1.4–7.3)				
Fasting glucose at 32–35 weeks of gestation			1.03* (1.003–1.05)	1.06* (1.02–1.1)		

Data are OR (95% CI). *Odds ratio per 5-mg/dl increase of fasting glucose.

identical subjects in each category. There were similar proportions of primiparae in each category (42.4, 42.7, and 46.1%, respectively) and of women with a positive history of LGA (11.3, 11.3, or 16.0%, respectively). We repeated the univariate analysis on a subgroup of women who had an ultrasound examination at 28 GA and returned for the 32 GA examination ($n = 141$). Again there was no correlation between a history of LGA and an AC ≥90th percentile in the 32 GA category. Similarly in the subgroup of women with an ultrasound examination in the 28 GA who returned for an ultrasound in the 36 GA category ($n = 74$), a history of LGA did not correlate with an AC ≥90th percentile in the 36 GA examination.

From successive multivariate logistic regression analysis significant predictive influences on accelerated fetal growth were determined (Table 3). At entry, independent predictors for an AC ≥90th percentile were a history of LGA and BMI ≥30 kg/m^2, but at the <24 GA examination, none of the measured parameters were predictive. At the 24 GA examination, a history of prior LGA was the only predictor. At the 28 GA examination, both history of LGA and a BMI ≥30 kg/m^2 yield to be the independent predictors for an AC ≥90th percentile. At 32 GA and 36 GA examinations, the fasting glucose of the profile at 32 GA examination was a stronger predictor than history of LGA and obesity. Finally, at birth, a history of prior LGA newborn and a BMI ≥30 kg/m^2 were predictive for an LGA infant.

Women with a BMI ≥30 kg/m^2 had a significantly higher rate of LGA infants than normal-weight women (25.0 vs. 15.5%, $P = 0.03$).

CONCLUSIONS

Our study attempted to determine the maternal parameters that strongly influenced fetal growth at time of diagnosis of glucose intolerance, at different GAs during diabetes therapy, and at birth. We found a history of a prior LGA newborn, maternal prepregnancy BMI, and the mean fasting glucose during the 32nd through the 35th week as recurring factors that independently predicted, either alone or in combination, fetal macrosomia at different periods of pregnancy or at birth.

The independent predictors for fetal macrosomia can be considered to represent the three determinants of fetal growth, i.e., history of a prior LGA newborn reflecting recent genetic and prior epigenetic influences, maternal obesity reflecting maternal factors, and third trimester maternal glucose levels reflecting stimulation of fetal insulin secondary to the transport of maternal glucose. The predominant influence of a history of LGA in the late second trimester appears to express the strong influence of genetic as well as epigenetic factors of the prior pregnancy on earlier fetal growth. This may reflect the period when the growth of non–insulin-sensitive tissues, e.g., bones, accounts for the main differences between fetal growth patterns. A pattern of early accelerated growth in diabetic pregnancies has been identified (11–13). Keller et al. (11) found that in infants of women with type 1 diabetes who showed accelerated growth before 24 weeks of gestation, approximately half exhibited symmetrical increased growth of both AC and head circumference in the presence of normal amniotic fluid insulin levels. Our model suggests that early accelerated growth may be less influenced by glycemia and more influenced by genetic and other epigenetic factors. We do not have an explanation as to why the history of LGA did not continue to be associated with fetal macrosomia after 32 weeks. However, at birth, having a history of a LGA newborn reemerged again to be an independent predictor for LGA. It has been well documented that women who have given birth to a LGA infant once before are much more likely to do so again (14). The fetal genotype has been estimated to account for ~15% of the variation in birth weight (15).

After 28 weeks, we found maternal obesity to become a predictor for fetal macrosomia and for LGA at birth. Maternal obesity has been shown to be a strong independent risk factor for newborn macrosomia regardless of whether maternal glucose tolerance is normal (16) or impaired (17). Obesity has been associated with a decreased insulin sensitivity and peripheral hyperinsulinism and subsequent fetal macrosomia in the face of normal maternal glucose levels (18,19). Maternal obesity has also been associated with increased levels of serum lipids and triglycerides, which in turn produce fetal macrosomia (20). Elevated lipid levels, similar to maternal levels, have been demonstrated in macrosomic infants born to obese women. In contrast, macrosomic infants born to lean women had normal lipid levels, similar to nonmacrosomic infants (21). In early pregnancy, maternal obesity appears to play less of a role in determining fetal growth. Thus, our finding that maternal obesity influences fetal growth later in pregnancy may reflect that fetal adipocyte proliferation and fetal storage of lipids occur primarily in the third trimester. In infants of diabetic mothers, the abdominal wall fat accounts for 63% of the variance of the AC and the greatest component of the difference in birth weight between normal size and LGA (22).

There is no doubt from the literature that maternal glycemia in women with GDM is involved in determining birth weight, but there is controversy about the influence of maternal glycemia on fetal macrosomia (4). It is also unclear when,

during gestation, maternal glycemia exerts its strongest effect on fetal growth. In a study examining women with type 1 diabetes, neither second nor third trimester glycemic control correlated with an AC ≥90th at 24 or 32 weeks (11) or LGA at birth (13). However, late accelerated growth beginning at ~32 weeks was associated with impressively higher fetal insulin levels as compared with early-accelerated or normal growth (11). In our study, maternal fasting glycemia during 32 through 35 weeks was the strongest predictor of accelerated growth in the late third trimester. Glucose levels measured outside of this period appeared to have less effect on the fetal macrosomia status and the birth weight. The period of 32 through 35 weeks coincides with the onset of accelerated growth at 30–33 weeks in diabetic pregnancies, as described in other studies (5,6). Similar to our findings in a study of insulin-dependent diabetic women, the third-trimester glucose was a stronger predictor for macrosomia at birth than glucose levels in early pregnancy (23). In contrast with others (23,24), we found the fasting but not the postprandial glucose at 32–36 weeks to be more predictive of LGA at birth.

Several limitations of our study should be noted. First, in this retrospective study, women entered care at different gestational ages and did not return for all scheduled subsequent ultrasound examinations. We cannot exclude bias in the selection of the specific cohorts for the different GA categories, e.g., due to a higher reliability to keep an examination appointment in women with a fetus with an AC >90th percentile in a prior examination. This might have had an influence on the rate of AC >90th percentile in each GA category than in the determination of predictors for AC >90th percentile since regression analysis was performed separately for every GA category. Secondly, our study population had moderate glucose intolerance and subsequent good glucose control during pregnancy, with only 9% requiring insulin therapy. However, our cohort was characterized by a high rate of obese women (29%) compared with the average German population (10%). The high rate of obesity likely accounts for the stronger influence of obesity compared with the possible influence of maternal glycemia on fetal growth in our study. There is a strong covariance between maternal obesity and higher levels of maternal glycemia that may account for the absence of the 32 GA fasting glucose level in the final model of independent predictors for LGA at birth.

In summary, we found that different predictors of fetal growth seem to play a predominant role at different gestational ages. In the late second and early third trimester, genetic, historic, and recent maternal factors appear to influence growth, while later in the third trimester, coincident with the period of maximum growth described in diabetic pregnancies, maternal glycemia predominates. There was a significant excess of LGA infants above the expected LGA in obese women (25%), although strict therapeutic thresholds were met throughout pregnancy. A modified approach targeting different parameters other than glucose alone at different stages of pregnancy may be more effective in lowering the LGA rates in diabetic pregnancies of obese women.

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