Maternal and cord blood levels of Insulin-like Growth Factors -I and -II and Insulin-like Growth Factor Binding Protein-1: correlation with birth weight and maternal anthropometric indices

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(Index words: Pregnancy, fetal growth, placenta)

Abstract

Objectives To study the correlation of maternal and cord blood insulin like growth factor (IGF)-I and -II and IGF binding protein (IGFBP)-1 levels with birth weight and maternal anthropometric indices.

Design Longitudinal prospective study.

Setting Academic Institutions and a Tertiary Care Maternity Hospital.

Participants Women with uncomplicated singleton pregnancy (N=35) and their newborns.

Measurements Maternal weight, height, symphysio-fundal height and serum levels of IGF-I, IGF-II, IGFBP-1 were measured thrice during the antenatal period, within 24 h of delivery and at 6 weeks and 6 months postpartum. Newborn anthropometric indices were recorded at birth, and at 6 weeks and 6 months of age. Cord blood levels of IGF-I, IGF-II, IGFBP-1, paternal height and weight, and placental weight measured.

Results Maternal and cord blood IGF-I levels were lower than values reported for Caucasians.

All newborns showed adequate growth at birth, and up to 6 months of age. Cord blood IGF-1 positively correlated with chest circumference ($r=0.4532$, $P=0.0262$), IGFBP-1, negatively with birth weight ($r=-0.4024$, $P=0.0461$) and IGF-II had no effect. Cord blood IGF-I positively correlated with maternal levels at 28 ± 2 ($r=0.4571$, $P=0.0247$) and 36 ± 2 ($r=0.4291$, $P=0.0364$) weeks of amenorrhoea, whereas IGF-II and IGFBP-1 did not correlate with maternal values. Maternal IGF-I, IGF-II and IGFBP-1 did not correlate with newborn or maternal anthropometric indices. Placental weight correlated significantly with birth weight ($r=0.5299$, $P=0.0348$) and head circumference ($r=0.5031$, $P=0.0470$).

Conclusions Cord blood IGFBP-1 and placental weight appear to be determinants of birth weight variation even among appropriately grown for gestational age newborns.

Introduction

Insulin-like growth factor (IGF)-I and IGF-II are single chain polypeptides implicated to exert effects on fetal growth [1]. They are produced in a variety of tissues and circulate bound to IGF binding proteins (IGFBPs) which modulate IGF actions by reducing availability at tissue level, prolonging half-life or regulating rate of transport from the vascular compartment. Six IGFBPs, named IGFBP-1 to -6 have been identified so far. Being the main secretory product of the decidua and the predominant form in amniotic fluid, IGFBP-1 is the most important type during pregnancy [2].

Several studies have examined the role of maternal and cord blood levels of IGF-I, IGF-II and IGFBP-1 in fetal growth, with inconsistent findings. A positive correlation between maternal IGF-I levels and the fetal bi-parietal diameter or birth weight was observed in some, but not in others [3-7]. Maternal IGF-I levels were not affected by having small for gestational age babies, but were low in fetal growth retardation from impaired placental function [8, 9]. A significant positive correlation between cord blood IGF-I and birth weight has been observed by some investigators, but not by others [8, 10-12]. A gender difference in fetal IGF-1 is reported with lower levels in male infants despite higher infant anthropometric variables [13, 14]. Others observed similar IGF-I levels in male and female newborns [15].

A negative correlation between maternal serum levels of IGFBP-1 and maternal size, placental weight or birth weight has been reported [6, 16]. Low cord blood IGFBP-1 levels were reported when placental weight/birth weight ratio was reduced [17]. Others reported higher cord blood IGFBP-1 levels in average than in small for gestational age babies [18]. Maternal IGFBP-1 levels were increased in pre-eclamptic toxemia [19, 20], a condition associated with poor placentation and intrauterine growth retardation. Evidence on the effects of maternal or cord blood IGF-II on fetal growth is inconsistent with reports of positive, negative or no correlation with birth weight [5, 12, 13, 15].

