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Original Article

Neonatology Section

Correlation of Changes in Cord Blood Insulin Like Growth Factor-1, Leptin level and Foetal Growth in Neonates Born at 28 Weeks of Gestation: A Cross-sectional Study

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ABSTRACT

Introduction: Insulin-like Growth Factor-1 (IGF-1) is a protein that is encoded by the IGF-1 gene in humans. IGF-1 is critical for prenatal and neonatal growth, as well as for cardiovascular system, neurological system and lung development. Leptin is produced by adipose tissue and heavily involved in the control of energy balance, body weight, metabolism, and endocrine responses. IGF-1 and leptin affect the regulation of somatic growth and the development and birth weight.

Aim: To estimate the level of cord blood IGF-1 and leptin levels in neonate born at ≥ 28 week of pregnancy and to correlate the cord blood level of IGF-1 and leptin in neonate with their foetal weight.

Materials and Methods: The present analytical cross-sectional study was conducted in the Neonatology department at SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai, Tamil Nadu, India, from June 2023 to October 2023. The study included 90 postpartum women most of the participants were in the age group between 20 to 35 years. Before delivering the placenta, cord blood sample was taken from the foetal side of the umbilical cord into appropriate tube, while serum IGF-1 and Leptin levels were measured using Enzyme Linked Immunosorbent Assay (ELISA). Billirubin was assessed using a Beckman Coulter auto analyser. Spearman's correlation was performed using Statistical Package for Social Sciences (SPSS) (27.0).

Results: The present study investigated the neonatal and demographic characteristics of pregnant women who were full term and newborns. Neonates were 2.7±0.6 kg on average, which is comparable with Appropriate for Gestational Age (AGA), however mother's mean BMI was 27±5 kg/m^2, which indicates overweight status. The results of the biochemical study indicated that the variability of leptin levels exceeded the mean. Elevated levels of IGF-1 (r=0.229, p=0.031) and leptin (r=0.250, p=0.018) were associated with greater foetal weight, according to Spearman's correlation, which showed a strong positive relationship between foetal growth and both biomarkers.

Conclusion: Cord blood analysis demonstrated a positive correlation between newborn weight and both IGF-1, leptin levels. IGF-1 and Leptin levels were observed to be elevated with increase in neonate birth weight.

Keywords: Adipogenesis, Body fat, Metabolic syndrome, Neonatal, Prenatal growth

INTRODUCTION

An important factor in an individual's later-life susceptibility to metabolic syndrome is their intrauterine condition. Hormones have a role in metabolic control, energy use, and somatic growth and development, involving leptin and IGF-1 [1]. Hormonal pathways governing foetal growth involve IGF-1 and leptin. IGF-1, derived from the human IGF1 gene, acts as an autocrine and paracrine mediator [2,3].

Structurally, it's a 70-amino acid single-stranded polypeptide chain and three disulfide linkages. IGF-1 plays a crucial role in prenatal and neonatal growth, influencing cardiovascular, neurological, and pulmonary development. Leptin, meanwhile, regulates body fat levels. IGF-I levels are positively correlated with birth weight. Insulin's role in foetal growth is generally permissive. Foetal IGF-I levels rise during the third trimester, coinciding with peak foetal weight gain [4].

The placenta is a key source of IGF-I, and the liver produces IGFBP-3. Insulin is widely acknowledged to stimulate foetal growth by increasing IGF-I production and potentially influencing adipogenesis [5-7]. Leptin, generated by adipose tissue, is regulating energy balance, metabolism, and fasting-related endocrine responses, it's significance even extends to foetal growth This hormone modulates food intake, energy expenditure, and thermogenesis to maintain optimal body fat levels and communicates fat storage status to the brain. Acting through the hypothalamus, leptin's adaptive responses Affect intrauterine development and potentially impacting early-life growth patterns based on available energy resources. Additionally, thyroid hormones play a vital role in intrauterine development, particularly in the second trimester of pregnancy [8-10].

