Third-Trimester Maternal Glucose Levels From Diurnal Profiles in Nondiabetic Pregnancies

Correlation with sonographic parameters of fetal growth

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OBJECTIVE — To assess the 24-h glucose levels in a group of nondiabetic, nonobese pregnant women and to verify the presence of correlations between maternal glucose levels and sonographic parameters of fetal growth.

RESEARCH DESIGN AND METHODS — A total of 66 Caucasian nonobese pregnant women with normal glucose challenge tests (GCT) enrolled in the study; from this population, we selected 51 women who delivered term (from 37 to 42 weeks completed) live-born infants without evidence of congenital malformations. The women were requested to have three main meals and to perform daily glucose profiles fortnightly from 28–38 weeks without modifying their lifestyle or following any dietary restriction. All subjects were taught how to monitor their blood glucose by using a reflectance meter. Fetal biometry was evaluated by ultrasound scan according to standard methodology at 22, 28, 32, and 36 weeks of pregnancy.

RESULTS — The overall daily mean glucose level during the third trimester was 74.7 ± 5.2 mg/dl. Daily mean glucose values increased between 28 (71.9 ± 5.7 mg/dl) and 38 (78.3 ± 5.4 mg/dl) weeks of pregnancy. We found a significant positive correlation at 28 weeks between 1-h postprandial glucose values and fetal abdominal circumference (AC). At 32 weeks, we documented positive correlations between fetal AC and maternal blood glucose levels 1 h after breakfast, 1 and 2 h after lunch, and 1 and 2 h after dinner. At 36 weeks, there was a positive correlation between fetal AC and 1- and 2-h postprandial blood glucose levels. In addition, there was a negative correlation between head-abdominal circumference ratio and 1-h postprandial blood glucose values.

CONCLUSIONS — This longitudinal study first provides a contribution toward the definition of normoglycemia in nondiabetic, nonobese pregnant women; moreover, it reveals significant correlations of postprandial blood glucose levels with the growth of insulin-sensitive fetal tissues and, in particular, between 1-h postprandial blood glucose values and fetal AC.

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Abbreviations: AC, abdominal circumference; AGA, appropriate for gestational age; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HC:AC, head-abdominal circumference ratio; LGA, large for gestational age; SGA, small for gestational age.

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

The complex phenomenon of fetal growth has been thoroughly investigated over past decades (1) but still remains to be fully understood. We know that maternal glucose is one of the most important factors of influence (1,2), and Reece et al. (3) showed that normoglycemia in pregnancy is associated with normal levels of other nutrients, such as amino acids and lipids. For this reason, glycemia is the single maternal metabolic parameter routinely assessed in diabetic pregnancies. Indeed, the criteria for metabolic control and therapeutic strategies of diabetes in pregnancy are based almost exclusively on maternal glucose levels (2). Although there is overwhelming evidence that good perinatal outcomes can be achieved in diabetic pregnancies only with the normalization of maternal glucose values (4–6), there is no clear definition of normoglycemia in nondiabetic pregnancies. In fact, a very limited number of studies have been performed thus far in the attempt to define maternal glucose levels in normal pregnancies; moreover, these studies involved small series of hospitalized subjects and considered only glycemic values collected during a single day in the third trimester (7–10).

RESEARCH DESIGN AND METHODS

— From June 1998 to December 1999, 66 pregnant women who were receiving care on an outpatient basis at the Perinatal Medicine Unit of the University of Florence were enrolled in the study. All 66 women met the following inclusion criteria: Caucasian race, singleton pregnancy, gestational age confirmed by first-trimester ultrasound, normal glucose challenge test (GCT) (1-h glucose value <135 mg/dl) (11) between 24 and 28 weeks of gestation, number of previous deliveries ≤2, pregestational BMI between 19 and 25 kg/m^2, and absence of chronic hypertension and gestational diabetes mellitus (GDM) in previous pregnancies. From this group, we selected 51

Table 1—*Maternal and neonatal characteristics* (n = *51*)

Maternal age (years)	30.0 (24–40)
Parity	1 (0–2)
BMI (kg/m^2)	21.0 (18–25)
Gestational age at GCT (weeks)	26.4 (24–28)
1-h Glucose screening result (mg/dl)	115.8 ± 15.7
Overall daily glucose level (mg/dl)	74.7 ± 5.2
Compliance (%)	96.9 ± 2.0
Weight gain during pregnancy (kg)	8.7 (7–12)
Normal spontaneous delivery	43 (84.3)
Cesarean section	8 (15.7)
Gestational age at delivery (weeks)	40 (37–42)
Birth weight (g)	3,301.5 ± 351.6
AGA	44 (86.3)
LGA	4 (7.8)
SGA	3 (5.9)

Data are median (range), means ± SD, or *n* (%).

women who did not receive drugs known to affect glucose metabolism (e.g., steroids and β_2-sympathomimetics) throughout gestation and delivered term (from 37 to 42 weeks completed) live-born infants without evidence of congenital malformations. Among the 15 women excluded, 7 discontinued the blood glucose self-monitoring, 4 received betamimetics or corticosteroids, 3 did not deliver at our clinic, and 1 had a spontaneous preterm delivery.

