

## Original Article

# Inverse Correlation between Insulin-like Growth Factor-1 and Leptin Levels in Preeclampsia

P. Panjeta, V. S. Ghalaut, J. Bala, S. Nanda<sup>1</sup>, Simmi Kharb

Departments of Biochemistry and <sup>1</sup>Obstetrics and Gynecology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India

## ABSTRACT

**Background:** Preeclampsia is the major cause of maternofetal and neonatal morbidity and mortality. Insulin-like growth factor (IGF) system has a crucial role in correct embryonic and placental development and growth. Conflicting data are available regarding IGF-1 in preeclamptic mothers. The extent to which leptin *per se* mediates the fetal growth and developmental abnormalities associated with preeclampsia remains to be clarified. **Aim:** Hence, the present study was planned to assess IGF-1 and leptin levels in maternal and cord blood of preeclamptics and to compare them with normotensive pregnant women. **Subjects and Methods:** The present study was conducted in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, Pt. B.D. Sharma, PGIMS, Rohtak. Totally, 25 normotensive pregnant and 25 preeclamptic women were enrolled, and serum leptin and IGF-1 levels were analyzed in maternal and cord blood of women by enzyme-linked immunosorbent assay. **Results:** IGF-1 levels were lowered in maternal blood of preeclamptic as compared to normotensive mothers ( $P < 0.001$ ). Leptin levels were significantly increased in preeclamptic mothers as compared to normotensive mothers ( $P < 0.001$ ). Leptin had a positive correlation with IGF in both groups and it is highly statistically significant in preeclamptic mothers. **Conclusion:** Findings of the present study suggest that IGF-1 and leptin play a central role in controlling fetal growth.

**KEY WORDS:** Cord blood, insulin-like growth factor-1, leptin, preeclamptics, pregnancy

## INTRODUCTION

The basic pathology of preeclampsia is intense vasospasm affecting whole of the vascular system, especially renal, uterine, and cerebral vessels, which is probably due to an increase in vasopressor substances such as angiotensin II, thromboxane A<sub>2</sub>, endothelin-1, and a decrease in vasodilator substances such as nitric oxide and prostacyclin due to endothelial cell dysfunction.<sup>[1]</sup>

The mechanisms regulating fetal growth are poorly understood. Apart from genetic predisposition, factors such as chromosomal aberrations, nutritional and environmental factors or toxic exposition during pregnancy, insulin, and insulin-like growth factors (IGFs) have been implicated as a primary determinant of fetal weight.

IGFs are released in response to growth hormone (GH) stimulation in the liver and act as hormones.<sup>[2]</sup> Furthermore, IGFs exerts

mitogenic actions through paracrine and autocrine mechanisms to stimulate cellular proliferation and differentiation. IGF-binding proteins (IGFBPs) modulate the function of IGF-1. IGFBP-1 is synthesized by the fetal liver and is highly expressed in the decidua during pregnancy.<sup>[3]</sup> IGF-1 has been detected in preimplantation embryo and in syncytiotrophoblasts and cytotrophoblasts throughout gestation. During placentation, IGF producing “intermediate” trophoblast of the anchoring villus invades the IGFBP-1-rich maternal decidua to gain access to the maternal blood vessels.<sup>[4]</sup>

IGF-1 and IGFBP-1 modulate placental growth and reduced levels of IGF-1 and IGFBP-1 during late first trimester has

### Address for correspondenc

Dr. Simmi Kharb,

Pt. B.D. Sharma PGIMS, No. 1396, Sector-1, Rohtak, Haryana, India.

E-mail: [simmikh@gmail.com](mailto:simmikh@gmail.com)

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been reported.<sup>[4]</sup> The mechanism of effect of IGF-1 on fetal growth is not clear as maternal IGF-1 cannot cross the placenta. IGF-1 levels in umbilical cord blood have been reported to positively correlate with birth weight.<sup>[5]</sup>

Mouse leptin is secreted into circulation by adipocytes and crosses blood-brain barrier to binds its hypothalamic receptor causing downregulation of neuropeptide Y. Consecutively, a loss of food intake and an increase in energy expenditure lead to a reduction of body fat and body weight. Human obesity in children and adults has been associated with elevated serum leptin levels indicating its role in the regulation of body weight in humans.<sup>[6]</sup>

Leptin modulates satiety, energy homeostasis, and also reproductive biology ranging from paracrine effects in the placenta to regulation of conceptus development and fetal growth. High leptin concentrations have been reported in pregnant women than nonpregnant women,<sup>[7]</sup> and leptin increases significantly in women with preeclampsia that occurs due to increase in placental leptin production in preeclampsia in response to hypoxia.<sup>[8]</sup> Insulin may increase leptin levels, and after birth, there is a direct functional relation between leptin, GH, and IGF-1.<sup>[3,4]</sup> Although leptin levels have been correlated with insulin and IGF-1 level, observational study in humans indicates that its effects on fetal growth are independent of these axis and of adiposity.<sup>[9]</sup>

