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Elevated insulin sensitivity and β-cell function during pregnancy in mothers of growth-restricted newborns

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Dalfrà MG, Pacini G, Parretti E, Ragazzi E, Mello G, Lapolla A. Elevated insulin sensitivity and β-cell function during pregnancy in mothers of growth-restricted newborns. *Am J Physiol Endocrinol Metab* 301: E25–E30, 2011. First published April 5, 2011; doi:10.1152/ajpendo.00024.2011.—The "Barker hypothesis" suggests that low birth weight might predict future risk of developing obesity, cardiovascular disease, and type 2 diabetes. Identification of the causes of fetal growth restriction (FGR) is critical for preventive and management strategies. Some studies indicate that maternal carbohydrate metabolism might be involved in FGR development. We aimed to evaluate, in a large number of normotensive pregnant women with normal glucose tolerance, the effect of insulin sensitivity and β-cell function on unexplained fetal growth. A total of 1,814 Caucasian pregnant women with normal prepregnancy body mass index were tested with a 75-g, 2-h glucose load (24–28 gestation wk). Insulin sensitivity was evaluated with fasting (QUICKI) and dynamic index (OGIS) and β-cell function with a modified insulinogenic index as $\Delta AUC_{insulin}/\Delta AUC_{glucose}$ and disposition index. FGR was a birth weight below the 5th percentile for gestational age. FGR developed in 99 (5.5%) pregnant women that showed significantly higher QUICKI, OGIS, insulinogenic, and disposition index with respect to women with normal-weight babies ($P < 0.0001$). By using multiple regression analysis in the FRG group, QUICKI and OGIS appeared as significant independent variables ($P < 0.0001$ and $P < 0.0366$, respectively). We conclude that elevated insulin sensitivity seems to be one of the factors involved in determining unexplained fetal growth retardation; its assessment, even only in the fasting state, could be useful to guide any possible monitoring and therapeutic strategies to reduce fetal complications.

oral glucose tolerance test; surrogate indices; metabolism

FETAL GROWTH RESTRICTION (FGR) is one of the leading causes of perinatal morbidity and mortality (3). In addition, the "Barker hypothesis" suggests that low birth weight might predict future risk of developing obesity, cardiovascular disease, and type 2 diabetes in both the newborn child and the adult as a result of stimulus or insult at a critical period of early development (15). Therefore, identification of the causes of FGR is critical for preventive and management strategies; FGR cannot always be attributed to well-known factors such as aneuploidy, placental insufficiency, and infection.

There is general consensus that birth weight is related directly to insulin resistance in normal and gestational diabetic pregnancies, indicating that maternal carbohydrate metabolism plays an important role in fetal growth (9). In addition, it has been observed that, post-glucose load, plasma insulin and glucose levels are lower in women with FGR fetuses than in women with a normal growing fetus (22, 25, 37, 39).

Caruso et al. (11) discovered that women with unexplained FGR (not attributable to genetic or diverse related factors) had higher insulin sensitivity, assessed by the euglycemic glucose clamp, than a control group with infants appropriate for gestational age. Therefore, a likely hypothesis is that undergrowth may be caused by elevated maternal insulin sensitivity, leading to reduced nutrient supply to the fetus (11). Thus, maternal carbohydrate metabolism might be one of the factors involved in the pathogenesis of FGR.

The euglycemic glucose clamp, the "gold standard" for assessing insulin sensitivity, has been used in pregnancy, but the test is complex, so most of the studies have been performed on a small number of patients (4, 8, 10). Studies on insulin secretion, which usually simply evaluated the area under the concentration curve (8, 10) and only rarely used the hyperglycemic glucose clamp (18), have involved a small number of subjects who, in most cases, were obese (10, 18). Evaluation of insulin sensitivity and secretion in large numbers of subjects or in particular conditions such as in pregnancy can be made only with simple tests. The oral glucose tolerance test (OGTT) is definitely "easier" to perform than the glucose clamp, can be applied in large populations, and provides indices that have already been applied with success for studies in pregnancy, albeit in a limited number of subjects (21, 23).