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Some of the previous studies did not consider appropriately grown for gestational age (AGA) neonates as a separate group, but analysed data for all births within a given period [4]. Others included mothers with medical or obstetric problems likely to affect fetal growth [14]. These could partly account for previous inconsistent findings. Furthermore, the available data on the IGF system are mostly for western populations. Studies on Asian populations are scarce and the IGF system has not been studied in Sri Lanka. The present study examined the relationship of maternal and cord blood levels of IGF-I, IGF-II and IGFBP-1 to birth size, and maternal anthropometric indices in normal singleton uncomplicated pregnancies in Sri Lankan women.

Materials and methods

A longitudinal observational study was done on healthy pregnant naturally conceiving women in their first or second pregnancy. The study was approved by the Institutional Review Board. Participants were recruited from an antenatal clinic at Castle Street Hospital for Women, Colombo, after obtaining written informed consent at the booking visit, at 14 $\pm$ 2 weeks of amenorrhoea (WOA) using a set of inclusion and exclusion criteria to exclude factors known to cause disordered fetal growth. None had a history of subfertility, other gynaecological or medical disorders. Those in the second pregnancy had no history of pregnancy induced hypertension, gestational diabetes mellitus or intrauterine growth retardation in the first. None had a family history of hypertension or diabetes mellitus.

Participants were examined at 14 $\pm$ 2, 28 $\pm$ 2 and 36 $\pm$ 2 WOA, within 24 h of delivery and at 6 weeks and 6 months postpartum. Those who developed medical or obstetric complications during pregnancy, or had clinical or ultrasound evidence of intrauterine growth retardation were excluded. Thirty-five participants completed the study. Height, weight and symphysio-fundal height (SFH) were measured at the examinations as appropriate. At every examination, a sample of venous blood (5 ml) was collected. All the neonates were delivered after 37th week of gestation. At birth, weight, crown-heel length, head circumference and chest circumference were measured. Samples of mixed cord blood were collected at delivery. Placentae were also collected from 15 women. During the postpartum examinations, health of mothers and their infants and infant weight gain were assessed. Paternal height and weight were recorded once.

All parental and neonatal anthropometric measurements were made by a single observer (ANP) using the same set of standardized instruments. (adult weight: beam balance, adult height: stadiometer, infant weight: Seca infant beam balance, crown-heel length: Shorr infantometer, head and chest circumferences: standard tape, placental weight: electronic balance). Serum was separated and stored in aliquots at -20°C until assayed using enzyme immuno-assay methods described

elsewhere [21]. Spearman Rank Correlation test (Prism 2.01, GraphPad Prism, San Diego, California, USA) was used to identify correlations between serum analytes and neonatal or maternal anthropometric indices, placental weight and neonatal anthropometric indices, and between neonatal and parental anthropometric indices.

Results

All 35 participants who completed the study were Sinhalese. Thirty were in their first pregnancy. On admission to the study, the participant's (mean $\pm$ SEM) age, body weight, height and BMI were 25.51 $\pm$ 0.64 years, 46.31 $\pm$ 1.13 kg, 1.54 $\pm$ 0.01 m and 19.60 $\pm$ 0.42 kg/m². Paternal weight, height and BMI (mean $\pm$ SEM) were 60.48 $\pm$ 1.9 kg, 1.66 $\pm$ 0.01 m, 25.52 $\pm$ 0.64 kg/m². Maternal weight, weight gain, BMI and SFH are shown in Figure 1. Weight and BMI of the study group increased progressively with gestational age as expected. Weight gain (mean $\pm$ SEM) was higher between the first and second examinations (6.67 $\pm$ 0.37 kg) than between the second and third (4.02 $\pm$ 0.32 kg). The total weight gain between 14 $\pm$ 2 and 36 $\pm$ 2 WOA was (mean $\pm$ SEM) 10.5 $\pm$ 0.57 kg. Symphysio-fundal height was appropriate for the gestational age.

Figure 1. Body weight (A), weight gain (B), body mass index (C) and symphysio-fundal height (mean $\pm$ SEM) in a group of healthy women with singleton, uncomplicated pregnancies (N=35).