All 51 selected women had uneventful pregnancies with normal fetal growth as assessed by sonographic measurements of fetal biometry (12); GCTs were performed in the clinical laboratory of the hospital, and glucose determinations were performed with the glucose oxidase method.

Women were asked to have three main meals at 8:00 A.M., 12:00 P.M., and 8.00 P.M. and to perform daily glucose profiles fortnightly from 28–38 weeks without modifying their lifestyle or following any dietary restriction. A nurse educator taught the women how to monitor their blood glucose by using a memory-based reflectance meter (Accutrend α; Boehringer Mannheim); measurements were obtained before meals, 1 and 2 h after meals, and every 2 h in the afternoon and during the night. Patient compliance with self-monitoring of blood glucose was defined as the percentage of the 30 glucose measurements, as prescribed by the protocol, that were actually performed during the 4 weeks before delivery (13).

Fetal parameters were evaluated by ultrasound scan (AU5EPI; Esaote, Genova, Italy) using a 3.5-MHz convex probe according to standard methodology (14) at 22, 28, 32, and 36 weeks of pregnancy. Parameters considered were biparietal diameter, head circumference, abdominal circumference (AC), head-abdominal circumference ratio (HC:AC), and femur length.

Infants were considered appropriate for gestational age (AGA) when their birth weights ranged between the 11th and the 89th percentile, large for gestational age (LGA) when their birth weights were ≥90th percentile, and small for gestational age (SGA) when their birth weights were ≤10th percentile on the basis of the growth standard development for our population (15). All subjects gave their informed consent, and the study was approved by the Institutional Review Board of the Department of Gynecology, Perinatology and Human Reproduction of the University of Florence.

Statistical analysis

Correlations between daily glucose profiles and ultrasound fetal parameters were estimated using Pearson's correlation coefficient. One-way analysis of variance was used to test for trends of overall glycemic values throughout gestation. $P < 0.05$ was considered statistically significant. Statistical analyses were performed by Stata statistical software release 5.0 (Stata Corporation, College Station, TX).

RESULTS — Maternal and neonatal characteristics are listed in Table 1. Women enrolled in the study underwent the screening test for GDM at a median gestational age of 26.4 weeks with a negative result (mean 1-h glucose value of 115.8 ± 15.7 mg/dl). The overall daily mean glucose level during the third trimester was 74.7 ± 5.2 mg/dl and compliance with self-monitoring was 96.9%. Median weight gain in pregnancy was 8.7 kg. The rates of AGA, LGA, and SGA infants were 86.3, 7.8, and 5.9%, respectively.

Fetal sonographic parameters at different gestational ages are summarized in Table 2, and daily glucose profiles obtained throughout the third trimester are shown in Table 3. The daily mean glucose values increased between 28 weeks (71.9 ± 5.7) and 38 weeks (78.3 ± 5.4) of pregnancy without, however, reaching statistically significant differences. It is noteworthy that the mean peak postprandial glucose response after meals is at the 1-h time point and that the mean postprandial glucose levels never exceed 105.2 mg/dl.

Correlations between maternal daily glucose levels and fetal sonographic parameters at various gestational ages are shown in Table 4. A significant positive correlation was found at 28 weeks between fetal AC and glucose values at 9:00 A.M., 1:00 P.M., and 9:00 P.M. (determinations achieved 1 h after a main meal). At 32 weeks, positive correlations were documented between fetal AC and maternal glucose levels at 9:00 A.M. (1 h after breakfast), at 1:00 P.M. and 2:00 P.M. (1 and 2 h

Table 2—*Fetal ultrasonographic parameters*

	22 weeks	28 weeks	32 weeks	36 weeks
Biparietal diameter (mm)	56.0 ± 2.9	71.5 ± 3.9	82.2 ± 2.6	89.0 ± 2.2
Head circumference (mm)	199.1 ± 9.8	264.2 ± 9.5	294.9 ± 10.3	322.5 ± 8.3
AC (mm)	181.1 ± 9.9	242.9 ± 10.1	279.1 ± 11.0	310.8 ± 14.1
HC:AC ratio	1.09 ± 0.98	1.08 ± 0.94	1.05 ± 0.93	1.03 ± 0.58
Femur length (mm)	39.0 ± 3.0	54.9 ± 1.9	63.8 ± 1.8	71.1 ± 1.5

Data are means ± SD.

