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Postpartum maternal levels of hemoglobin A_{1c} and cord C-peptide in macrosomic infants of non-diabetic mothers

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Objective: This study was designed to test the hypothesis that macrosomia in infants born to non-diabetic mothers is associated with an increased incidence of hyperinsulinemia and normal maternal glucose regulation in late pregnancy.

Methods: Twenty mothers and their macrosomic infants were chosen as the study group, and 20 mothers with their appropriate-for-gestational-age infants were chosen as the control group.

Results: No difference in postpartum mean hemoglobin A_{1c} levels was observed between the mothers of macrosomic infants and those of control infants. Cord plasma C-peptide levels were significantly higher in macrosomic than in control infants.

Conclusions: This study revealed that macrosomic infants of non-diabetic mothers were significantly more likely to have hyperinsulinemia than were normal-sized infants, and this hyperinsulinemia was not caused by dysregulation in glucose metabolism.

INTRODUCTION

Multiple factors influence birth weight, including parity, fetal sex, maternal height, prepregnancy weight and weight gain in the pregnancy, as well as maternal birth weight and socioeconomic status[1]. Fetal hyperinsulinemia has been documented in diabetic pregnancies in humans by analysis of total insulin, C-peptide and free insulin in umbilical plasma[2] Maternal glucose intolerance is associated with an increased rate of fetal macrosomia. The cause, according to the expanded Pedersen hypothesis, is believed to be fetal hyperinsulinemia resulting from increased transplacental supplies of glucose, amino acids and free fatty acids[3]. Sosenko and co-workers[4] found fetal hyperinsulinemia as a result of maternal hyperglycemia in late pregnancy in infants of diabetic mothers. The stimulus for fetal hyperinsulinemia is not well-established.

This study was undertaken to test the hypothesis that macrosomia in infants born to non-diabetic mothers is associated with an increased incidence of hyperinsulinemia and normal maternal glucose regulation in late pregnancy.

METHODS

The subjects were infants delivered at Zeynep Kamil Women and Infants Hospital between February 2000 and May 2000. Twenty mothers who delivered a macrosomic fetus (16 vaginal, four Cesarean deliveries) and 20 infants of these mothers were included in the study. Twenty mothers with normal vaginal delivery ($n = 18$) and Cesarean section ($n = 2$) and their infants were chosen as the control group. The informed consent of all the families was obtained.

The inclusion criteria were as follows: no diagnosis of diabetes in any first-degree relative; not being diagnosed as diabetic; and having normal blood glucose measurements during the pregnancy. All mothers had a normal 50-g 1-h oral glucose tolerance test performed at 24 weeks of pregnancy.

The mean weights before pregnancy and the average pregnancy numbers were calculated for mothers with macrosomic and appropriate-for-gestational-age (AGA) infants. The gestational age of infants of 38–42 weeks was

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determined by either known last menstrual period or midtrimester ultrasound examination and was confirmed by Dubowitz assessment at the time of birth.

Birth weights at 10–90th centiles were grouped as AGA, whereas those above the 90th centile were accepted as large for gestational age (LGA). For every parameter of the AGA and LGA infants the mean and standard deviations were calculated. Of the 20 term macrosomic infants (14 males, six females) 16 were born by spontaneous vaginal delivery and four by Cesarean section. Eighteen of the 20 term AGA infants (12 males, eight females) were delivered vaginally, and two of them were delivered by Cesarean section.

Five milliliters of venous blood was drawn from the mothers in the postpartum 24-h period, and was collected in tubes containing ethylene diamine tetra-acetic acid.

The samples were preserved at 2–6°C and hemoglobin A_{1c} measurements using the column chromatography method were made within 10 days. The normal range for hemoglobin A_{1c} values with this method is 5–7%. Reagents from Biosystems SA (Costa Brava, Barcelona, Spain) were used for hemoglobin A_{1c} determination. Venous cord blood is routinely collected in tubes containing lithium–heparin immediately after delivery and transported to the laboratory where it is centrifuged at 2500–3500 rpm for 10 min and, after measurement of blood glucose levels, the plasma is stored at −70°C for C-peptide determinations. The limit for hypoglycemia was accepted as 40 mg/dl. Blood glucose determinations were made by the glucose dehydrogenase method. C-peptide levels were determined by radioimmunoassay using INCSTAR RIA kits.

Statistical analysis

The data are given as mean ± standard deviation. Student's *t* test was used for assessing differences between the mothers in terms of mean hemoglobin A_{1c} levels and between the LGA and AGA infants with respect to C-peptide levels. The relationship between hemoglobin A_{1c} and C-peptide levels, and C-peptide levels and birth weights, were assessed using linear regression analysis.