The aim of our study was to evaluate, in a large number of normotensive pregnant women with normal glucose tolerance, possible relationships between metabolic parameters such as maternal insulin sensitivity and β-cell function and unexplained fetal growth restriction. Moreover, we evaluated the predictive capacity of those parameters toward the insurgence of FGR.

STUDY DESIGN AND METHODS

Among the population of pregnant women tested for gestational diabetes mellitus (GDM) using a 75-g, 2-h glucose load during the period between 24 and 28 wk of gestation at the Perinatal Medicine Unit of the University of Florence, subjects who met the following inclusion criteria were invited to take part in this prospective longitudinal study: Caucasian ethnicity, no smoking, absence of hyperemesis that can affect adequate food consumption, singleton pregnancy, absence of chronic hypertension, absence of chronic illness that can affect fetal growth, pregestational body mass index (BMI) between 19 and 25 kg/m^2, and absence of GDM as recommended by the Fourth International Workshop Conference on Gestational Diabetes Mellitus (32). We tried to elude those conditions, which are more prevalent in individuals with a history of low birth weight, to avoid a possible

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impact of low maternal birth weight on fetal growth. Nonetheless, in our studied women, a history of maternal low birth weight (<2,500 g) was present in 11.1% of the FGR women and in 9.1% of the control women (P = not significant), thus having no impact on sample heterogeneity.

All women were instructed to follow a correct meal plan with an adequate caloric intake calculated on prepregnancy BMI; the meal plan was adjusted during pregnancy to be suitable throughout pregnancy, and its adherence during pregnancy was regularly checked. Women were also instructed to follow a moderate physical activity (30 min of walking per day).

The study protocol, carried out according to the Helsinki Declaration, was approved by the local ethics committee, and written informed consent was obtained from each subject before they joined the study protocol. A total of 1,814 women were recruited. Following a 10- to 12-h overnight fast, fasting blood samples were taken, and then a solution containing 75 g of glucose was ingested, and venous blood samples were drawn for glucose and insulin determination at 60 and 120 min.

Plasma glucose levels were measured using the glucose oxidase method (19) and plasma insulin levels using a double antibody radioimmunoassay (16). Plasma glucose values <95 mg/dl at fasting, 180 mg/dl at 60 min, and 155 mg/dl at 120 min were considered normal (32). Insulin resistance was assessed with the homeostatic model (HOMA), calculated as the product of fasting glucose and insulin. However, for characterizing the metabolic state of the mothers, we instead used measurements of insulin sensitivity (33). In particular, in fasting conditions, we adopted the quantitative insulin sensitivity check index (QUICKI) = 1/[log (fasting glucose) + log (fasting insulin)] (20), whereas, in dynamic "postprandial" conditions, i.e., during the OGTT, we adopted the oral glucose insulin sensitivity (OGIS) index (ml·min^{-1}·m^{-2}) (30). This index, whose calculation is available at http://webmet.pd.cnr.it/ogis/ (last check: March 15, 2011), derives from a mathematical model of glucose kinetics after an oral load of glucose and quantifies glucose clearance per unit change of insulin. OGIS has thus been found to represent total glucose disposal, i.e., whole body insulin sensitivity (1). Both indices, which have previously been validated against the euglycemic clamp (20, 29, 30, 41), are widely used (1) also in pregnancy (26, 35). The areas under the concentration curve (AUC) were calculated with the trapezoidal rule. β-Cell function was calculated with a modified insulinogenic index as $\Delta AUC_{insulin}/\Delta AUC_{glucose}$ ($\mu U_{insulin}/mg_{glucose}$). Both the capacity of the β-cell to adapt to changes in insulin sensitivity and the ability of insulin to dispose of glucose in relation to the prevailing insulin concentration are described by the product OGIS × ($\Delta AUC_{insulin}/\Delta AUC_{glucose}$), sometimes called disposition index, and have already been widely exploited in previous studies (e.g., Ref. 27). All these indices provide a quantitative figure of the overall metabolic status by simultaneously accounting for insulin action and secretion.

