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Original Article

Comparison of Maternal Serum and Umbilical Cord Blood Leptin Level in IUGR Neonates

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ABSTRACT

Background: Gestational weight gain is an impressive factor in the fetal outcome. Intrauterine growth restriction (IUGR) is one of the most important problems during fetal period that may lead to many perinatal and long-term complications and growing neonatal morbidities and mortalities. The aim of the study was to ascertain the relationship between umbilical cord blood leptin concentration and fetal growth in neonates born with intrauterine growth restriction.

Methods: Maternal serum and umbilical cord blood leptin concentration were measured by immune radiometric assay at term gestation. The study was conducted on 22 women with uncomplicated singleton pregnancies as control group (group A) and 22 women with fetal growth restriction in singleton pregnancies as case group (group B). All subjects had normal pregravid body mass index (BMI).

***Results*:** The results of the study showed that maternal serum leptin concentrations were significantly higher in group B comparing to group A (44ng/ml [28.9-58.2] vs. 24.6ng/ml [18.8-33.3]; P<0.001). However, umbilical cord blood leptin levels were significantly lower in group B comparing to group A (8.6 ng/ml [range 4.5-12.7] vs. 14.6 ng/ml [11.7-16.7]; P<0.001). Moreover, umbilical cord blood leptin levels were directly correlated with maternal BMI and neonatal birth weight in both groups.

Conclusion: In growth-restricted fetuses at term, umbilical cord blood leptin concentrations were significantly lower than normal fetuses, suggesting that fetal adipose tissue is a major source for leptin production. Maternal serum leptin concentrations were higher in the presence of a growth restricted fetuses. This increas may be due to early hypoxia or an intrinsic placental mechanism, by which small placenta produces more leptin as a compensatory mechanism. Human recombinant leptin may have some roles in the treatment of IUGR fetuses in future.

Keywords: Adipose tissue, Intrauterine growth restriction, Leptin, Umbilical cord

Introduction

Gestational weight gain is an impressive factor in the fetal outcome. Intrauterine growth restriction (IUGR) is one of the major fetal problems that may contribute to some perinatal and long-term complications and neonatal morbidity and mortality increase (1). According to the most widely used definition, IUGR is a condition in that a fetus weight is below 10th percentile for the gestational age (2). Some of the risk factors of IUGR included small size and poor nutrition of mothers, social exclusion, neonatal infections, congenital abnormalities, chromosomal aneuploidy, teratogens, chronic hypoxia, renovascular disease of mother, and placental and umbilical cord disorders (3).

Leptin is a 167 amino acid protein encoded by obese (ob) gene that is essentially produced by adipocytes (4). The amount of adipose tissue is the most significant factor determining serum leptin concentration (5). Another source of leptin secretion is placenta in humans (but not in all other species) that is one of the most significant sources of leptin for the fetus during pregnancy through umbilical cord blood. The mammary glands are the sources of leptin production during the early phase of lactation which transfers leptin

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during newborn breastfeeding (6).

Leptin as the adipocytokine has different and impressive biological functions. As a pleiotropic hormone, it plays an important role in the regulation of food intake, energy balance, and fat storage through a feedback from fat cells to the central nervous system.

Other biological effects are in peripheral tissues that modulate the cell proliferation and differentiation in adipose tissues, pancreas, stomach, liver, kidney, arteries, and immune cells. Moreover, it modulates gastro protective activity (7). There is another hypothesis that leptin plays an important role in intrauterine growth. Infants suffering from IUGR have a lower level of serum leptin in comparison with normal infants due to the subcutaneous fat formation in the last weeks of pregnancy. The expansion of fat tissue is the most important determining factor of serum leptin level (8).

The general objective of the study is to compare maternal serum and umbilical cord blood leptin level between normal and IUGR neonates.