During the twenty eight weeks of pregnancy, foetal leptin levels are influenced by both transplacental delivery and placental leptin production [11].Two key hormones involved in regulating somatic growth and organ development during early foetal life are leptin and IGF-1. In humans, insulin regulates and increases leptin levels, while in postnatal life, leptin is directly associated with growth hormone and circulating IGF-1 concentrations. Therefore, it is reasonable to hypothesise that leptin's impact on embryonic growth could be mediated by insulin and IGF-1. The objective of the present study was to determine whether leptin independently influences foetal growth, as the combined roles of the IGF system and leptin in foetal growth have not been concurrently investigated [12].

An Brazil study found that elevated levels of leptin and IGF-1 were associated with increased foetal growth and higher birth weights consistent with the present study findings [13]. Additionally, serum leptin levels and birth weight in obese and non-obese pregnant women conducted in Spain also observed similar findings, where higher maternal leptin levels were linked to greater birth weight in full term pregnancies [14-16]. A previous study [16], suggest that maternal overweight may indirectly influence foetal growth through IGF-1 and leptin alterations, highlighting the complex link between maternal health and neonatal outcomes.

With this background, present study was conducted to estimate the level of cord blood IGF-1 and leptin levels in neonate born at ≥ 28 week of pregnancy, also, to correlate the cord blood level of IGF-1 and leptin level in neonate with their foetal weight.

MATERIALS AND METHODS

The present cross-sectional study was carried out at SRM Medical College Hospital and Research Centre, located in Kattankulathur, Chennai, Tamil Nadu, India, from June 2023 to October 2023. Following the study protocol, Written informed consent was obtained from each participant, after the approval of the Institutional Ethics Committee (SRMIEC-ST0323-426). This study comprised 90 postpartum women and most of the participants were in the age group between 20 to 35 years.

Inclusion criteria: Single tone foetus, Mothers age between 20-35 years (since we can only observe IGF-1 and leptin complications in this age range [17], Gestational age ≥ 28 weeks (Because, IGF-1 and leptin are often measured as they are key indicators of foetal growth and development, and their levels can be affected by factors like gestational age and maternal health).

Exclusion criteria: Mothers with preeclampsia/eclampsia, diabetes mellitus (Type 1 and 2) or gestational diabetes mellitus, history of hypertension, severe anaemia in pregnancy (Hb<7gm/dL) and perinetal asphysia or respiratory distress were included.

Sample size calculation:

Sample size calculated was n=90 using the formula,

$n=\{(z_{\alpha/2}+z_{1-\beta})^2 (\sigma_1^{2+}\sigma_2^2)\} (\mu_1+\mu_2)^2$ where,

n: sample size required for each group, $z_{\alpha/2}$: z-score corresponding to the desired significance level (α) for a two-tailed test, $z_{1-\beta}$: z-score corresponding to the desired power (1-β) for the test, σ_1^2 and σ_2^2: variances of two population, μ_1 and μ_2: means of the two population.

But in present study the sample size was taken as 90.

$n=z_\alpha^2/2\ \alpha^2/d^2$

$n=(2.58)^2\ (1.9)^2/(0.78)^2$

n=6.6564×3.61/0.6084

n=24.029604/0.608

n=39.4 n= 90 [18]

Study Procedure

Statification of study group based on the gestational age:

Small Gestational Age (SGA): A foetus or newborn baby that is less than the usual or expected size for their gestational age is referred to as "SGA". In particular, a baby classified as SGA is born weighing less than the 10th percentile of newborns born at the same gestational age.

Large Gestational Age (LGA): A foetus or newborn baby that is larger than the usual or expected size for their gestational age is referred to as "LGA". In particular, the birth weight of an LGA baby is greater than the 90th percentile for infants born at the same gestational age.

Appropriate Gestational Age (AGA): When a foetus or newborn baby's size falls within the typical range for their gestational age, it is said to be AGA. An AGA newborn is defined as a baby who's birth weight falls between the 10th and 90th percentiles for that gestational age group [19].