Table 1. Anthropometric indices (mean $\pm$ SEM) at birth and at 6 weeks and 6 months of age of infants (N=35) born at term following singleton uncomplicated pregnancies

	Birth	6 weeks	6 months
Weight (g)	2.97 $\pm$ 0.07	4.28 $\pm$ 0.10	7.17 $\pm$ 0.19
Crown-heel length (cm)	53.14 $\pm$ 0.51	57.09 $\pm$ 0.40	66.89 $\pm$ 0.54
Head circumference (cm)	33.33 $\pm$ 0.30	37.57 $\pm$ 0.21	41.74 $\pm$ 0.24
Chest circumference (cm)	32.73 $\pm$ 0.31	36.97 $\pm$ 0.29	42.33 $\pm$ 0.39

Table 2. Geometric mean (95% confidence limits) of IGF-I, IGF-II and IGFBP-1 in maternal and cord blood in women with singleton uncomplicated pregnancies (N=35). Commonly used metric values are given within square parenthesis. WOA: week of amenorrhoea

Sample	IGF-I nmol/L [ng/mL]	IGF-II nmol/L [ng/mL]	IGFBP-1 nmol/L [g/L]
Maternal			
14±2 WOA	9.42 (8.20, 10.64) [72.46 (63.08, 81.85)]	146.20 (129.40, 165.56) [1124.62 (995.38, 1273.54)]	3.11 (2.62, 3.71) [77.75 (65.5, 92.75)]
28±2 WOA	14.76 (12.69, 16.82) [113.54 (97.62, 129.38)]	159.95 (144.19, 177.80) [1228.00 (1109.15, 1367.69)]	3.78 (3.24, 4.42) [94.50 (81.00, 110.50)]
36±2 WOA	19.18 (16.94, 21.43) [147.54 (130.31, 164.85)]	165.17 (147.21, 184.89) [1270.54 (1132.38, 1422.23)]	4.50 (3.94, 5.14) [112.50 (98.50, 128.50)]
24 h of delivery	11.04 (8.71, 13.37) [84.92 (67.00, 102.85)]	128.81 (113.74, 145.86) [990.85 (874.92, 1122.00)]	3.08 (2.50, 3.80) [77.00 (62.50, 95.00)]
6 weeks postpartum	6.41 (4.68, 8.15) [49.31 (36.00, 62.69)]	Not measured	0.27 (0.17, 0.41) [6.75 (4.25, 10.25)]
6 months postpartum	4.73 (3.27, 6.19) [36.38 (25.15, 47.62)]	Not measured	0.13 (0.09, 0.18) [3.25 (2.25, 4.50)]
Cord blood	1.11 (0.93, 1.32)	71.11 (59.70, 84.71)	1.69 (1.42, 2.01)

All the neonates were appropriately grown for gestational age, healthy and had no clinical evidence of hereditary or congenital disorders. Seventeen were males. Weight, crown-heel length and head and chest circumferences at birth and during the post-natal period are shown in table 1. Females had slightly lower values than males, but the differences were not statistically significant (data not shown). Maternal and cord blood levels of IGF-I, IGF-II and IGFBP-1 are given in table 2. Commonly used metric values are given within square parenthesis for ease of comparison with data from other populations reported in the literature. Maternal and cord blood IGF-I levels were lower than the values in Caucasians. Pattern of secretion of maternal IGF-I, IGF-II and IGFBP-1 have been described elsewhere (21).

Cord blood levels of IGF-I, IGF-II, IGFBP-1 were lower than the maternal levels and did not significantly differ between male and female newborns (data not shown). Cord blood IGF-I correlated positively with chest circumference ($r=0.4532$, $P=0.0262$) and with maternal IGF-I at 28±2 ($r=0.4571$, $P=0.0247$) and 36±2 ($r=0.4291$, $P=0.0364$) WOA. Cord blood IGFBP-1 levels negatively correlated with birth weight ($r=-0.4024$, $P=0.0461$) whereas IGF-II showed no correlation with any of the neonatal anthropometric indices. Maternal serum levels of these analytes did not correlate with maternal weight, weight gain or BMI, or with neonatal anthropometric indices (data not shown).

Placental weight positively correlated with birth weight ($r=0.5299$, $P=0.0348$) and head circumference ($r=0.5031$, $P=0.0470$), but not with crown-heel length ($r=0.1937$), chest circumference ($r=0.2030$) or Ponderal index ($r=0.0840$). Placental weight thus contributed respectively to approximately 28% and 25% variation in birth weight and head circumference. Maternal and paternal anthropometric indices did not correlate with newborn anthropometric indices (data not shown).

