

Maternal Insulin Sensitivity and Cord Blood Peptides: Relationships to Neonatal Size at Birth

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Objective: To examine the relationship of multiple maternal and cord blood correlates of newborn size to determine the relative strength of the insulin-like growth factor-I association.

Methods: Thirty-seven venous cord blood specimens were obtained at the time of delivery. Ponderal index and birth weight percentile were calculated at birth. Neonatal length estimates were performed with a measuring board. All mothers were nonsmokers and had normal glucose tolerance. There was a wide range of maternal prepregnancy body mass indexes (BMI) (19.6–43.4). Neonates had a wide range of ponderal indexes (2.12–2.75) and birth weight percentiles (7–99th percentile). Univariate correlation coefficients were calculated to determine simple relationships. Stepwise linear regression analyses were performed to determine the relative contribution of potential explanatory variables to both ponderal index and birth weight percentile. Potentially explanatory independent variables included maternal prepregnancy BMI, weight gain in pregnancy, and maternal insulin sensitivity at 32 weeks' gestation. Maternal insulin sensitivity was estimated using the minimal model technique. Neonatal variables included sex, cord blood albumin, insulin, insulin-like growth factor-I, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3.

Results: Significant positive univariate correlations were identified between cord blood insulin-like growth factor-I and insulin-like growth factor-binding protein-3 with neonatal ponderal index and birth weight percentile. Maternal insulin sensitivity demonstrated a negative correlation with birth weight percentile ($r = -.35, P < .05$). Cord blood insulin correlated positively with birth weight percentile (r

$= .32, P < .05$). There were no significant associations of cord blood insulin-like growth factor-binding protein-1 or albumin with either index of newborn size. Stepwise logistic regression analysis demonstrated an independent association of insulin-like growth factor-I with ponderal index ($r^2 = .41, P < .001$). Both insulin-like growth factor-I and male sex were associated independently with birth weight percentile ($r^2 = .38, P < .001$). No additional independent variables contributed to the prediction of ponderal index or birth weight percentile.

Conclusion: These data support a unique relationship between cord blood insulin-like growth factor-I and newborn size under normal growth conditions. This is manifest by the strength and independence of the association between insulin-like growth factor-I and neonatal birth weight percentile ponderal index. (*Obstet Gynecol* 1997;90:780–3. © 1997 by The American College of Obstetricians and Gynecologists.)

Insulin-like growth factor-I is a cell growth stimulator as well as a potent mitogen.¹ Insulin-like growth factor-I, most consistently among cord blood proteins, has demonstrated a strong positive association with neonatal size.^{1–4} Additionally, insulin-like growth factor-I has been found to be a reliable marker of nutritional status during childhood.⁵ As a result of these relationships, it is uncertain whether the relationship of insulin-like growth factor-I to newborn size reflects a common response to intrauterine starvation, or whether insulin-like growth factor-I is linked mechanistically to overall fetal growth. To determine if the relationship of cord blood insulin-like growth factor-I levels to fetal growth is unique, we chose to examine several cord blood proteins whose concentrations reflect nutritional status. To further clarify the strength of the association of cord blood insulin-like growth factor-I to newborn size, we examined the independent contribution of maternal factors to neonatal size at birth. These include maternal prepregnancy body mass index (BMI), maternal weight gain in pregnancy, and maternal insulin sensitivity.^{6–8}

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Materials and Methods

We recruited 47 women with singleton pregnancies over a 30-month period who were evaluated initially at 32 weeks' gestation. Ten women did not complete the protocol; two women withdrew, and cord blood samples were not obtained on eight. Thirty-seven mother-infant pairs remained for analysis. All were nonsmokers, all had normal glucose testing according to the criteria of O'Sullivan and Mahan⁹ and were free of medical complications known to affect fetal growth. At 32 weeks' gestation each woman had a 3-hour intravenous glucose tolerance test using 300 mg of glucose per kilogram body weight. An intravenous bolus of regular insulin (0.05 units/kg) was administered 20 minutes after the glucose. Insulin sensitivity was calculated according to the minimal model of Bergman.¹⁰ A reduced frequency (12 samples) blood drawing protocol was employed.¹¹

Maternal glucose was measured by the glucose oxidase technique employing a glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Maternal and neonatal insulin values were determined using a radioimmunoassay kit (Diagnostic Products Corp., Los Angeles, CA). Glucose and insulin measurements were performed in duplicate with the mean value used for reporting. The coefficient of variation with these assays was 3.3% for glucose and 6.7% for insulin. At birth, venous cord blood samples were collected and the serum was separated for analysis of albumin, insulin, insulin-like growth factor-I, and insulin-like growth factor-binding proteins 1 and 3. All serum samples were stored at -70°C and analyzed in group runs. Cord blood albumin was measured with a multichannel random access analyzer (Vitros 950; Johnson and Johnson, Rochester, NY) using a colorimetric analysis at 37°C at a wavelength of 630 nm. Insulin-like growth factor-I, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3 were measured in cord blood sera using radioimmunoassay kits provided by Diagnostics Systems Laboratories (Webster, TX).

