Hyperinsulinemia in Macrosomic Infants of Nondiabetic Mothers

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OBJECTIVE — We tested the hypothesis that macrosomic infants of nondiabetic mothers are more likely to have hyperinsulinemia and increased subcutaneous fat.

RESEARCH DESIGN AND METHODS — Plasma insulin concentrations were measured in cord blood from 50 macrosomic infants and 32 normal-sized (control), term infants. All mothers had had a normal 50-g 1-h GCT. Skin-fold measurements of the triceps and subscapular area were done on 44 macrosomic infants with a Halpern caliper.

RESULTS — No difference was observed in GCT between mothers of macrosomic (5.8 ± 1.0 mM) and normal (5.7 mM) infants. The insulin level in macrosomic infants (18.75 ± 19.08 μU/ml) was significantly higher than in control infants (8.67 ± 6.64 μU/ml). Macrosomia was a predictor of hyperinsulinemia and vice versa (R^2 = 0.26). Maternal height, prepregnancy weight, and weight gain were predictors for macrosomia (R^2 = 0.26). No differences were noted in anthropometric measurements between hyperinsulinemic and normoinsulinemic infants.

CONCLUSIONS — A subset of macrosomic infants have hyperinsulinemia. Maternal anthropometric factors as well as hyperinsulinemia are correlated with macrosomia. The macrosomia may be causally related to the high insulin levels.

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 (1,2,3). Maternal glucose intolerance is associated with an increased rate of fetal macrosomia (4). The cause, according to the expanded Pedersen hypothesis, is believed to be fetal hyperinsulinemia consequent to increased transplacental supplies of glucose, amino acids, and free fatty acids (5). Whitelaw (6) found a positive correlation between neonatal skin-fold thickness and maternal glucose levels in infants of diabetic mothers. In addition, it has been reported that infants of nondiabetic mothers are more likely to be macrosomic if the 2-h value on a 3-h OGTT is higher compared with those with lower values (7).

This study was undertaken to test the hypothesis that macrosomia in infants born to nondiabetic mothers is associated with an increased incidence of hyperinsulinemia and an associated increase in subcutaneous fat.

RESEARCH DESIGN AND METHODS

— The subjects were infants delivered at Women and Infants' Hospital of Rhode Island between August 1986 and March 1987: 50 consecutively born infants identified from the delivery log book with birth weights >95th percentile for gestational age and sex and corrected for maternal height (1). Gestational age was determined by either known last menstrual period or midtrimester ultrasound and was confirmed by Dubowitz assessment at the time of birth. Control subjects were 32 consecutively born infants whose weights were in the 25th–75th percentile with corrections as for the macrosomic infants (1). Mothers of macrosomic infants were asked to give informed consent for their offspring to have skin-fold thickness measured. The protocol was approved by the of Women & Infants' Hospital of Rhode Island Human Subjects Committee. Two mothers refused to participate, and one infant was excluded because of nonimmune hydrops and congenital malformations. Women in labor routinely receive intravenous infusion of lactated Ringer's solution, a non–glucose-containing volume expander.

Only infants of term gestations (37–42 completed wk) whose cord

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GCT, GLUCOSE CHALLENGE TEST; OGTT, ORAL GLUCOSE TOLERANCE TEST; IRI, IMMUNOREACTIVE INSULIN; CV, COEFFICIENT OF VARIATION; NS, NO SIGNIFICANCE.

Table 1—*Maternal characteristics (macrosomic versus control infants)*

	N	MEAN ± SD	P VALUE
AGE (YR)			
MACROSOMIC	49	27.4 ± 4.6	
CONTROL	32	26.9 ± 4.0	NS
PARITY			
MACROSOMIC	50	0.7 ± 0.9	
CONTROL	32	0.8 ± 1.1	NS
WEIGHT, PREPREGNANCY (KG)			
MACROSOMIC	50	64.22 ± 9.71	
CONTROL	31	59.54 ± 10.82	<0.05
WEIGHT GAIN (KG)			
MACROSOMIC	50	18.67 ± 6.41	
CONTROL	31	15.26 ± 4.85	<0.02
HEIGHT (CM)			
MACROSOMIC	46	165.7 ± 6.38	
CONTROL	29	160.5 ± 6.48	<0.001
WEIGHT/HEIGHT (G/CM)			
MACROSOMIC	46	384.1 ± 52.6	
CONTROL	29	365.4 ± 58.8	0.16
WEIGHT GAIN/HEIGHT (G/CM)			
MACROSOMIC	46	113.3 ± 38.4	
CONTROL	29	92.3 ± 27.66	<0.01

blood was available and whose mothers had normal GCTs during pregnancy were included as study participants and control subjects. A normal GCT was defined as a venous plasma glucose of <7.2 mM at 1 h after oral ingestion of 50 g of glucose at 24- to 28-wk gestation.