Conflicting data are available regarding IGF-1 in preeclamptic mothers. The possible association between fetal growth and levels of IGFs later in life needs to be explored. Furthermore, the extent to which leptin *per se* mediates the fetal growth and developmental abnormalities associated with preeclampsia remains to be clarified. Hence, the present study was planned to assess IGF-1 and leptin levels in maternal and cord blood of preeclamptics and to compare them with normotensive pregnant women.

## SUBJECTS AND METHODS

The present study was conducted during 2011–2012 in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, Pt. B. D. Sharma, PGIMS, Rohtak. This study was approved by the Ethics Review Committee of the institute. Fifty pregnant women attending the outpatient Department of Obstetrics and Gynaecology were randomly enrolled and divided into two groups: Group I (control,  $n = 25$ ) normotensive women with singleton pregnancy at the time of delivery; and Group II (study,  $n = 25$ ) age- and gestation-matched women with singleton pregnancy and systolic blood pressure  $\geq 140$  mm Hg or diastolic blood pressure  $\geq 90$  mm Hg with or without proteinuria at the time of delivery.

Informed consent was taken from all the patients. Women with a history of chronic hypertension, any metabolic disorder before or during pregnancy, or presence of high-risk factors such as heart disease, diabetes, renal disease were excluded.

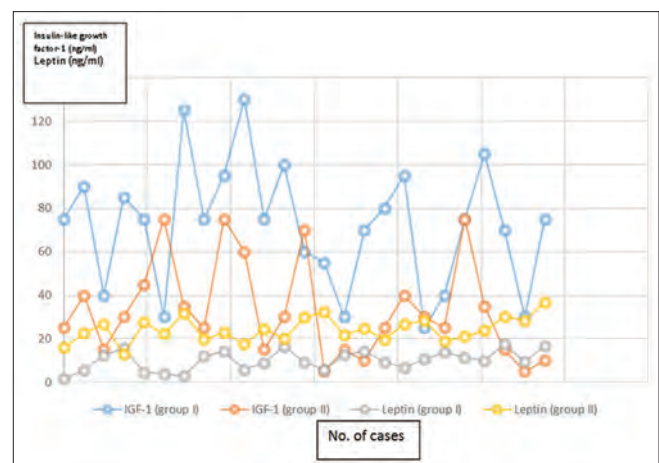
Five milliliters of blood was drawn aseptically, and serum was separated by centrifugation. Ten milliliters of umbilical cord blood was drawn, and serum was separated. Routine investigations and serum leptin and IGF-1 levels were analyzed in maternal and cord blood of women with preeclampsia and normotensive pregnant women. DRG enzyme-linked immunosorbent assay (ELISA) kit for IGF-1 and leptin ELISA Kit for leptin estimation were based on solid phase ELISA (based on the sandwich principle).<sup>[10]</sup> Data were expressed in mean  $\pm$  standard deviation; Student's *t*-test and Pearson correlation were used. SPSS, version 17.0 was used in the analysis (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.).

## RESULTS

IGF-1 levels were lowered in maternal blood of preeclamptic as compared to normotensive mothers ( $P < 0.001$ ) [Table 1]. Leptin levels were significantly increased in preeclamptic mothers as compared to normotensive mothers ( $P < 0.001$ ) [Table 1 and Figure 1]. Cord blood IGF-1 levels were significantly decreased in

**Table 1: Maternal and cord blood insulin-like growth factor-1 and leptin in both groups (mean $\pm$ standard deviation)**

parameters	Group I (control) maternal	Group I (control) cord blood	Group II (study) maternal	Group II (study) cord blood
Insulin-like growth factor-1 (ng/ml)	259 (45.39)	72.2 (28.65)	73.2 (48.69)	33.2 (22.21)
Leptin (ng/ml)	21.77 (6.30)	10.02 (4.57)	57.48 (18.67)	24.27 (5.64)



**Figure 1: Cord blood IGF-1 and leptin levels in both the groups**

preeclampsia mothers as compared to the normotensive mothers ( $P < 0.001$ ) [Table 1], while serum leptin levels were significantly increased in preeclampsia mothers as compared to the normotensive mothers ( $P < 0.001$ ) [Table 1 and Figure 1]. Maternal leptin and IGF-1 levels were about two-fold higher than fetal levels in both groups.