RESULTS

No difference in postpartum mean hemoglobin A_{1c} levels ($p > 0.05$) or mean weights before pregnancy ($p > 0.05$) was observed between the mothers of macrosomic infants and those of control infants. The mean birth weights and gestational ages of the macrosomic infants were 4204 ± 250 g (4000–5000 g) and 41 (40–42) weeks, respectively. The mean birth weights and gestational ages of control infants were 3300 ± 272 g (2850–3750 g) and 40.3 (39–41) weeks, respectively. The difference in the mean gestational ages between the two groups was statistically non-significant ($p > 0.05$). The indications for Cesarean section in the macrosomic infants were cephalopelvic disproportion in three and fetal distress in one. Two AGA infants were born by elective Cesarean section. All infants were clinically well without any anomaly. Only two LGA infants received intensive care, because of hypoglycemia at the 2nd hour postpartum. The hemoglobin A_{1c} levels of these mothers were not higher than those of mothers who delivered macrosomic infants. The C-peptide levels of the two infants with macrosomia plus hypoglycemia were found to be two standard deviations higher than those of macrosomic infants without hypoglycemia. Cord plasma C-peptide levels were significantly higher in macrosomic than in control infants (0.82 ± 0.7 vs. 0.4 ± 0.17 pmol/ml; $p < 0.01$) (Table 1). Only in macrosomic infants was a significant correlation between birth weight and cord blood C-peptide level demonstrated ($r = 0.46$, $p < 0.05$). There was no significant association between the C-peptide levels of the macrosomic infants and control infants, or the hemoglobin A_{1c} levels of their mothers ($r = 0.2$, $p > 0.05$ and $r = 0.0037$, $p > 0.05$).

Table 1 Clinical data of macrosomic and control infants

	Macrosomic ($n = 20$)	Control ($n = 20$)	p Value
Birth weight (g)	4204 ± 250	3300 ± 272	0.001
Gestational age (weeks)	41 ± 1.1	40.3 ± 0.08	0.88
Maternal weight before pregnancy (kg)	62 ± 8.8	60 ± 10	0.64
Maternal parity	2	2	
Apgar score at 5 min	8	8	
Mode of delivery (Cesarean section vs. vaginal)	4/16	2/18	
Cord blood glucose levels (mg/dl)	76 ± 13.2	83.6 ± 11.8	
Maternal hemoglobin A_{1c} level (%)	5.12 ± 1.28	4.98 ± 0.64	0.92
Cord blood C-peptide (pmol/ml)	0.82 ± 0.7	0.4 ± 0.17	

Where applicable, values are mean ± SD

DISCUSSION

The predominant role of insulin in fetal growth is demonstrated by the phenotypes that characterize the extremes of insulin secretion. Caballero and colleagues[5] demonstrated that neonates who are hyperinsulinemic have macrosomia, whereas severe growth restriction accompanies hypoinsulinemia. As in the Pedersen hypothesis[3], Sosenko and co-workers[4] found that macrosomic infants of diabetic mothers had high cord C-peptide levels and these mothers had high hemoglobin A_{1c} levels. In contrast, Brans and co-workers[6] showed that hemoglobin A_{1c} measurement did not differentiate between those mothers of macrosomic neonates who were diabetic and those who were not. According to Schwartz and associates[7], macrosomia in the fetus of diabetic mothers is due to fetal insulinism, but glycosylated hemoglobin is a weak predictor of birth weight. In our study, we found that macrosomic infants of non-diabetic mothers were significantly more likely to have hyperinsulinemia than were normal-sized infants.

In this study, all women had normal glucose levels 1 h after a 50-g oral glucose load and no significant difference was noted in glycosylated hemoglobin in mothers of hyperinsulinemic newborns compared with mothers of normal newborns. It is possible that subtle maternal hyperglycemia accounted for the increased fetal insulin levels and macrosomia. Kalkhoff and colleagues[8] and Lepercq and colleagues[9] reported that fetal weight may also be influenced by maternal plasma amino acid concentrations.

In conclusion, fetal hyperinsulinism is the cause of fetal macrosomia whether the mother has glucose intolerance or not. In diabetic mothers the cause of fetal hyperinsulinemia was clearly maternal hyperglycemia. However, in non-diabetic mothers, the cause of fetal hyperinsulinemia was unclear, and it may be important to investigate this issue further.

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