Fetal growth restriction was defined as a birth weight below the 5th percentile for gestational age according to Italian birth weight distribution (34) in the absence of preeclampsia, autoimmune disease, type 1 or 2 diabetes, uterine malformations, fetal congenital malformations or chromosomal abnormalities, viral infections, or drug or alcohol abuse during pregnancy.

Statistical analysis. Data are expressed as means ± SD. ANOVA or Student's t-test for unpaired data was used for the comparison of continuous variables between groups. When kurtosis and skewness values indicated a nonnormal distribution, statistical difference between groups was determined according to the nonparametric Wilcoxon-Mann-Whitney test; median values were presented.

Simple linear regression and multiple regression were used to explore the linear relationship among the variables. The general equation was of the form $Y = a + b_1 \times X_1 + b_2 \times X_2 + \ldots + b_p \times X_p$, where the regression coefficient b_p indicates the independent contributions of each independent variable to the prediction of the dependent variable. ANOVA statistics were used to assess the significance of the regression and accepted for $P < 0.05$.

Receiver-operating characteristic curves [ROC; a graph of sensitivity vs. (1-specificity)] (17) were constructed on a logistic regression to compare the ability of the various parameters of insulin resistance to discriminate between the patients according to the presence or not of FGR. Sensitivity and specificity, statistical measurements of the performance of a diagnostic test, were calculated and reported for the optimal cutoff value.

RESULTS

By applying the selection criteria, among the 1,814 studied women, 99 (5.5%) have had a baby with birth weight below the 5th percentile for gestational age (FGR group). The remaining women (n = 1,715) were considered as control subjects (CNT). The characteristics of the two groups are reported in Table 1. At the time of the study (27th gestation wk), fasting glucose was identical in the two groups, whereas insulin was lower in FGR group. This fact yielded a lower fasting insulin resistance (HOMA) and consequently a fasting insulin sensitivity (QUICKI) that was much higher in the FGR group. FGR women delivered earlier with respect to CNT (36.1 ± 2.4 vs. 39.4 ± 1.3 gestational wk, $P < 0.0001$) and had a lower weight gain during pregnancy. The anthropometric characteristics of the newborn are reported in Table 1. Furthermore, no sex differences were found between the two groups (CNT group: males 51%, females 49%; FGR group: males 50%, females 52%; $P = 0.3$).

Glucose and insulin levels during OGTT obtained in the two groups are reported in Table 2 along with the dynamic parameters. The glucose and insulin patterns were significantly lower at any measured data point in the FGR group. These women exhibited higher dynamic insulin sensitivity (OGIS) and β-cell function (insulinogenic index), which in turn yielded more elevated disposition index.

The presence of a correlation between newborn weight and glucometabolic indices (QUICKI, OGIS, and $\Delta AUC_{insulin}/\Delta AUC_{glucose}$) was evaluated by using multiple regression analysis (Table 3). Considering the subjects altogether, the three metabolic indices resulted as significant contributors to the overall variability in newborn weight ($P < 0.0001$). Conversely, considering the CNT group of subjects, only OGIS was a predictive variable ($P < 0.0001$) for the newborn weight. Considering the FRG group, QUICKI and OGIS appeared as

Table 1. *Clinical characteristics and pregnancy outcome of the 2 groups of women studied*

	FGR (n = 99)	CNT (n = 1,715)	P Value†
Age, yr	30 ± 5	31 ± 4	0.07568
Body mass index, kg/m^2	22.11 ± 2.12	21.90 ± 1.90	0.29000
Gestational week*	27.45 ± 0.92	27.31 ± 0.84	0.12195
Newborn birth weight, g	1.861 ± 451	3.380 ± 392	<0.00001
Newborn birth length, cm	45.9 ± 1.8	49.2 ± 1.8	<0.00001
Ponderal index, g/cm^3	2.6 ± 0.3	2.9 ± 0.4	<0.00001
Birth weight percentile	3.4 ± 0.9	56.5 ± 23.7	<0.00001
Weight gain during pregnancy, kg	7.1 ± 2.9	11.8 ± 3.6	<0.00001

Data are expressed as means ± SD. FGR, women with fetal growth-restricted newborn; CNT, control women. *When the study was performed. †Statistical assessment of differences between the 2 groups was obtained by Student's t-test.