Venous cord blood is routinely collected in EDTA tubes immediately after delivery and transported to the laboratory where it is centrifuged at 2500–3500 rpm for 10 min and the plasma stored at 5°C. The cord plasma was frozen at −40°C within 36 h of delivery.

IRI was measured in cord plasma using guinea pig anti-human insulin serum, recombinant human insulin standard insulin, and ^{125}I(A14) human insulin in a double-antibody radioamminoassay. Antisera were obtained from Linco Research (Eureka, MO). Labeled and unlabeled peptides were provided by Dr. Bruce H. Frank, Lilly (Indianapolis, IN). Intraassay and interassay CVs were 4 and 6%, respectively.

Anthropometric measurements were obtained on 44 of 50 macrosomic infants in the first 24 h of life. A Halpern caliper was used to measure skin-fold thickness of the right triceps and right subscapular area. Two measurements were taken on each infant, and the mean value was used. Skin-fold measurements, all done by one observer (B.H.), were done as described by Tanner and Whitehouse (8). Reproducibility was tested by repeating the measurements on the same infant on both sides 10 times. The CV for the triceps measurements was 7.2% on both sides, and it was 6.2% for the subscapular measurements. Abdominal circumference was measured with a tape measure at the level midway between the costal margin and the iliac crest at a time when the infant was not crying. On 10 repeated measurements on the same infant, the CV was 2%.

Statistical analysis

The significance of differences between the means was evaluated by grouped Student's *t* test; F test was used to determine if two groups had equal variance. If not, separate variance estimates were used. If variance was equal, the pooled variance estimate was used. Log transformation was applied to the insulin data to correct for nonnormal distributions. Pearson's χ^2 test was used for frequencies. Intercorrelation coefficients were computed for all variables. Regression analysis was done four times, including

Table 2—*Maternal characteristics (hyperinsulinemic versus normoinsulinemic)*

	N	MEAN ± SD	P VALUE
WEIGHT (KG)			
NORMAL INSULIN	64	62.19 ± 9.74	
HIGH INSULIN	17	63.32 ± 12.64	NS
WEIGHT GAIN (KG)			
NORMAL INSULIN	64	16.44 ± 5.88	
HIGH INSULIN	17	20.84 ± 5.61	<0.01
HEIGHT (CM)			
NORMAL INSULIN	61	163.7 ± 6.2	
HIGH INSULIN	14	163.7 ± 9.5	NS
WEIGHT/HEIGHT (G/CM)			
NORMAL INSULIN	61	376 ± 52.9	
HIGH INSULIN	14	380 ± 67.4	NS
WEIGHT GAIN/HEIGHT (G/CM)			
NORMAL INSULIN	61	99.7 ± 34.9	
HIGH INSULIN	14	128.9 ± 31.54	0.005

Hyperinsulinemia is defined as mean ± 2 SD for control infants.

Table 3—*Neonatal characteristics*

	N	MEAN ± SD	*P* VALUE
BIRTH WEIGHT (G)			
MACROSOMIC	50	4,541 ± 227	
CONTROL	32	3,320 ± 187	–
BIRTH WEIGHT (G)			
INSULIN NORMAL	65	3,960 ± 640	
INSULIN HIGH*	17	4,468 ± 437	<0.001
GESTATIONAL AGE (WK)			
MACROSOMIC	50	40.68 ± 1.05	
CONTROL	32	39.80 ± 1.53	NS
SEX DISTRIBUTION (MALE/FEMALE)			
MACROSOMIC	25/25		
CONTROL	18/14		NS

*Hyperinsulinemia is defined as mean ± 2 SD for control infants.

and excluding infants with missing data points, and including and excluding the other dependent variable (log insulin and birth weight). A stepwise procedure was used and limited to three independent variables. The SPSS-X package, version 3.1 for IBM machines, was used in the calculations.

RESULTS — Clinical characteristics of the mothers of the study infants are shown in Table 1. No difference in maternal age or parity was observed between the mothers of macrosomic infants and those of control infants. Mothers of the macrosomic infants weighed more before pregnancy (64.22 ± 9.71 vs. 59.54 ± 10.82 kg, $P = 0.05$), gained more weight during pregnancy (18.67 ± 6.41 vs. 15.26 ± 4.85 kg, $P < 0.02$), and were taller ($P < 0.001$). Weight/height was 384.1 ± 52.6 g/cm for mothers of macrosomic infants and 365.4 ± 58.9 g/cm for control mothers ($P = 0.16$). Weight gain/height, however, was significantly higher in macrosomic versus control mothers (113.3 ± 38.4 vs. 92.3 ± 27.66 g/cm, $P < 0.01$).