Anthropometric Measurement: Anthropometry of the newborn babies was documented at birth, consisting of weight, length and head circumference using a standard scale measured by the attending midwife.

Blood Collection and Technique: Before delivering the placenta, 3 mL of cord blood sample was taken from the foetal side of the umblical cord into appropriate tubes (plain tubes). The tubes were centrifuged at 3000 rpm for 10 minutes until serum was obtained. Then the umblical cord serum Sample was stored at -80°c for estimating IGF-1 and leptin.

Then, after the collection of 90 samples IGF-1 and leptin were determined by the ELISA (human IGF-1,R and D systems, USA, and human leptin R and D systems, USA) at the Research Laboratory at Department of Biochemistry, SRM Medical College Hospital and Research Centre.

STATISTICAL ANALYSIS

The entirely of the analysis were performed utilising the Statistical SPSS version 27.0 software. Foetal growth and other parameters were analysed using Pearson's or Spearman's rho correlation. The comparison of IGF-1 and leptin levels among was analysed least significant difference Kruskal-Wallis and Mann-Whitney tests, if p<0.05 the result is considered statistically significant.

RESULTS

As a result of this cross-sectional study, 90 healthy, normal pregnant women participated at the time of delivery in order to get cord blood. The majority of the newborns were males (51), with 39 females. Maternal ages were between 20 and 35 years. The mean neonatal birth weight of 2.7±0.6 kg indicated AGA status, while the average maternal BMI was 27±5 [Table/Fig-1].

Maternal characteristics	Mean±SD
Age (years)	27±7
Weight (kg)	67±11
Height (cm)	157±8
BMI (kg/m^2)	27±5
GA (weeks)	36.3±2.7
Neonatal characteristics	
Foetal Weight (kg)	2.7±0.6
Head circumference (cm)	36±5.8
Chest circumference (cm)	35±2.9
Length (cm)	46±3.3
Parity (multi para)	32
Gravida (multi gravida)	58
Mode of delivery	C-section=34.2% Normal=46.8%

[Table/Fig-1]: Participants' demographic characteristics.
BMI: Body mass index; GA: Gestational age

In present study, the mean IGF-1 level was 8.2±5.3 and median leptin level was 1.47 with inter-quartile range of (0.6-8.1) [Table/Fig-2].

Biochemical parameters	Mean±SD
IGF-1 ng/mL	8.2±5.3
Leptin ng/mL	1.47 (0.6-8.1)
Total bilirubin mg/dL	10±3. 6
Direct bilirubin mg/dL	1.6±0.7

[Table/Fig-2]: Neonatal biochemical parameters.

There was no significant difference in IGF-1 levels between the groups (p=0.062). However, leptin levels were significantly higher in the LGA group compared to the SGA and AGA groups (p=0.028) [Table/Fig-3]. Spearman's correlation reveals that foetal growth has positively strong correlation with IGF-1 and Leptin. Therefore, it was found that higher levels of leptin and IGF-1 were positively correlated with increased foetal weight [Table/Fig-4]. Cut-off point IGF-1 for prediction of foetal growth is 19.45ng/mL with 45% sensitivity, 36% specificity and accurancy 47% and leptin for prediction of foetal growth is 2.85 ng/mL with 36% sensitivity, 25% specificity and accurancy 31%.

Parameters	SGA (>1500) n=20	AGA (<2500) n=37	LGA (>2500) n=33	p-value
IGF-1 ng/mL	6.46±3.30	8.44±5.28	10.1±6.61	0.062
Leptin ng/mL	1.35 (3.74)	1.50 (2.4)	2.95 (10.1)	0.028*

[Table/Fig-3]: Comparison of neonatal biochemical parameters level in all three categories.