Table 2. *OGTT values and derived fasting and dynamic metabolic parameters*

	FGR (n = 99)	CNT (n = 1,715)	P Value†
Fasting glucose, mg/dl	75.3 ± 8.4 (74)	75.4 ± 7.5 (75)	0.5296
Glucose, mg/dl			
At 60 min	98.1 ± 16.1 (99)	116.2 ± 17.8 (123)	<0.0001
At 120 min	91.1 ± 16.1 (90)	103.9 ± 18.2 (105)	<0.0001
Fasting insulin, μU/ml	4.20 ± 3.90 (2.89)	6.67 ± 6.58 (5.23)	<0.0001
Insulin, μU/ml			
At 60 min	54.67 ± 34.51 (44.60)	61.87 ± 33.03 (55.40)	0.0044
At 120 min	40.22 ± 24.64 (35.90)	52.14 ± 36.93 (43.40)	0.0003
HOMA-IR	0.77 ± 0.75 (0.57)	1.23 ± 1.32 (0.93)	<0.0001
QUICKI	0.460 ± 0.133 (0.420)	0.396 ± 0.061 (0.387)	<0.0001
$AUC_{insulin}$, U/l in 2 h	4.6 ± 2.6 (3.8)	5.5 ± 2.9 (4.9)	0.0009
OGIS, $ml \cdot min^{-1} \cdot m^2$	466.4 ± 69.9 (466.9)	444.4 ± 65.3 (440.5)	0.0022
Insulinogenic index, μU/mg	222 ± 196 (154)	160 ± 110 (134)	0.0192
Disposition index	981 ± 802 (719)	700 ± 512 (583)	0.0006

Data are expressed as means ± SD (median in parentheses). OGTT, oral glucose tolerance test; HOMA-IR, homeostatis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; AUC, area under the concentration curve; OGIS, oral glucose insulin sensitivity. †Statistical difference between the 2 groups was determined according to Wilcoxon-Mann-Whitney nonparametric test.

significant independent variables ($P < 0.0001$ and $P = 0.0366$, respectively).

The relevance of QUICKI as regressor against newborn weight was further individually evaluated by simple linear regression. As shown in the scatter plot of Fig. 1, a significant regression was obtained for FRG and also for the subjects altogether, but no significant regression was detected for the CNT group only, indicating that the contribution of CNT group to the overall correlation is only marginal.

To evaluate the possible role of the metabolic indices as predictors of newborn weight, a binary logistic regression was fitted according to the occurrence or not of FRG. As Fig. 2 shows, the fitted curve model was significant ($P < 0.0001$), and consequently, a ROC curve was performed. The AUC under the ROC curve (AUCr) was 0.68, and the specificity 82%, with sensitivity of 46% at a cutoff QUICKI value of 0.44. Considering the other metabolic indices, a quite lower performance of the tests was found from ROC curve analysis (Table 4).

Regarding the clinical factors that could predict the newborn weight, the multiple regression analysis with birth weight as dependent variable and prepregnancy BMI, age, gestational week of OGTT evaluation, weight gain during pregnancy, and gestational age at delivery as independent variables yielded that age, gestational age at delivery, and weight gain were predictors (respective multiple regression coefficients were 7.45, 108.92, and 85.12, all $P < 0.0001$), whereas no significant relation was found for BMI (−0.37, $P = 0.93$) nor for gestational week of OGTT evaluation (−13.94, $P = 0.12$).

DISCUSSION

The results of our study show that women with FGR babies had increased insulin sensitivity with respect to control mothers. Insulin sensitivity evaluation with QUICKI at fasting and with OGIS in dynamic conditions suggests that both parameters are related to fetal growth. Previous studies have analyzed FGR mothers but almost exclusively in a restricted group of subjects. Here, we were able to study a very large group of well-characterized subjects and, therefore, to segregate a quite high number of mothers who gave birth to small babies. It is worth noting that we selected pregnant women with normal body weight to avoid any modification of insulin sensitivity related to overweight and or obesity (14).