Table 3—*Diurnal glucose profiles (mg/dl) at different gestational ages*

Hours	28 weeks	30 weeks	32 weeks	34 weeks	36 weeks	38 weeks
08.00	54.8 ± 6.2	55.9 ± 4.9	53.7 ± 4.2	56.3 ± 4.7	57.2 ± 3.9	59.0 ± 4.1
09.00	92.0 ± 7.5	94.2 ± 5.9	95.2 ± 4.3	96.5 ± 5.1	101.2 ± 4.9	104.2 ± 5.1
10.00	78.2 ± 5.8	80.5 ± 6.7	82.9 ± 6.5	83.7 ± 9.8	90.1 ± 4.9	89.2 ± 9.5
12.00	67.1 ± 5.5	66.2 ± 5.5	63.4 ± 4.8	66.3 ± 5.9	68.1 ± 6.7	64.2 ± 6.2
13.00	92.9 ± 7.1	94.9 ± 4.8	95.9 ± 6.8	98.8 ± 4.5	101.9 ± 3.4	105.2 ± 4.9
14.00	85.2 ± 4.9	82.5 ± 4.7	87.4 ± 6.6	87.9 ± 3.9	94.2 ± 4.1	95.0 ± 6.2
16.00	70.1 ± 5.8	66.1 ± 4.0	68.1 ± 5.7	66.1 ± 7.0	69.8 ± 5.6	68.2 ± 6.1
18.00	63.0 ± 6.5	61.9 ± 5.1	63.4 ± 3.6	65.9 ± 3.9	65.1 ± 5.0	66.2 ± 5.0
20.00	62.4 ± 4.1	62.9 ± 4.8	63.3 ± 2.8	64.0 ± 3.1	64.9 ± 4.1	65.1 ± 7.7
21.00	91.1 ± 7.8	92.5 ± 7.5	94.9 ± 4.7	99.0 ± 4.5	102.2 ± 3.2	105.2 ± 4.0
22.00	79.5 ± 6.3	81.1 ± 5.7	85.2 ± 3.6	89.5 ± 8.4	93.5 ± 5.1	95.2 ± 4.2
00.00	64.5 ± 5.1	62.1 ± 7.6	64.5 ± 4.4	60.8 ± 7.7	64.9 ± 5.9	69.2 ± 7.0
02.00	60.5 ± 3.9	64.0 ± 4.4	64.0 ± 5.2	66.3 ± 3.4	67.1 ± 4.1	66.2 ± 4.6
04.00	59.8 ± 3.4	60.8 ± 3.7	61.2 ± 5.6	64.2 ± 4.1	61.5 ± 5.8	63.1 ± 3.8
06.00	58.7 ± 6.0	59.7 ± 4.2	58.8 ± 5.1	60.3 ± 5.9	59.8 ± 4.1	60.1 ± 3.2
Overall	71.9 ± 5.7	72.3 ± 5.3	73.4 ± 4.9	75.0 ± 5.4	77.4 ± 4.7	78.3 ± 5.4

Data are means ± SD.

after lunch), and at 9:00 P.M. and 10:00 P.M. (1 and 2 h after dinner). With respect to the correlations present at 36 weeks, there was a positive correlation between fetal AC and maternal glucose levels at 9:00 A.M. and 10:00 A.M. (1 and 2 h after breakfast), at 1:00 P.M. and 2:00 P.M. (1 and 2 h after lunch), and at 9:00 P.M. and 10:00 P.M. (1 and 2 h after dinner). Furthermore, there was a negative correlation between HC:AC and glucose values at 9:00 A.M., 1:00 P.M., and 9:00 P.M. (1 h after a main meal). Significant correlations were not found between maternal daily glucose levels and any other sonographic parameter investigated during gestation.

CONCLUSIONS — It is generally believed that glycemic targets in diabetic pregnancies should mimic those found in normal pregnancies (16), and that the treatment should be aimed at producing a metabolic state such that the fetus does not recognize its diabetic mother (4). Paradoxically, however, few studies have been performed thus far to define what should be referred to as normoglycemia in normal pregnancy. In addition, many different goals for glycemic control in diabetic pregnancies have been suggested; in most instances, these goals were inferred from glycemic values associated with a decreased incidence of diabetic complications similar to that found in nondiabetic pregnancies. However, in this respect, the understanding and determination of normoglycemic values in normal pregnancy would probably be more valuable than

Table 4—*Pearson's correlation coefficient between diurnal profiles of maternal glucose and fetal ultrasound parameters at 28, 32, and 36 weeks' gestation*