Methods

In this case-control study, 22 neonates with IUGR and 22 cases with normal weight were assigned to the case and control groups, respectively, during a twelve months period. Inclusion criteria were :1) singleton neonate with Apgar score $\geq$7, 2) lack of congenital abnormalities, 3) lack of any disorders, such as preeclampsia, eclampsia, diabetes, gestational diabetes mellitus (GDM), thyroid disorders, hepatic, and cardiac diseases , 4) and lack of any history of smoking, alcohol consumption, and receiving steroids by their mothers. On the other hand, the control group included term neonates with birth weight (BW) 2500-4000 g. Those with birth weight less than 2500 and more than 4,000 g were excluded from the study.

The case group included neonates who had IUGR based on clinical or ultrasound findings. IUGR neonates were considered term neonates with BW<2500 g and less than the 10th percentile in CDC growth charts for normal term neonates. They were also diagnosed by serial sonography with IUGR. Ultrasonography criteria were presence of oligohydramnios without ruptured membranes and abdominal circumference below the 10th percentile of reference values for fetuses of similar age. All of the neonates in case and control groups were term (38- 40 week) based on gestational age and preterm neonates were excluded from the study.

Furthermore, a written consent was obtained from all cases. All participants were asked to complete a form including general information (e.g., medical history and previous pregnancies). The physical examination (e.g., height and weight of mothers, demographic information, height, weight, and head circumference of neonates) of the subjects were measured by a pediatric resident. A Seca scale was used to weigh the infants.

At the time of delivery, 5cc of mothers' venous blood and 5cc of umbilical cord venous blood were sampled under sterile condition by a trained nurse and stored at -80°c temperature for further evaluations.

Enzyme-linked immunosorbent assay (ELISA) technique and kits (Media Noist Germany) were used for measuring leptin, by a trained institutional laboratory staff in Imam Hosein hospital, Tehran, Iran. All statistical tests were considered two-tailed with 95% confidence interval. All data were analyzed in SPSS software (version17).

This study was approved by Ethical Committee of Shahid Beheshti University of Medical Sciences Tehran, Iran (IR.SBMU.MSP.REC.1394.9).

Results

In this study a comparison was made between 22 neonates with IUGR and 22 cases with normal weight neonates as the case and control groups, respectively. The purpose of the study was to compare the amount of leptin level of venous umbilical cord blood between infants with IUGR and their maternal serum and normal weight infants and their mothers. The means of head circumference in the case and control groups were 32.2±1.2 (30-34) and 34.7±1.3 cm (33-37 cm), respectively. There was a significant difference in averages of infants' head circumference within two groups (P<0.001).

Ponderal index means in control and case groups were 2.7±0.3 (2.2-3.2) and 4±0.2 (2.0-3.0), respectively. There was a significant difference in Ponderal indexes within two groups (P=0.001). Moreover, serum leptin levels in mothers of control group were 24.6±3.3 ng/ml (18.8-33.3 ng/ml) and in the case group were 44.0±8.2 ng/ml (28.9-58.2 ng/ml). There was a significant difference in maternal serum leptin level in mothers within two groups (P<0.001; Figures 1-2).

In addition, Leptin level of the umbilical cord in control group was 14.6±1.4 ng/ml (11.7-16.7 ng/ml) and in the case group was 8.6±2.4 ng/ml (4.5-12.7 ng/ml). There was a statistically