The demographic and gross biologic features of the study subjects are listed in Table 1. All subjects except one were white. There was a wide range of prepregnancy BMI with 12 subjects (32%) having BMIs greater than the 85th percentile for age and therefore classified as obese. There was a nonsignificant tendency toward an inverse relationship between maternal prepregnancy BMI and weight gain in pregnancy ($r = -.312$, $P = .06$).

All neonatal measurements were obtained within 48 hours of birth. Newborn length was estimated using a measuring board and ponderal index was calculated ($\text{g}/\text{cm}^3 \times 100$). Newborn birth weight percentile was

Table 1. Maternal Characteristics

	Mean \pm SD	Range
Age (y)	31.1 \pm 5.9	19-42
Parity	0.78 \pm 0.79	0-3 (41% nulliparous)
Prepregnancy BMI (kg/m^2)	25.9 \pm 5.7	19.6-43.4
Pregnancy weight gain (kg)	11.2 \pm 4.8	-3.0-19.1
Insulin sensitivity (10^{-4} $\text{min}/\mu\text{U}/\text{mL}$ at 32 weeks' gestation)	1.32 \pm 0.78	0.19-3.16

SD = standard deviation; BMI = body mass index.

calculated to the nearest fifth based on local birth weight nomogram developed from 9553 singleton births without anomalies born at our institution.¹²

Statistical analysis was performed by simple correlation and stepwise linear regression. $P < .05$ was accepted for significance. All participants provided informed written consent and this project was reviewed and approved by the University of Vermont Committee on Human Research in the Medical Sciences.

Results

All infants born to study mothers were delivered at term. There were no anomalies noted among the newborns. The mean (\pm standard deviation [SD]) duration of pregnancy was 39.6 ± 0.9 weeks with a range of 39-42 weeks gestation at birth. Mean (\pm SD) birth weight was 3437 ± 374 g with a range of 2948-4760 g. The mean birth weight percentile was 53.4 with a range of 7-99th. The range of newborn ponderal index was 2.12-2.75 with a mean of 2.36 ± 0.14 . There were 18 female and 19 male infants. Maternal insulin sensitivity correlated negatively with prepregnancy BMI ($r = -.48$, $P = .003$), but was not correlated with weight gain in pregnancy ($r = -.011$, $P = .95$).

Simple correlations of birth weight percentile and ponderal index with both maternal and cord blood variables are listed in Table 2. Maternal insulin sensitivity and cord blood insulin demonstrated significant associations with newborn birth weight percentile. Cord blood insulin was directly related to newborn birth weight percentile and maternal insulin sensitivity was inversely related to birth weight percentile. Cord blood insulin-like growth factor-I and insulin-like growth factor-binding protein-3 both demonstrated strong positive correlations with newborn birth weight percentile as well as ponderal index. Mean (SD) values for insulin, albumin, insulin-like growth factor-I, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3 were 7.7 (6.0)

Table 2. Correlations With Birth Weight Percentile and Neonatal Ponderal Index

Variables	Birth weight percentile		Ponderal index	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Maternal				
Maternal prepregnancy BMI	.11	.95	.002	.99
Maternal weight gain	.21	.66	.09	.61
Maternal insulin sensitivity	-.35	<.05	-.19	.16
Cord blood				
Insulin	.32	<.05	.25	.14
Albumin	.19	.27	.06	.83
IGF-I	.53	<.001	.64	<.001
IGF-binding protein-1	-.18	.31	-.31	.07
IGF-binding protein-3	.44	<.001	.56	<.001

BMI = body mass index; IGF = insulin-like growth factor.

$\mu\text{U/mL}$, 4.0 (0.6) g/dL , 70.9 (40.6) ng/mL , 132.8 (126.9) ng/mL , and 1667.2 (336.1) ng/mL , respectively.

Stepwise linear regression demonstrated an independent association of insulin-like growth factor-I with ponderal index ($r^2 = .41$). Both insulin-like growth factor-I and male sex were associated independently and positively with birth weight percentile (Table 3).