Discussion

Our study describes the relationship of maternal and cord blood IGF-I, IGF-II and IGFBP-1 to birth size and maternal anthropometric indices in term, singleton, uncomplicated pregnancies resulting in AGA newborns. IGF-I concentrations in both maternal and cord blood samples were lower than the values in Caucasian and Jamaican women [4, 5, 22] but similar to levels in Japan and Saudi Arabia [3, 6]. Whether these are racial differences in IGF-I levels or arise from differences in assay methods used is not clear. Others have reported lower levels of IGF-I in Asian-American women compared to Caucasians and Hispanics within the same study, but the difference was not statistically significant [23].

The positive correlation between cord blood IGF-I and chest circumference in the absence of a significant

correlation with other newborn anthropometric variables is probably a fortuitous finding. Previous reports of positive correlations between IGF-I and birth weight were mostly from growth-restricted neonates. Our inability to find such a correlation perhaps resulted from limiting the study to AGA newborns. Fetal IGF-I and birth weight did not correlate in monochorionic twins with no twin-to-twin transfusion syndrome [12] or in normotensive women [10]. Most of the previous studies reporting a positive correlation with birth weight used assays estimating total IGF-I similar to the assay we used. Our findings and previous reports thus suggest that cord blood IGF-I is not a determinant of birth weight variation in AGA neonates.

Maternal and cord blood levels of IGF-II observed by us were similar to values reported in some studies on Caucasians [22]. Absence of a significant correlation between cord blood IGF-II and neonatal anthropometric indices confirm previous findings [24]. Others have observed reduced cord blood IGF-II in intrauterine growth retardation, and similar levels in appropriate and large for gestational age fetuses [22]. Although deletion of IGF-II severely retards fetal growth [25], it is now suggested that the growth promoting role of IGF-II is dominant in the embryonic stage and IGF-I takes over as pregnancy advances [26].

Comparison of IGFBP-1 levels between studies is difficult as the assay methods used probably measured different phosphovariants. In one study which compared three ethnic groups, IGFBP-1 levels in Asian-American women were lower than in Caucasians, but higher than in Hispanics, though the differences were not statistically significant [23]. The negative correlation between cord blood IGFBP-1 and birth weight we observed agrees with previous reports [4, 12, 14, 15]. IGFBP-1 binds to and influences IGF-I bioavailability with some phosphovariants reducing and others enhancing IGF-I action. The phosphovariants we measured are those known to facilitate IGF-I action [2]. A direct effect of IGFBP-1 on fetal growth cannot be excluded in view of previous reports of such effects on other biological functions [27].

Maternal IGF-I, IGF-II or IGFBP-1 did not correlate with maternal weight or weight gain in our study, unlike in some previous studies [4]. Limiting the study to women with normal uncomplicated pregnancies with adequate fetal growth perhaps contributed to our findings. Cord blood and maternal IGF-I significantly and positively correlated in mid and late but not in early gestation. Others reported a significant positive correlation between cord blood and maternal IGF-I, despite similar IGF-I levels in umbilical arterial and venous blood suggesting the fetal origin of cord blood IGF-I (8). We did not observe any correlation between cord blood and maternal levels of IGF-II or IGFBP-1.

In our study, placental weight significantly correlated with birth weight and head circumference, but not with

crown-heel length, chest circumference or Ponderal index. In a study on 216 neonates, where data were available for 193, placental weight significantly correlated with birth weight, length, head circumference, and Ponderal index [17]. The correlation coefficients were similar to ours for birth weight and head circumference, but higher for length and Ponderal index. Thus the smaller number we studied does not solely account for our findings. It is likely that the gain in weight and length during fetal life are differentially regulated.

Our observations suggest that the placental weight and cord blood IGFBP-1 levels are determinants of birth weight variation even among AGA newborns, born following uncomplicated singleton pregnancies in healthy women. Cord blood IGF-I and IGF-II are unlikely to contribute to birth weight variation when fetal growth is adequate, but larger numbers are needed to confirm this. Similarly, further studies are needed to ascertain reasons for lower IGF-I levels that we observed.

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