Maternal IGF-1 had a strong inverse correlation with leptin levels in preeclamptic mothers ( $r = -0.528, P < 0.01$ ). No correlation was found between normotensive mother IGF-1 and leptin levels. Cord blood IGF-1 had a negative correlation with cord blood leptin levels in both groups; however, it was statistically not significant in neither of these groups ( $r = -0.145, r = -0.246, P = 0.49, P = 0.24$ ). IGF-1 has a negative correlation in normotensive mothers ( $r = -0.024$ ), while it has a positive correlation in preeclamptics ( $r = 0.407$ ), although none of these correlations were significant. Leptin has a positive correlation with IGF in both groups and it is highly statistically significant in preeclamptic mothers ( $r = 0.231, r = 0.687; P = 0.27, P < 0.001$  at both levels). Correlation between maternal and cord blood IGF-1, leptin is depicted in Table 2.

## DISCUSSION

Conflicting evidence regarding alterations of IGFs in preeclamptic pregnancies are available in literature. Vatten *et al.* observed an increase in IGF-1 from the first to second trimester associated with preeclampsia, which the authors concluded was the result of placental disease.<sup>[11]</sup> Contradicting these findings, Ning *et al.* reported a decrease in free IGF-1 levels in early pregnancy associated with the risk of developing preeclampsia.<sup>[12]</sup> Ingec *et al.* observed lowered IGF-1 levels in late pregnancy in women who developed moderate and severe preeclampsia and eclampsia.<sup>[13]</sup> Cooley *et al.* and Hübinette *et al.* reported that IGF-1 levels are not changed in women with preeclampsia.<sup>[14,15]</sup> Wilson *et al.* reported the higher concentration of IGF-1 in the third trimester, probably reflecting placental contribution.<sup>[16]</sup>

The present study demonstrated significantly decreased serum IGF-1 levels in preeclampsia mothers as compared to the normotensive mothers.

IGF-1 is mainly expressed at the maternal-fetal interface in early human pregnancy. The trophoblast columns express

high values of IGF-messenger (mRNA), with the greatest abundance at the invasive front, strongly suggesting the involvement of IGF in trophoblast invasive activity.<sup>[17]</sup> Reduced placental perfusion causes placental ischemia, angiogenic imbalance, and endothelial dysfunction leading to maternal hypertension. As a result of decreased IGF-1 levels in preeclampsia, there is inadequate trophoblast invasion resulting in reduced placental perfusion. *In vitro* studies have shown that IGF-1 administration increases trophoblast invasion and glucose transport activity in first-trimester trophoblast cells lines, hence suggesting that IGF-1 may promote uterine spiral artery remodeling to provide adequate perfusion and nutrient supply to the uteroplacental unit.<sup>[18,19]</sup> Significantly lowered level of IGF-1 in preeclamptic mothers in the present study signifies the important role of this system in normal pregnancy.

Cord blood IGF-1 levels of preeclamptic mothers were significantly decreased as compared to cord blood of normotensive mothers.

Reduced placental perfusion pressure results in intrauterine growth restriction in offspring born of preeclamptic pregnancies.<sup>[20]</sup> Studies have reported that high maternal levels of IGF-1 regulate fetal weight and divert nutrients from mother to fetus, while maternal IGF-2 regulates placental development and maternal hemodynamic adaptation to pregnancy by increasing the maternal plasma volume.<sup>[21,22]</sup> Similarly, Bankowski *et al.* also showed that preeclampsia is associated with a decrease of IGF-1 content in the umbilical cord artery. Studies have reported that low IGF-1 levels are associated with endothelial dysfunction in hypertensive patients.<sup>[23]</sup>

The present study also showed that serum leptin levels of preeclampsia mothers were significantly increased as compared to normotensive mothers. It was also found that cord blood leptin levels in preeclamptics were also significantly increased as compared to normotensive mothers.

A considerable amount of leptin is secreted from the placental trophoblastic cells into the maternal circulation during pregnancy.<sup>[24]</sup> Metabolic changes such as glucose intolerance and insulin resistance encountered in obesity can also be seen in preeclampsia. Mise *et al.* showed an increase in placental leptin mRNA expression proportional to an increase in serum leptin levels in these patients.<sup>[8]</sup> Similarly, many studies have also detected a significant increase in plasma leptin levels in preeclamptic cases.<sup>[25-27]</sup>

The present study showed that cord blood IGF-1 and leptin levels were significantly lowered in both groups as compared to respective maternal levels.