Table 2 lists characteristics for mothers of hyperisulinemic versus normoinsulinemic infants. Mothers of hyperinsulinemic infants had a larger absolute weight gain (20.84 ± 5.61 vs. 16.44 ± 5.88 kg, $P < 0.01$) and gained more weight for height (128.9 ± 31.54 vs. 99.7 ± 34.9 g/cm, $P = 0.005$). No difference was observed in height among the two groups.

Selection of cases resulted in a significant ($P < 0.001$) difference in birth weight among the macrosomic and control infants, as shown in Table 3. Hyperinsulinemic infants were also significantly ($P < 0.001$) heavier than normoinsulinemic infants. There was no difference in gestational age, and the distribution of females and males was even (χ^2 0.31).

Table 4 shows GCT values, in which no difference was observed between mothers of macrosomic (5.8 ± 1.0 mM) and control infants (5.7 ± 0.9 mM). GCTs of mothers of hyperinsulinemic infants (6.1 ± 0.8 mM) were not different from those of normoinsulinemic infants (5.6 ± 0.77 mM).

Cord plasma IRI (Table 5) was significantly higher in macrosomic than in control infants (18.75 ± 19.08 vs. 8.67 ± 6.64 μU/ml, $P < 0.001$). When hyperinsulinemia was defined as the mean ± 2 SD (21.95 μU/ml) for control infants, we found that 17 of 50 macrosomic infants and 2 of 32 control infants (χ^2 6.70, $P < 0.01$) had hyperinsulinemia. The log-transformed values show that the difference found between macrosomic and control infants was not a result of differentially skewed distributions.

Regression analysis was done with birth weight as the dependent variable and log-insulin included as a potent independent variable. Maternal height and log-insulin were highly significant predictors. When analysis did not include macrosomic infants with missing data, weight gain was the first independent variable to enter the equation. However, after height and log-insulin had entered the regression, weight gain was no longer a significant predictor ($P = 0.06$). In both analyses, the regression analyses were highly significant. The R^2 were almost identical, 0.34 for all macrosomic infants ($n = 82$), and 0.36 when excluding cases with missing data ($n = 75$). For analyses of insulin with birth weight, separately analyzing all macrosomic infants and then excluding infants with

Table 4—*Maternal GCT values (macrosomic versus control, hyperinsulinemic versus normoinsulinemic)*

	N	MEAN ± SD	*P* VALUE
GCT VALUES (MM)			
MACROSOMIC	50	5.8 ± 1.0	
CONTROL	32	5.7 ± 0.9	NS
INSULIN NORMAL	65	5.6 ± 1.0	
INSULIN HIGH	17	6.1 ± 0.8	NS

Serum glucose values 1 h after a 50-g oral glucose load. Hyperinsulinemia is defined as mean ± 2 SD for control infants.

Table 5—*Umbilical cord insulin and distribution of hyper- versus normoinsulinemia by subject group*

	N	MEAN ± SD	P VALUE
INSULIN (μU/ML)			
MACROSOMIC	50	18.75 ± 19.08	
CONTROL	32	8.67 ± 6.64	<0.002
LOG-TRANSFORMED INSULIN VALUES			
MACROSOMIC	50	2.56 ± 0.88	
CONTROL	32	1.87 ± 0.80	0.001
DISTRIBUTION BY SUBJECT GROUP (INSULIN NORMAL/INSULIN HIGH)			
MACROSOMIC	35/15		
CONTROL	30/2		<0.01

missing data, birth weight was the first predictor ($R^2 = 0.27$ for $n = 82$, and $R = 0.26$ for $n = 75$).

Intercorrelation coefficients were computed for all variables (Table 6). Birth weight is significantly correlated with log-insulin, height, weight gain for height, weight gain, and weight. Height, however, is not correlated with log-insulin, whereas weight gain and weight/height are.

Skin-fold measurements and abdominal circumferences did not differ significantly between hyperinsulinemic and normoinsulinemic macrosomic infants (Table 7).

CONCLUSIONS — Macrosomic infants of nondiabetic mothers are significantly more likely to have hyperinsulinemia than are normal-sized infants. Other authors also have reported a positive correlation between fetal insulin levels and birth weight in infants of women whose diabetic status was unknown (9,10). Furthermore, it has been observed that patients with glucose intolerance who are monitored closely and treated aggressively with insulin (11) as well as those receiving prophylactic insulin (12) are less likely to give birth to macrosomic infants. We have shown that among macrosomic infants of mothers documented to have normal glucose tolerance, a subset have increased circulating insulin levels.