Pregnancy is characterized by changes in women's hormonal status and metabolism (13, 24). The ability to regulate nutrient balance during this period is critical to the health of the mother and of the growing fetus. An important metabolic change is a decrease in insulin sensitivity that helps to optimize metabolic efficiency playing an important role in regulation of maternal fat accretion and fetal growth. Several authors have shown that, in physiological pregnancy, mothers' anthropometric characteristics and carbohydrate metabolism are the most important determinants of fetal growth (2, 7). It is well known that an increase of maternal insulin resistance, as happens for example in gestational diabetic patients and/or in obese women, can cause an excessive fetal growth (6, 14, 36, 38). However, much less information is available on the interaction between maternal metabolism and FGR. Some

Table 3. *Parameters obtained with multiple regression analysis of the data assuming the weight of newborn as dependent variable and the glucose metabolic indices as independent (explanatory) variables*

Groups of Subjects	a (Intercept)	Independent Variables		
		QUICKI	OGIS	Insulinogenic index
All subjects (n = 1814)	4,250.913	$b_1 = -1{,}220.863$, $P < 0.0001$	$b_2 = -0.8631$, $P < 0.0001$	$b_3 = -43.2098$, $P < 0.0001$
CNT (n = 1715)	3,661.338	$b_1 = 90.5437$, $P = 0.5835$	$b_2 = -0.6845$, $P < 0.0001$	$b_3 = -7.3312$, $P = 0.4054$
FGR (n = 99)	3,233.129	$b_1 = -1{,}456.155$, $P < 0.0001$	$b_2 = -1.5163$, $P = 0.0366$	$b_3 = 0.4072$, $P = 0.9869$

Multiple regression was fitted to the following model: [newborn weight] = $a + b_1 \cdot$QUICKI + $b_2 \cdot$OGIS + $b_3 \cdot \Delta AUC_i/\Delta AUC_g$. a is the intercept with the y-axis; b_1, b_2 and b_3 are the respective regression coefficients of the 3 independent variables.

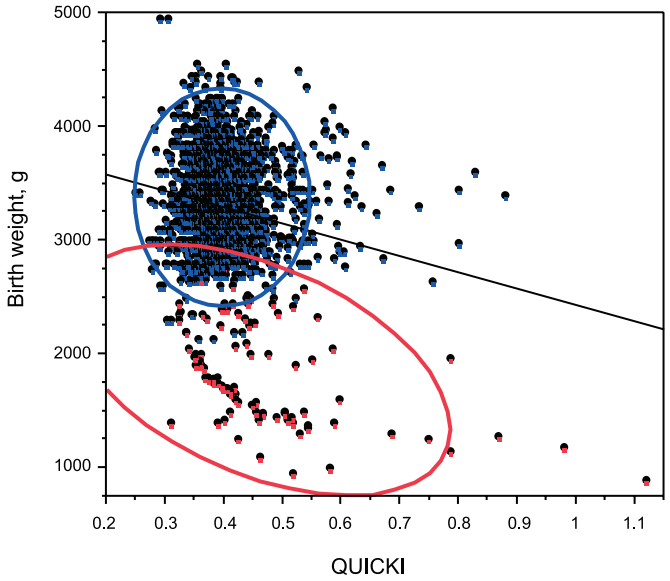

Fig. 1. Correlation between birth weight and quantitative insulin sensitivity check index (QUICKI) for all subjects (n = 1,814). Linear regression: birth weight = 3,869 − 1,431 × QUICKI; Pearson's correlation coefficient r = −0.187, $P < 0.0001$. For fetal growth restriction (FGR) only (n = 99; red points), linear regression: birth weight = 2,592 − 1,589 × QUICKI; r = −0.470, $P < 0.0001$. For control (n = 1,715; blue points), linear regression was not statistically significant: birth weight = 3,402 − 58 × QUICKI, r = −0.009, $P = 0.707$. Ovals indicate the respective 95% confidence areas for the 2 groups of subjects.