	28 weeks		32 weeks		36 weeks			
	AC		AC		AC		HC:AC	
Hours	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
08.00	0.38	0.11	0.18	0.45	0.24	0.32	−0.25	0.30
09.00	0.52	0.02	0.55	0.02	0.58	0.008	−0.51	0.01
10.00	−0.75	0.71	0.3	0.2	0.45	0.04	0.04	0.83
12.00	0.38	0.15	−0.07	0.72	0.3	0.19	−0.32	0.15
13.00	0.77	0.0003	0.7	0.0002	0.85	0.0002	−0.62	0.001
14.00	0.41	0.06	0.57	0.01	0.64	0.004	0.09	0.74
16.00	0.38	0.19	0.08	0.72	0.2	0.4	−0.12	0.67
18.00	0.30	0.21	0.34	0.14	0.3	0.21	−0.14	0.60
20.00	0.25	0.35	0.3	0.2	0.02	0.92	0.04	0.83
21.00	0.57	0.01	0.72	0.0002	0.7	0.0005	−0.60	0.001
22.00	0.18	0.6	0.61	0.0004	0.53	0.008	−0.01	0.93
00.00	0.22	0.40	0.4	0.1	0.25	0.29	−0.11	0.67
02.00	0.13	0.60	−0.07	0.72	0.40	0.08	−0.40	0.10
04.00	−0.02	0.8	0.3	0.2	−0.06	0.75	0.06	0.82
06.00	0.10	0.6	0.15	0.57	0.2	0.4	−0.18	0.45

any other parameter of clinical outcome in directing insulin therapy in diabetic pregnancies. On the other hand, the criteria of glycemic normality determined in nonpregnant women, because they do not consider the impact of pregnancy on maternal metabolism, seem inadequate both for assessing gestational disturbances in intermediary metabolism and for evaluating the efficacy of therapeutic measures designed to achieve metabolic rectification (8).

Our study was performed on a consistent number of nonhospitalized women; with respect to this, it is worth remembering that some previous investigators reported results achieved in only six or eight hospitalized women (7,8).

Because factors such as race and obesity are known to influence the incidence of diabetes as well as glucose values, only Caucasian nonobese women were enrolled in the study. The rates of AGA, LGA, and SGA infants were those expected in the normal obstetric population (15).

Overall daily mean glucose levels showed a slight but progressive increase from 28 weeks (71.9 ± 5.7 mg/dl) to 38 weeks (78.3 ± 5.4 mg/dl); this deterioration of glucose tolerance during the course of normal pregnancy results from insulin resistance that mirrors the fall in insulin action (2). Regarding the glucose values documented at different gestational ages, our findings are not directly comparable with those reported by others because in our study, these values were longitudinally evaluated in nonhospitalized women by use of a reflectance meter, whereas in most previous studies women were hospitalized and plasma glucose determinations were achieved by a glucose oxidase method. In our study, 1-h postprandial glucose values were found to positively correlate with fetal abdominal growth as early as 28 weeks' gestation, and this correlation was maintained through the third trimester. These findings are in agreement with those of diabetic pregnancies, in which a 1-h postprandial maternal blood glucose concentration in the third trimester is considered a strong predictor of infant birth weight and fetal macrosomia (17). Also, in diabetic pregnancies, fetal hyperinsulinism and birth weight have been found to correlate best with 1-h postprandial glucose values, as the postprandial glucose peak would breach the placental barrier (18). With respect to this, our results seem to suggest that fetal AC, which is a parameter of growth of insulin-sensitive tissues, is influenced by postprandial glucose peaks even in nondiabetic pregnancies. This observation would confirm that glycemia in pregnancy can be regarded as a continuum ranging from normal glucose metabolism to overt diabetes and that the consequences of hyperglycemia in terms of clinical outcome can be understood as an exaggeration of a mechanism that also actually occurs in normoglycemic pregnancies.

In this study, mean postprandial glucose levels never exceeded 105.2 mg/dl, a value well below the currently accepted thresholds for good metabolic control in diabetic pregnancies, thus suggesting that only blunting the peak postprandial response to such an extent can result in a decreased rate of macrosomia and lead to the absolute normalization of fetal growth.

Interestingly, the variability of postprandial glucose values as assessed by the SD is generally greater in the morning, as previously reported for women with GDM (19).

The physiologic occurrence of reciprocal changes in insulin action and secretion throughout the third trimester might explain both the negative correlation found at 36 weeks between HC:AC and 1-h postprandial glucose values and the observation that 2-h postprandial glucose levels correlate with fetal AC later in pregnancy when compared with the correlation of 1-h glucose values.

In conclusion, we believe that our longitudinal study provides valuable insights toward the definition of normoglycemia in normal pregnant women and reveals significant correlations between postprandial glucose levels and insulin-sensitive fetal tissues.

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