**Table 2: Correlation between maternal and cord blood insulin-like growth factor-1 and leptin levels in both groups**

Maternal versus cord blood (ng/ml)	Group I		Group II	
	r	P	r	P
Insulin-like growth factor-1	-0.024	0.910	0.231	0.27
Leptin	0.407	0.044	0.687	<0.001

There was a strong significant inverse correlation of maternal IGF-1 had with leptin levels in preeclamptic mothers. Cord blood IGF-1 also had a negative nonsignificant correlation with cord blood leptin levels in both groups. No correlation was noted between normotensive mother IGF-1 and leptin levels. However, Hartman *et al.* reported that no correlation existed between IGF-1 and leptin.<sup>[28]</sup>

Renal dysfunction occurs in pregnant women with preeclampsia, and decreased renal clearance may be responsible for high leptin levels in preeclamptic women. Decreased plasma volume sometimes seen in preeclampsia may have a role in the increase in serum leptin level by causing hemoconcentration.

IGF-1 had a negative correlation in normotensive mothers while it had a positive correlation in preeclamptics although none of the correlation was significant. Leptin had a significant positive correlation in both groups. McCarthy *et al.* found a strong correlation between the maternal plasma leptin concentrations and umbilical cord blood leptin concentrations in preeclampsia.<sup>[25]</sup>

Taking into account the lack of a correlation between the maternal and umbilical cord blood leptin levels during normal pregnancy, it may be stated that the fetoplacental leptin regulation is a noncommunicating, double-compartment model. However, in preeclampsia, the strong correlation between the maternal and fetal leptin concentrations is indicative of a change resulting in communication between the two compartments.<sup>[25]</sup>

Placental hypoperfusion produces local hypoxia which consequently augments leptin gene expression in the placenta.<sup>[8]</sup> Inflammatory mediators such as tumor necrosis factor- $\alpha$  and interleukin-6 increase plasma leptin concentration.<sup>[29]</sup> Since leptin activates the sympathetic nervous system and stimulates catecholamine secretion, it is plausible that elevated leptin levels in maternal circulation may aggravate hypertension.<sup>[30]</sup>

Thus, there are several possible explanations for higher leptin concentrations in pregnancies complicated by preeclampsia. The exact mechanism underlying the increase in circulating leptin concentration in preeclampsia awaits further clarification.

The present study showed a significant inverse correlation of maternal IGF-1 with leptin levels in preeclamptics and no correlation was noted between normotensive mother IGF-1 and leptin levels. Cord blood IGF-1 had a negative nonsignificant correlation with cord blood leptin levels in both groups. Similarly, Lepercq *et al.* and Christou *et al.*

did not find any correlation between IGF-1 and leptin in normotensive pregnancies.<sup>[31,32]</sup>

IGF-1 had a positive correlation with birth weight in both normotensive and hypertensive groups; however, it is statistically significant only in cord blood of normotensive mothers. Reduced placental perfusion pressure results in intrauterine growth restriction in offspring born of preeclamptic pregnancies.<sup>[20]</sup> Clinical studies have reported a deficit in circulating and cord blood IGF-1 levels in intrauterine growth-restricted newborns and a correlation between IGF-1 levels and birth weight.<sup>[33,34]</sup> Studies report that high maternal levels of IGF-1 regulate fetal weight and divert nutrients from mother to fetus. Wang *et al.* showed that the mean serum IGF-1 levels in the small-for-gestational-age group were significantly higher than those in average-for-gestational-age neonates.<sup>[35]</sup> Since IGF-1 cannot cross the placenta, circulating IGF-1 may only be a secondary reflection of local tissue events involved in fetal growth.

Leptin showed a positive correlation with birth weight in normotensive mothers but a negative correlation in hypertensive mothers in the present study. There are many reports of positive correlation of birth weight and leptin among normotensive pregnancies in the literature.<sup>[32]</sup> The basis of this correlation may be due to direct relationship between adipose tissue mass and circulating leptin concentrations, and also from the placental source of leptin production.<sup>[24,36]</sup> Moreover, cord leptin levels are decreased by conditions that lead to low birth weight, such as maternal smoking and prematurity.<sup>[37]</sup> Whether leptin is directly implicated in determining fetal growth, or it simply represents a marker for fetal nutrition and growth, remains to be shown by future interventional studies. Serum leptin level has been reported to decrease following expelling of placenta after delivery<sup>[8]</sup> indicating that leptin increase in preeclamptics is related to placental production. Increase in placental leptin production reflects placental hypoperfusion and/or hypoxia, and hypoxia increases placental leptin production by inducing expression of placental genes in trophoblastic cells.<sup>[37-39]</sup>

There is increasing evidence that the foundations of life-long health are, in part, laid in the uterus. It seems likely that IGF-1 and leptin play a central role in controlling fetal growth.<sup>[37-39]</sup>

## CONCLUSION

Findings of the present study suggest that IGF-1 and leptin play a central role in controlling fetal growth.

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No financial assistance was available and no grant was received for this project.

## Conflicts of interest

There is no conflicts of interest.

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