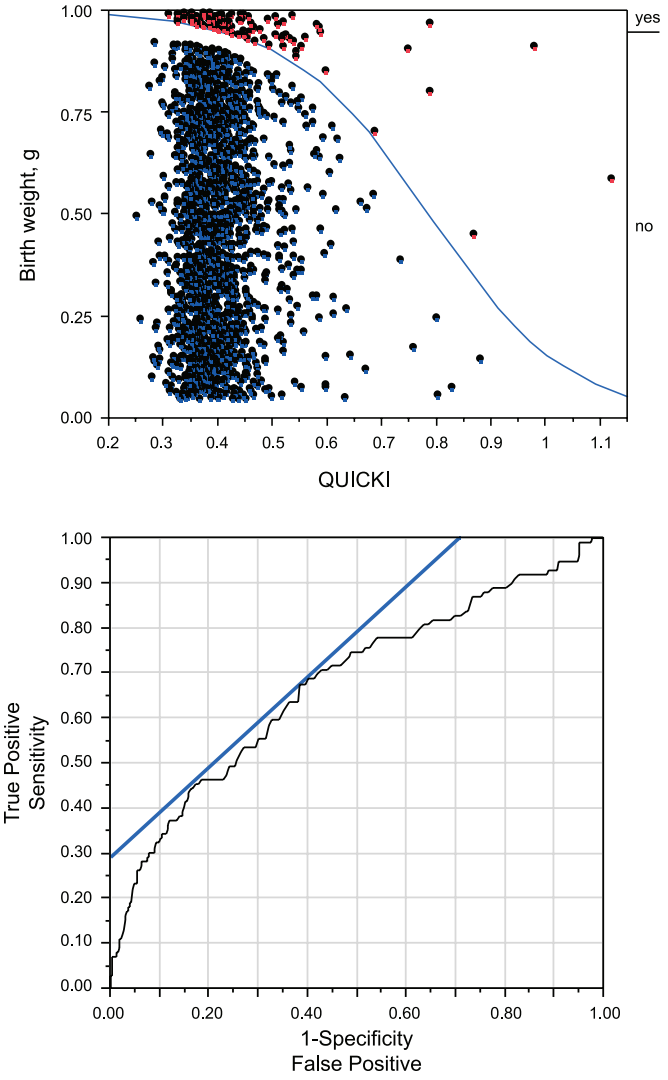

Fig. 2. Logistic regression (*top*) and consequent receiver-operated characteristic (ROC) curve (*bottom*) for the parameter QUICKI to discriminate between the patients according to FGR. Area under ROC curve was 0.68; sensitivity was 46% and specificity 82% at the cutoff QUICKI value of 0.44. See also Table 4 for other metabolic parameters considered.

authors have reported a link between reduced birth weight and low glucose and insulin levels after glucose load (22, 25, 37, 39). Caruso et al. (11) have shown, with the hyperinsulinemic euglycemic clamp, an increase in insulin sensitivity in eight mothers with unexplained FGR newborns. Our study, simply utilizing the data obtained from an OGTT, confirms in a large number of patients the conclusions of Caruso et al. (11) and demonstrates that some indices of insulin sensitivity are predictive of unexplained FGR.

The normal response in pregnancy of decreased maternal insulin sensitivity to allow the passage of glucose to the developing fetus would seem to be reduced or absent in the mothers of FGR fetuses. When, for whatever reasons, this maternal adaptation that is essential for fetal growth is compromised, the result could be undernourished fetuses. So we can speculate that women with pregnancy complicated by FGR failed to develop the "diabetogenic state" of pregnancy; the lack of increasing insulin resistance can induce a reduction of nutrients' availability to the fetus, resulting in FGR.