The role of insulin in fetal growth has been studied by several investigators. Studies in the pregnant Rhesus monkey have demonstrated that fetal infusion with exogenous insulin, resulting in hyperinsulinemia without changes in glycemia, produced macrosomia in the fetuses (13). The hyperinsulinemic fetuses also had increased abdominal circumferences and subcutaneous fat, and organomegaly. Tallarigo et al. (6) reported an increase in macrosomia among offspring of nondiabetic women with higher 2-h OGTT values compared with those of women with lower values. The authors concluded that even a limited degree of maternal hyperglycemia, considered to be in the normal range, may affect fetal weight. A correlation between neonatal macrosomia and exogenous insulin bound to antibodies and transferred from mother to fetus has recently been reported: the authors suggested that the transferred insulin has biological activity (14). Hypoinsulinemia, on the other hand, is associated with fetal growth retardation accompanied by low circulating levels of insulinlike growth factors (somatomedins) (15,16). Economides et al. (17) recently reported decreased in-

Table 6—*Correlation coefficients*

	SEX	BIRTH WEIGHT	INSULIN	LOG-INSULIN	HEIGHT	WEIGHT	WEIGHT GAIN	WEIGHT/HEIGHT	WEIGHT GAIN/HEIGHT
SEX	1.00	−0.14	0.05	0.11	−0.06	−0.05	−0.04	−0.08	−0.04
BIRTH WEIGHT	−0.14	1.00	−0.33*	0.40*	0.39*	0.26†	0.36*	0.21†	0.38*
INSULIN	0.05	0.33	1.00	0.82*	−0.15	−0.08	0.16	−0.09	0.21†
LOG-INSULIN	0.11	0.40*	0.82*	1.00	−0.09	−0.01	0.31*	0.01	0.34*
HEIGHT	−0.06	0.40*	−0.15	−0.09	1.00	0.61*	0.25†	0.42*	0.14
WEIGHT	−0.05	0.26†	−0.08	0.01	0.61*	1.00	0.31*	0.98*	0.25†
WEIGHT GAIN	−0.04	0.36*	0.16	0.31*	0.25†	0.31*	1.00	0.29†	0.99*
WEIGHT/HEIGHT	−0.08	0.21†	−0.09	0.01	0.42*	0.98*	0.29†	1.00	0.24†
WEIGHT GAIN/HEIGHT	−0.04	0.38*	0.21†	0.34*	0.14	0.25†	0.99*	0.24†	1.00

Two-tailed Student's *t* test.
*$P = 0.01$.
†$P = 0.05$.

Table 7—*Anthropometric measurements*

	N	MEAN ± SD	*P* VALUE
TRICEPS			
INSULIN NORMAL	29	6.1 ± 1.3	
INSULIN HIGH	15	6.4 ± 0.8	NS
SUBSCAPULAR			
INSULIN NORMAL	29	6.3 ± 1.3	
INSULIN HIGH	15	6.5 ± 1.1	NS
ABDOMINAL CIRCUMFERENCE (CM)			
INSULIN NORMAL	29	37.1 ± 1.0	
INSULIN HIGH	15	37.6 ± 1.1	NS

sulin and glucose levels in growth retarded fetuses at different gestational ages, when compared with normal fetuses.

In this study, all women had normal glucose levels 1 h after a 50-g GCT, and no significant difference was noted in GCT levels 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. Excesses of other substances that function as secretogogues for fetal pancreatic β-cells (e.g., amino acids) may lead to fetal hyperinsulinemia. Alternatively, innate differences in pancreatic β-cell sensitivity to glucose might be present. Finally, differences in fetoplacental degredation of insulin might account for these observations. Genetic factors may play a role in whether a fetus is hyperinsulinemic, as well as in which hyperinsulinemic fetuses macrosomia will develop. Jackson (18) found that infants of diabetic and prediabetic fathers were more likely to be macrosomic than were infants of nondiabetic fathers. These hypotheses must be considered untested at present.

Correlation coefficients show a large number of significant correlations other than hyperinsulinemia, among them maternal height, weight gain, and weight gain/height with birth weight. Hyperinsulinemia is strongly correlated with birth weight and maternal weight and weight gain when controlled for height. The majority of cases of macrosomia were not related to fetal hyperinsulinemia, thus it should not be concluded that that the fetal growth-promotin activity of insulin is the only operative factor.

In conclusion, we have shown that a subset of macrosomic infants of nondiabetic mothers manifests hyperinsulinemia at birth. Furthermore, we speculate that in these infants, fetal hyperinsulinemia may be causally related to macrosomia.

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