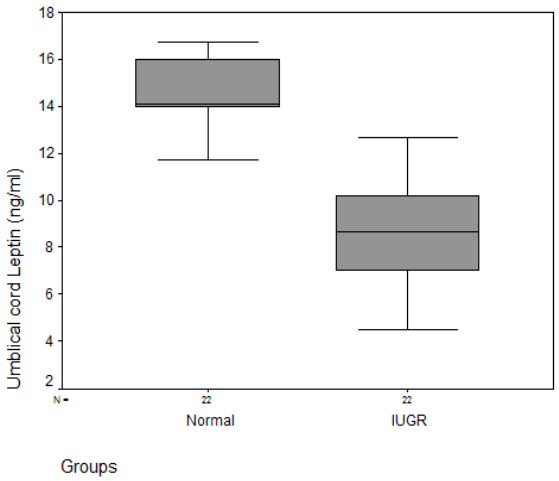

Figure 1. Umbilical cord leptin level in case and control groups

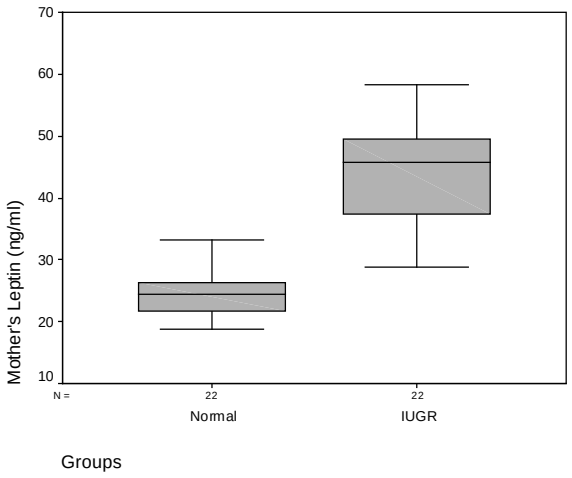

Figure 2. Maternal serum leptin level in case and control groups

Table 1. Characteristics of case and control groups and their mothers

	Case	control	P-Value
Gender	11 females (50%) 11males (50%)	13 females (59%) 9 males (41%)	=0.763
Age of mothers	26.6±5.8 years (17-36)	28.5±5.4 years(21-42)	=0.263
Birth weight	2371±136.1gr (2050-2490 gr)	3240.9±366.3 gr (2700-4000gr)	<0.001
Birth height	46.2±1.2cm (42-49)	49.4±2.1cm (45-55)	<0.001
Mothers' weight	73.5±10.7kg (52-90)	82.6±15.8kg (54-112)	=0.031
Mothers' height	159.7±5.9cm (145-172)	158.1±5.1cm (147-166)	=0.342
Mothers' BMI	28.8±3.8kg/m^2 (23.4-34.6)	33.0±5.9kg/m^2 (22.1-46.3)	=0.007
Mothers' BMI before pregnancy	24.3±3.3kg/m^2 (19.5-32.0)	28.0±5.3kg/m^2 (16.9-39.6)	=0.008

significant difference in averages of serum leptin level within two groups (P<0.001; Figures1-2).

With regard to the control group, leptin level of umbilical cord blood was 14.6±1.0 ng/ml in females and 14.7±1.7 ng/ml in males. There was no significant difference in leptin levels of umbilical cord within two genders (P=0.952). Moreover, in the case group, the leptin levels of umbilical cord blood were 9.3±2.5 ng/ml and 7.8±1.8 ng/ml in females and males, respectively. Statistically, there was no significant difference in average leptin level of umbilical cord within two genders (P=0.105, Table 1).

A significant relationship between leptin level of infants' umbilical cord and mothers' BMI in delivery time was also observed (r=0.425, P=0.004). In addition, there was a significant relationship between leptin level of infants' umbilical cord blood and their Ponderal index and birth weight (r=0.366, P=0.016 and r=0.918, P<0.001, respectively). However, a significant inverse association between mothers' serum leptin level and their infants' birth weight was observed (r=-0.794, P<0.001).

Discussion

Maternal serum leptin level rises during pregnancy and its peak is in the second trimester and remains steady until term. Leptin level of umbilical cord increases about the 34th week of pregnancy (9). In newborns, its level decreases to the lowest level in 4th week then it will rise from 4 to 14 weeks after birth (10).

Leptin level has direct relevance to body fat mass in neonates. Since fat storage significantly is taken in last weeks of pregnancy, the neonates with IUGR have a lower level of leptin in comparison with normal neonates (8, 11).