The AUCr is related to the ability of the test to discriminate between subjects. An AUCr of 1 describes a perfect test, with a sensitivity of 100% and specificity of 100%; in general, AUCr of 0.5–0.7 is associated with marginally useful tests, AUCr of 0.7–0.9 is associated with a good test, and AUCr >0.9 is associated with an excellent test. Since the AUCr obtained with the considered parameters was in the range of 0.58 to 0.68, we cannot recommend them as the only variables to be directly screened for the prediction of growth-restricted newborns. However, although caution must be used in interpreting data emanating from them, they clearly represent interesting and informative parameters to be monitored in pregnancy. Moreover, the present data suggest an acceptable level of performance; since when a test becomes more sensitive it becomes less specific and vice versa, we just looked for the cutoff values, allowing the best combination of sensitivity and specificity. The test appeared to display a very good specificity (that is, the probability of a negative test among subjects

Table 4. *Parameters obtained from ROC curve after nominal logistic regression on different metabolic parameters as ability to discriminate between FGR and CNT subjects*

Parameter	AUC Under ROC Curve	Cutoff Value	Sensitivity, %	Specificity, %
QUICKI	0.68	0.44	46	82
OGIS	0.59	497	39	81
Insulinogenic index	0.58	2.02	41	79
Disposition index	0.61	631.5	65	58

ROC, receiver-operated characteristics.

without the pathology, i.e., true negative), but to the detriment of sensitivity (the probability of a positive test among subjects presenting the pathological characteristic under study, i.e., true positive). From the above results it seems that QUICKI, which reflects changes mainly in hepatic insulin sensitivity, is a better predictor of FGR with respect to OGIS, which correlates better with total (mostly peripheral) glucose disposal. Endogenous hepatic glucose production was shown to remain sensitive to increased insulin concentration in normal pregnancy (96% suppression) but less sensitive in GDM (80% suppression) (5). Increased insulin sensitivity in the women in our study suggests that the suppression of endogenous hepatic glucose production may increase with less availability of glucose to dispose of. Moreover, our results suggest that the chronic resistance state, such as that reflected by the fasting measurements, plays a more superior role than the acute one reflected by the dynamic OGTT. Thus, simple fasting indices of insulin action, such as QUICKI, could provide a noninvasive way for wide-scale screening for insulin sensitivity and risk of FGR.

Methods of proven efficacy for prevention of FGR are not available; however, some evidence suggests that perinatal outcome can be improved by a strict obstetrical management and optimization of the timing of delivery. Since the glucose tolerance test is already widely used for gestational diabetes screening, the simple addition of a fasting insulinemia assay, using the same blood drawing for plasma glucose, would enable a further possibility for improving the care to pregnant women so to reduce the neonatal morbidity and mortality. The possible impact of dietary advice and the type of dietary advice in the behavior of fetal growth in these women remain to be established.

As for the relationship between weight gain during pregnancy, gestational age at delivery, and fetal growth, we found that these data can be related to the fact that women with FGR babies delivered earlier than control ones, even in absence of maternal and/or placental disease. Some studies have shown a strong correlation between low weekly maternal weight gain during pregnancy ($<$0.2 kg/wk) and fetal undergrowth (40). In our study, the weight gain during pregnancy was never below 0.2 kg/wk. As for delivery, there are no clear recommendations for the best mode and timing in the presence of FGR babies; however, it has been demonstrated that perinatal mortality and morbidity is markedly increased in FGR fetuses (12, 28). Therefore, time of delivery is crucial to avoid fetal complications, and this justifies the prudent approach of the gynecologists involved in this study to deliver the growth-restricted infants before term, as soon as fetal lung maturity has been achieved (28).

A limitation of this study is the lack of blood analysis of hormones, such as TNFα, human placental lactogen, human placental growth hormone, and adiponectin, known to be related to the development of insulin resistance during pregnancy (31). The strength is nonetheless that, to the best of our knowledge, this is the largest sample of normal-weight, normotensive pregnant women with normal glucose tolerance studied so far with respect to carbohydrate metabolism and unexplained FGR.

In conclusion, elevated insulin sensitivity seems to be one of the factors involved in determining unexplained fetal growth retardation; its assessment, even only in the fasting state, could be useful to guide any possible monitoring and therapeutic strategies to reduce fetal complications.

DISCLOSURES

The authors declare no conflicts of interest related to this work.

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