

# SERUM LEPTIN LEVELS OF MATERNAL-CORD PAIRS IN INTRAUTERINE GROWTH RETARDED AND NORMAL TERM NEONATES

R Iranpour MD<sup>(1)</sup>, A Havai MD<sup>(2)</sup>, R Kelishadi MD<sup>(3)</sup>  
S Asgary PhD<sup>(4)</sup>, M Hashemipour MD<sup>(5)</sup>

## Abstract

**INTRODUCTION:** It is well documented that low birth weight may increase the risk of chronic diseases, notably atherosclerotic cardiovascular disease, later in life. However, the mechanisms of maternal and fetal weight regulation during pregnancy are not clearly defined, and leptin might play a role in this process. To compare the serum leptin levels in normal and intrauterine growth retarded (IUGR) term neonates. In addition, we aimed to determine the relationships of maternal and neonatal leptin concentrations with birth weight.

**METHODS:** From April 2005 to December 2005, serum leptin concentration were measured in umbilical cord and maternal venous blood samples of 32 mother-infant pairs with IUGR full term neonates and 34 mother-infant pairs with normal full-term neonates. Independent sample t-test was used for the comparisons. The correlation analysis was performed by Pearson correlation coefficient.

**RESULTS:** The mean leptin concentration in newborns with IUGR and in their mothers ( $2.82 \pm 1.95$  and  $3.16 \pm 2$   $\mu\text{g/L}$ , respectively) was lower than in infants with normal growth and their mothers ( $3.04 \pm 1.74$  and  $3.18 \pm 1.97$   $\mu\text{g/L}$ , respectively) but these differences were not significant. Cord blood leptin concentrations did not correlate with birth weights ( $r=0.02$ ), BMI of neonates ( $r=0.033$ ) and leptin concentrations of their mothers ( $r=0.17$ ). When data of all newborn infants were analyzed together, cord blood leptin concentration in the IUGR group correlated with BMI of neonates ( $r=0.36$ ,  $P=0.03$ ) but not with birth weight ( $r=0.22$ ,  $P=0.20$ ). There was no significant difference in terms of gender.

**CONCLUSIONS:** Cord blood leptin levels appear to correlate with BMI, as an indicator of fat mass, but not the birth weight of IUGR neonates. In addition, maternal leptin concentration cannot be considered as an accurate indicator of fetal growth.

**Keywords:** Leptin, intrauterine growth retardation, cord blood, neonate.

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## Introduction

Leptin is a 16-kDa, 167-amino-acid protein discovered in 1994 as the product of the obese (ob) gene.<sup>1</sup> Leptin interacts with specific long-form leptin receptors (OB-Rb) in the hypothalamic nuclei to reduce appetite and increase energy expenditure.<sup>2-3</sup> Leptin is primarily produced in white adipose tissue but has also been shown to be produced in the human placenta and gastric epithelium.<sup>4</sup>

It has been shown to regulate body weight through a negative feedback loop between adipose tissue and

the hypothalamic satiety centers. Although the majority of leptin research in humans has so far focused on adults, it is well documented that both in children and adults, the leptin concentration in the peripheral blood is positively correlated with body weight.<sup>5</sup>

Leptin has been detected in amniotic fluid and cord blood of the newborn.<sup>6</sup>

It is possible that leptin has some other unknown functions as a kind of growth factor in early human development. In one report, leptin was detectable in

(1) Ramin Iranpour MD. Assistant Professor of Neonatology, School of Medicine Isfahan University of Medical Sciences, Isfahan, Iran. Tel (office): +98 (311) 6249032, Cell: +98 913 113 1653, Fax: +98 (311) 6684510, Email: iranpour@med.mui.ac.ir

(2) Ali Havai MD. Resident of Pediatrics, Isfahan University of Medical Sciences

(3) Roya Kelishadi MD. Associate Professor of Pediatrics, Head, Preventive Pediatric Cardiology Department, Isfahan Cardiovascular Research Center (ICRC)

(4) Sedigheh Asgary PhD. Associate Professor, Pharmacognosist, Basic Research Department, Isfahan Cardiovascular Disease Research Center (ICRC)

(5) Mahin Hashemipour MD. Professor, Pediatric Endocrinologist, Isfahan University of Medical Sciences, Iran

*Corresponding author:* Ramin Iranpour

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cord blood at birth, and it correlated with birth weight,<sup>7</sup> but in some reports, there was a positive correlation between cord leptin levels and body mass index (BMI) and not body weight.<sup>8</sup> This relationship suggests that leptin may have a role in fetal growth, but this role still needs to be defined.

In this study, we aimed to compare the serum leptin concentration of maternal-cord pairs, in normal and intrauterine growth retard (IUGR) term neonates. We also investigated the correlations between leptin concentrations and birth weight, maternal weight and the body mass index (BMI) of neonates.