Plasma leptin concentrations reflect the amount of adipose tissue and have a positive

correlation with obesity, insulin resistance, and type 2 diabetes mellitus in adults (5). On the other hand, leptin level of maternal serum has a direct relationship with BMI before pregnancy, during childbirth, and arm circumference (11, 12). Maternal obesity does not have any effect on leptin level of umbilical cord blood ;however, exogenous corticosteroid usage by mothers rises the neonatal leptin level (13).

Neonates with small for gestational age grow rapidly in the early postnatal period due to increased insulin sensitivity. Moreover, they gain higher body fat mass during childhood and adulthood; small for gestational age is associated with the highest risk of insulin resistance in adulthood (14).

Pighetti et al. evaluated leptin level of the umbilical cord and maternal serum in 43 uncomplicated singleton pregnant women and 27 pregnant women with IUGR neonates in Italy, in 2003. Serum leptin level of mothers with IUGR neonates was higher than that of mothers with normal neonates. The leptin levels of the umbilical cord of IUGR neonates was lower than that of term neonates. In addition, maternal serum leptin level showed no association with BMI of mothers and neonatal weight in both groups ; however, there was a relation between leptin level of umbilical cord blood and neonates weight within both groups (9).

In a study conducted by Kocevska et al. on the evaluation of serum leptin and adiponectin level correlation with anthropometric parameters in 110 newborns, it was shown that leptin and adiponectin levels were positively correlated with birth weight (15).

Marsoosi et al. investigated the maternal serum, umbilical cord blood leptin, and adiponectin level at term in 22 women with normal singleton pregnancies and 22 ones with singleton growth-restricted fetuses. All women had normal pregravid body mass index. There was no significant differences in maternal serum within two groups (16) ; however, growth-restricted fetuses had significantly lower leptin and adiponectin levels in venous umbilical cord blood. The results of the current study were in line with the aforementioned findings in that leptin levels of umbilical cord was lower in IUGR neonates comparing to neonates with a normal weight ($P<0.001$).

Leptin level is proportionate with the amount of adipose tissue; therefore, it can be different regarding gestational age and metabolic status of mothers. Pardo et al. demonstrated a gender difference in 2004. Higher levels of leptin in females' neonates suggest the sexual dimorphism in relation to body composition (17) .However, in the current study, no differences regarding two genders were observed ($P=0.763$). Furthermore, in a study conducted by Cetin et al. there was no gender differences in the findings (18).

In another study performed by Zarean et al. on 40 women with singleton pregnancy and IUGR neonates and 40 pregnant women with normal fetal growth , it was demonstrated that mean fetal leptin level was lower in IUGR neonates and abnormal color Doppler sonographic indices (19).

Greece Karakosta et al, evaluated growth indices and HOMA-IR of 80 newborns and their mothers. Resistin, leptin, and insulin levels were measured in the aforementioned study. The results showed a significant positive correlation between cord blood leptin and neonatal BMI, ponderal index, HOMA-IR, and fat percentage (20).

Leptin level measurement in 100 pregnant women who gave birth to an equal number of full-term infants was performed by Miami et al. they found no correlation between maternal leptin level and maternal weight; however, positive correlation between cord serum leptin and fetus weight was observed (21). These findings were in line with the present study results in that leptin level of the umbilical cord had association with birth weight and ponderal index.

Limitations of this study are small sample size and presence of controversies for differentiation between IUGR and early gestational age of (SGA) neonates.

Conclusion

Leptin levels correlate positively with anthropometric parameters in IUGR infants. Maternal serum leptin concentrations are higher in the presence of a growth restricted fetus. It has been suggested that recombinant leptin for treatment of pregnancies with intrauterine growth restriction in clinical trials and animal studies and subsequent studies will be done with more sample size, health centers, and some other laboratory biomarkers.

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Conflicts of interests

None declared.

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