Parameters		r-value	p-value
Foetal weight	IGF-1 ng/dL	0.229	0.031*
	Leptin ng/dL	0.250	0.018*

[Table/Fig-4]: Spearman's correlation of IGF-1 and leptin with foetal weight at birth. Spearman's correlationa) correlation small (0.3 to 0.1); b) shows moderate correlation (0.5 to 0.3); c) indicates highly significant (1.0 to 0.5).

DISCUSSION

The study investigates various characteristics of mothers, neonates and cord blood samples to understand their interactions and implications. Maternal factors such as age, weight, height and BMI, along with neonates factors like gestational age and newborn weight as well as neonates details including age, length, head and chest circumference were examined.

The present study found that although the average foetal weight of 2.7 kg indicated normal growth (AGA), with no negative impacts on foetal development, the mean BMI of 27 kg/m^2 classified participants as overweight. Studies suggest that macrosomia is not necessarily caused by maternal overweight, especially in the absence of gestational diabetes or hypertension Martino J et al., [16]. However, Laraia BA et al., observed a stronger correlation between maternal overweight and macrosomia and neonatal hypoglycaemia, indicating the need for additional study on maternal health variables [20].

The findings showing that overweight mothers can still have healthy babies are supported by the 2.7 kg foetal weight, which is within the typical range for full-term infants (2.5-4.0 kg). According to Joseph KS et al., BMI and birth weight are correlated [21]. However, Oken E et al., discovered that treating conditions such as gestational diabetes can lead to AGA infants [22]. Maternal overweight carries risks for gestational diabetes, preterm birth and complications such as caesarean delivery or neonatal respiratory issues even though it did not cause macrosomia in this study [23,24]. Normal growth is shown by the study's mean IGF-1 level of 8.2±5.3 ng/mL, a level within the normal range for full-term neonates (5-15 ng/mL). But the variation found implies that maternal health conditions like obesity or diabetes can affect IGF-1 levels Reed J et al., [25].

The study's leptin levels (1.47 ng/mL, IQR 0.6-8.1 ng/mL) exhibit a great deal of variation, which is in line with studies that associate greater leptin levels with higher birth weights and maternal obesity Gęca T et al., [26]. In line with normal newborn leptin levels (0.5-10 ng/mL), this demonstrates how maternal variables affect neonatal leptin concentrations. The analysis's mean total bilirubin level of 10±3.6 mg/dL is consistent with the normal physiologic rise in bilirubin observed in the first few days of life and falls within the normal range for full-term newborns Josefson JL et al., [27]. Levels over 12 mg/dL, however, may indicate pathologic jaundice and call for additional testing. Mild direct hyperbilirubinaemia is suggested by the mean direct bilirubin level of 1.6±0.7 mg/dL, which is marginally higher than the typical range for full-term newborns. Even though this does not suggest pathologic jaundice, if levels keep rising or if additional clinical symptoms appear, more research including liver function is advised to rule out hepatic diseases Patra LB et al., [28].

The outcomes of this study, which demonstrate positive relationships between IGF-1, leptin and foetal growth, are consistent with earlier studies by Tamai J et al., and Lerer R et al., [29,30], which also connected higher levels of IGF-1 and leptin with higher foetal weight, especially in infants born to mothers who were obese or had altered glucose metabolism. According to these findings, foetal growth patterns may be influenced by maternal health concerns Tamai J et al., [29]. In summary, significant positive correlations between foetal weight and IGF-1 and leptin underscore their importance in foetal development. Further research is needed to understand the mechanisms involved and to develop clinical interventions that promote healthy foetal growth.

Limitation(s)

The limitation of this research is the very small sample size, which could potentially impact the generisability of the study findings. As a cross-sectional study, it also can't prove that biomarker levels cause foetal growth. This shows how important long-term studies are to better understand the temporal relationship and possible clinical outcomes.

CONCLUSION(S)

Cord blood analysis demonstrated a positive correlation between newborn weight and both IGF-1, leptin levels. These findings emphasise the importance of IGF-1 and leptin in foetal development and highlight the need for further research to develop clinical interventions that promote healthy foetal growth.

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