### Materials and methods

From April 2005 to December 2005, sixty-six full-term neonates and their mothers who delivered at Shahid-Beheshti Hospital, a teaching hospital affiliated to Isfahan University of Medical Sciences, Iran, were enrolled in this study. Based on birth weight, we selected normal and IUGR neonates. The first group (n=34), included normal deliveries at term (gestational age  $\geq 37$  weeks) and birth weight  $\geq 2500$  g and the second group (n=32) consisted of IUGR neonates, i.e. term neonates (gestational age  $\geq 37$  week) and birth weight of  $\leq 2500$  g.

The Ethics Committee of Isfahan Cardiovascular Research Center approved the study and informed written consent was obtained from mothers before their accouchement.

Anthropometric data from mother and newborn pairs, as well as umbilical cord and maternal venous blood samples were gathered within 12 hours of delivery. Information on estimated gestational age, based on the date of last menstrual period, and characteristics of the birth and neonatal period were extracted from the medical records.

Exclusion criteria were premature birth (gestational age  $< 37$  week), medical conditions that could cause low birth weight, i.e. multiple gestation, pre-eclampsia, psychiatric, kidney or cardiac disease, gestational diabetes, history of repeated urinary infections, seizure disorders requiring daily medication, ingestion of corticosteroid, systolic blood pressure  $\geq 140$  mmHg, or diastolic blood pressure  $> 90$  mmHg. Blood samples were collected from each mother-infant pair in trace metal-free tubes. Venous maternal blood was obtained within 12 hours of delivery. Placental blood from the umbilical vein was taken from the newborn at the time of delivery. The serum was immediately separated and frozen at  $-20$  °C until analysis. All of the parents of the newborns gave

their informed consent prior to enrollment. Serum leptin concentration was measured by a commercial Human Leptin Assay Kit (IBL Co., Ltd; JAPAN) in the laboratory of Isfahan Cardiovascular Research Center. The minimal detectable concentration of leptin was 0.5 ng/ml. The intra- and inter-assay coefficients of variation (CVs) were 7.8% and 5.1%, respectively.

#### Statistical analysis:

Data were stored in a computer data base and were analyzed after data management to exclude outliers. All analyses were performed using SPSS for windows version 10.5 (Chicago Inc. USA). Difference between means was assessed by independent samples t-test. Bivariate correlation between quantitative variables was tested by Spearman's coefficient. P values of less than 0.05 were considered significant. The study received the approval of the Ethics Committee of Isfahan cardiovascular research center.

### Results

Clinical characteristics of the newborns and their mothers in both groups are shown in Table 1.

As presented in Table 2, the mean leptin concentration in IUGR neonates was lower than in normal-weight groups, but this difference was not significant.

The mean leptin concentration in mothers of IUGR group and normal weight groups were not significantly different (Table 2). There was no gender difference in leptin concentrations in IUGR neonates ( $3 \pm 2.24$  vs.  $2.35 \pm 0.71$   $\mu\text{g/L}$ ;  $P=0.4$  in female and male infants, respectively) and in normal-weight neonates ( $3.65 \pm 2.41$  vs.  $2.77 \pm 1.41$   $\mu\text{g/L}$ ;  $P=0.19$  in female and male infants, respectively). Cord blood leptin concentrations did not correlate with birth weights ( $r=0.02$ ), BMI of neonates ( $r=0.033$ ) and leptin concentrations of their mothers ( $r=0.17$ ) when the data of all newborn infants were analyzed together. Serum leptin concentrations of mothers did not correlate with birth weight of their neonates ( $r=0.03$ ), maternal BMI at delivery ( $r=0.13$ ), or BMI of their neonates ( $r=0.01$ ) when data of all newborn infants and mothers were considered together.

In the IUGR group, cord blood leptin concentration correlated with BMI of neonates ( $r=0.36$ ,  $P=0.03$ ) but not with birth weight ( $r=0.22$ ).

In the normal-weight group, cord blood leptin concentration did not correlate either with the BMI of neonates ( $r=0.18$ ), or with their birth weight ( $r=0.1$ ).