Discussion

The biologic actions of insulin-like growth factor-I make it a candidate for an important role in the growth and development of the fetus. Significant positive associations of cord blood insulin-like growth factor-I with indices of newborn size have supported a potential mechanistic role for insulin-like growth factor-I in the growth of fetal tissues. A majority of circulating insulin-like growth factor-I is bound to protein carriers. Two distinct IGF binding proteins predominate in the fetal serum during intrauterine life. These are insulin-like growth factor-binding protein-1 and insulin-like growth factor-binding protein-3. These peptides follow distinct patterns of appearance in the fetal serum. In the early third trimester, there is a shift in the fetal serum in the relative abundance insulin-like growth factor-binding protein-1 and insulin-like growth factor-binding protein-3.¹³ Insulin-like growth factor binding

protein-3 begins to increase relative to insulin-like growth factor-binding protein-1. Insulin-like growth factor-binding protein-3 is the classic endocrinologically responsive binding protein. It is secreted by the liver in parallel with insulin-like growth factor-I in response to growth hormone in later childhood.¹⁴ These factors also support the potential for an active endocrine mechanism that influences fetal growth in the third trimester similar to the somatotrophic axis that is active during other stages of human development. Despite these pieces of supportive evidence, the relative strength and uniqueness of the relationship between insulin-like growth factor-I and newborn size is unclear.

In this study we examined the relative strength of the association of cord blood insulin-like growth factor-I with two indices of newborn size (birth weight percentile and ponderal index), in a population of women with normal glucose tolerance and no additional maternal or fetal maternal disorders that would be expected to affect the fetal growth rate. In order to determine the relative strength of this association we examined additional correlates of newborn size. These included maternal insulin sensitivity and cord blood insulin concentrations.

Maternal insulin resistance and elevated cord blood insulin levels underlied the fetal macrosomia identified in the infant of the diabetic mother as outlined in the Pedersen et al hypothesis.¹⁵ This hypothesis of fetal hyperinsulinemia leading to overgrowth has been supported by nonhuman primate experimental models.¹⁶ In populations of women with diabetes in pregnancy, cord blood insulin levels demonstrate a strong relationship to newborn size.¹⁷ We included a measure of third-trimester maternal insulin sensitivity because Catalano et al⁸ have shown that insulin sensitivity at 34–36 weeks' gestation (measured by the hyperinsulinemic euglycemic clamp) has a strong inverse correlation with neonatal birth weight ($r^2 = .28$). We used the minimal model assessment of insulin sensitivity that was used previously in pregnancy by Buchanan et al.¹⁸ Our estimates of the univariate relationship between third-trimester maternal insulin sensitivity and birth weight percentile ($r = -.35$, $r^2 = .12$) are somewhat lower than those demonstrated by Catalano et al⁸ with birth weight. In our stepwise analysis maternal insulin sensitivity provided no independent contribution to either newborn ponderal index or birth weight percentile. Additionally, cord blood albumin measured as serum albumin has been a standard used in the assessment of individual nutritional adequacy.¹⁹ No significant relationship of cord blood albumin to neonatal size was identified.

The lack of association between maternal prepreg-

Table 3. Prediction of Birth Weight Percentile

Stepwise regression	Regression coefficient	<i>P</i>	Independent R^2	Total R^2
Independent variable				
Step 1: IGF-I	0.3360	.9992	.2835	.2835
Step 2: male sex	16.3217	.9732	.1003	.3838
Final <i>F</i> value 10.2761				
<i>F</i> probability .9994				

IGF = insulin-like growth factor.

nancy BMI and weight gain in pregnancy with the estimates of newborn size appears to be the result of a combination of factors. These include the small sample size and the high frequency of obesity in the population examined.

The pattern of the cord blood insulin-like growth factor-binding proteins is consistent with previous observations. There was a high correlation of both insulin-like growth factor-binding protein-3 and insulin-like growth factor-I with newborn size and with each other. There was an inverse relationship of insulin-like growth factor-binding protein-1 with insulin-like growth factor-I and newborn size. Overall these data point to a unique relationship of cord blood insulin-like growth factor-I with newborn size. The strong relationship of insulin-like growth factor-binding protein-3 with both insulin-like growth factor-I and newborn size supports the concept of an endocrine somatotrophic axis influencing fetal growth at term. This axis appears to contribute a significant percentage of the variance identified in both birth weight percentile and ponderal index under conditions of normal fetal growth.

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