**TABLE 1.** Characteristics (mean  $\pm$  SD) of newborns and mothers

	IUGR Group (n=32)	Normal-weight Group (n=34)	P value
Newborn characteristics n= 66			
Female, n (%)	23 (71.87%)	16 (47%)	0.04
Male, n (%)	9 (28.15%)	18 (53%)	
Birth weight, g	2150.94 $\pm$ 314.28	3144.12 $\pm$ 262.99)	<0.0001
Head circumference, cm	33.21 $\pm$ 0.99	35.01 $\pm$ 1.06	<0.0001
Length, cm	46.95 $\pm$ 2.61	50.70 $\pm$ 1.9	<0.0001
Body mass index, kg/m <sup>2</sup>	9.75 $\pm$ 1.02	12.23 $\pm$ 0.87	<0.0001
Maternal characteristics (n=66)			
Age, years	27.31 $\pm$ 5.78	24.73 $\pm$ 4.41	0.045
Prepregnancy body mass index, kg/m <sup>2</sup>	22.95 $\pm$ 3.47	22 $\pm$ 2.58	0.23
Weight gain during pregnancy, kg	11.06 $\pm$ 2.85	14.98 $\pm$ 3.39	<0.0001
Height, cm	162.03 $\pm$ 6.83	167.26 $\pm$ 7.85	0.005
Body mass index at delivery, kg/m <sup>2</sup>	27.19 $\pm$ 3.66	27.41 $\pm$ 2.70	0.78

**TABLE 2.** Maternal and newborn serum Leptin concentration in the IUGR and normal group

	leptin level ( $\mu$ g/L)			
	Mothers		Newborns	
	IUGR	normal	IUGR	normal
n=66	32	34	32	34
Mean value	3.16	3.18	2.82	3.04
SD	2	1.97	1.95	1.74
95% CI	-22.36, 0.96		-14.47, 3.23	
P value	0.97		0.63	

### Discussion

Our data indicate that cord leptin concentration was not different in IUGR and normal weight newborns at a gestational age of more than 37 weeks (term neonates). Also, cord leptin level did not correlate with the birth weight and BMI of neonates when IUGR and normal weight neonates were considered as one group. Interestingly, our data revealed that cord leptin level correlated only with BMI of IUGR neonates but not with their birth weight. This finding is consistent with some previously published data which demonstrated a positive correlation between leptin levels and BMI (which indicates fat mass) in adults and children.<sup>5,9</sup> Different studies have yielded conflicting results about the relationship of cord leptin level and newborn weight. The majority of studies reported the association between cord leptin at delivery and birth weight, as well as other anthropometric markers of fetal growth.<sup>10,11</sup> In these studies, IUGR infants had decreased leptin but there is at least one study in which the IUGR infants had increased leptin.<sup>12</sup> Similar to our findings, some previous studies reported only a significant correlation between neonatal cord leptin and the BMI of IUGR neonates.<sup>12,13</sup> Although such variations in

the results may be due to study design or genetic variations in different populations, it seems that body fat content is a major factor in regulating the leptin concentration, even though fetuses do not need to control their appetite, but rather completely depend on trans-placenta uptake for their energy supply.

In the present study, no correlation was found between maternal leptin serum concentration and cord blood leptin level of any of the two groups. Many previous studies have also confirmed this finding.<sup>10-13</sup> Leptin has been detected in amniotic fluid and cord blood of the newborn.<sup>6</sup> Amniotic fluid leptin is derived from the mother, whereas cord blood leptin is derived from the placenta and fetal tissues.<sup>4</sup> Although cord blood leptin levels appear to correlate with anthropometric markers of neonates, maternal leptin concentration is not an accurate indicator of fetal growth. This finding can be explained by the difference between the source of leptin in mothers and neonates.

A gender difference in leptin level of adults showing higher concentrations of leptin in females is documented.<sup>14,15</sup> This has not been detected in newborns at birth in any of the previous studies.<sup>5,16</sup> Similarly, we did not detect any gender difference for

leptin concentrations of newborn infants. At birth, there is no gender difference in concentrations of prolactin, estradiol, or dehydroepiandrosterone sulfate,<sup>17</sup> suggesting that there are few, if any, hormonal gender differences in humans at birth. Our data showed that the BMI at delivery and maternal weight did not correlate with leptin levels in maternal serum. This might suggest that during gestation or at least at birth, the regulation of leptin levels differs from that in non-pregnant females in whom leptin levels are highly correlated with BMI and fat mass.<sup>5,18</sup> Alternatively and most likely, the fact that there is a poor correlation between BMI or weight and maternal leptin serum concentration at birth may simply reflect the inability to directly measure fat mass. Lastly, a general increase in fat mass in all subjects towards the end of pregnancy might mask the original differences in fat mass and subsequently leptin levels in these subjects. In fact, extracellular fluid expansion takes place during pregnancy and might override changes in fat mass.<sup>19</sup> In conclusion, our results indicate that cord blood leptin levels appear to correlate with BMI, as an indicator for fat mass of IUGR neonates, but not with their birth weight. In addition, maternal leptin concentration cannot be an accurate indicator of fetal growth. Also, we found no gender difference in leptin concentration at birth. Considering the long-term impact of IUGR on atherosclerotic cardiovascular disease later in life, more research is needed in this field.

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