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Original Articles

Leptin Concentrations in Maternal and Umbilical Cord Blood in Relation to Maternal Weight, Birth Weight and Weight of the Placenta

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Abstract

Objective: *Leptin is a hormone which regulates adipose tissue mass of the body. Substantial increase of leptin during pregnancy and detection of leptin and leptin receptor in placenta have led to the speculation that leptin is a gestational hormone with a possible role in regulation of fetal growth. The study was done to find out whether maternal and cord blood leptin correlate with birthweight and weight of the placenta.*

Materials and methods: *A prospective cross sectional study was undertaken in the Department of Obsterics and Gynecology, Bangabandhu Sheikh Mujib Medical University from January 2005 to June 2005. The study was carried out on 39 pairs of mothers and newborns. Maternal venous blood was sampled just before delivery. Cord blood was obtained, birth weight and placental weight measurements were taken just after delivery of the baby. Serum leptin levels were measured by enzyme linked immunosorbent assay.*

Results: *Maternal serum leptin was 24.50 ng/ml (range- 13.15-45.60 ng/ml) and cord serum leptin was 6.50 ng/ml (range- 2.02-12.30 ng/ml). There was no correlation between maternal leptin and birth weight or between maternal leptin and placental weight. Cord leptin was significantly correlated with birth weight but not with placental weight. There was no correlation between maternal and cord blood leptin. There was no significant gender differences in cord blood leptin concentrations.*

Conclusions: *There may be an important role of leptin in regulation of fetal growth and development. Placenta may not be a major source of leptin in maternal and feto-placental circulation. Maternal leptin cannot be a reliable marker of fetal growth.*

Keywords: *Serum leptin, birth weight, placental weight*

Introduction

Leptin is a protein encoded by obesity gene ('ob' gene). The obesity gene was first positionally cloned in 1994.[1] In 1995 it was reported that the obese (ob/ob) mouse which is markedly hyperphagic and obese is leptin deficient due to mutation of ob gene. When given leptin, food intake is reduced and the mouse loses weight.[2]

Leptin is primarily produced by adipocytes and its principal physiologic function is to suppress body fat. Leptin produced from adipocytes exerts a negative feedback effect on hypothalamic centre for satiety. It decreases food intake and causes thermogenesis and energy expenditure. Leptin concentration in man is postitively correlated with body mass index: a measurement of adipose tissue mass. So obese individuals with increased body mass index has decreased sensitivity to leptin or in other words obesity is a leptin resistant state.[3,4]

Pregnancy is associated with profound alteration in the hormonal environment associated with adipose tissue metabolism. There is hyperinsulinemia and insulin resistance together with a large increase in the concentration of cortisol, estrogen and progesterone. Leptin is one other hormone that has a

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physiological role outside pregnancy but has increased serum levels during gestation.

Serum leptin levels are higher in pregnant women compared to body mass index matched non-pregnant women. Leptin increases as pregnancy advances peaking towards the mid third trimester.[5] At term leptin levels in pregnant women approximates those found in obese adults. After delivery there is a sharp decline in the concentration of leptin.[6] However the effect of pregnancy on leptin concentration is prolonged, with changing leptin levels present up to 2 years post partum.[7]

During pregnancy there is increase in body fat mass of the mother. However elevation of leptin levels in the pregnant women cannot be entirely explained by the increase in adiposity[5,6] . Circulating leptin load of the pregnant women has a contribution from the feto placental unit. There is evidence of leptin and leptin receptor expression in placenta.[8] Leptin concentration in maternal serum falls postpartum after placental delivery. So it can be postulated that placenta synthesizes and secrets leptin into maternal circulation.

Leptin is present in amniotic fluid, venous and arterial cord blood. Since leptin plays a central role in the regulation of appetite and energy expenditure, circulating leptin levels may provide a growth promoting signal in the fetus, which depends completely on transplacental uptake for its energy supply.

With these informations in background, the study was undertaken to define the source of leptin in fetal and maternal circulation and the role of leptin in regulation of fetal growth. We hypothesized that levels of leptin in maternal and cord blood serum correlate with birth weight and weight of the placenta.

Materials and Methods:

The study was carried out in the Department of Obstertics and Gynaecology and the Department of Biochemistry of Bangabandhu Sheikh Mujib Medical University over the period from January 2005 to June 2005. Forty six pregnant women who were to be delivered by caesarean section at 34-41 wks gestation were included. Exclusion criteria were diabetes in present or previous pregnancy, preeclampsia, chronic hypertension or other chronic medical conditions, current steroid therapy, membrane ruptured more than six hours before or any evidence of chorioamnionitis. Seven women were excluded, because blood sampling was inadequate or EIA kit did not permit, analysis of more samples. Thirty nine women sampled in this way and their newborns formed the study group.

Maternal blood was obtained from a cannulated vein 30 minutes before delivery with the women lying supine in the operation theatre. Five to ten ml blood thus extracted was collected in plain test tubes for leptin measurement. Cord blood samples were collected immediately after delivery of the baby but before delivery of the placenta. A 10 cm (minimum segment) of cord was doubly clamped immediately after delivery and before the first breath of the baby. Five ml of blood was taken by a syringe from the umbilical vein (single, large caliber, thin walled vessel) at the placental side of the umbilical cord before cutting it in between the clamps. The blood was collected in plain test tube.

The serum was separated by centrifugation (at 4000 rpm for 5 minutes), immediately frozen and stored at —35^0 c until further analysis.

Birth weight was measured within 15 minutes of birth and recorded to the nearest 100 gm using a pediatric scale (spring balance, made in China) with a pan. The newborns were weighed naked. Care was taken to ensure that the neonate was placed on the pan scale so that the weight was distributed equally about the centre of the pan. Once the neonate was lying quietly, weight was recorded to the nearest 100 gm.

Placental weight was recorded to the nearest 25gm. Umbilical cord was cut having 20cm of its length to placenta. Membranes (amnion and chorion) were trimmed by means of a scissor. The placenta was laid on the palmer surface of left hand with the maternal surface facing upwards. Extra blood was allowed to drain out. The remaining blood was absorbed on a dry mop. The placenta was then placed within a light polythene bag (<0.5gm) and weighed on the standard paediatric blance. Care was taken to place it at the centre of the pan.

For each measure, three separate measurements were taken and the mean value recorded. All measurements were made by the same person. All specimens were analysed for serum leptin level using enzyme linked immunosorbent assay (EIA kits from Caymen Chemical Company, Ann Arbor, MI48105,USA) .

Statistical analysis was done with SPSS software (SPSS for windows, version 11.0 SPSS Inc Chicago, Illionis,USA)

Results

A total of 39 women who delivered near or at term and their new borns formed the study group. The mean maternal age was 26.97±5.05 and mean maternal BMI was 28.57±7.21. Maternal and cord blood leptin levels were not normally distributed. Therefore median values were more appropriate than the mean values. The median (range) maternal serum concentration was 24.50ng/ml (Range- 13.15-45.60 ng/ml) and median (range) cord serum leptin concentration was 6.40ng/ml (Range- 2.02-12.30 ng/ml). The median (range) serum leptin in cord blood of male newborns was 6.54 ng/ml (Range-2.02-12.30 ng/ml) and the median (range) serum leptin in cord blood of female newborns was 5.84ng/ml (Range-3.02-10.81ng/ml). There was no significant difference in cord leptin concentration of male and female newborns. Cord serum leptin concentration was significantly lower than maternal serum leptin concentration. There was no significant correlation between maternal leptin and placental weight (Fig 1), maternal leptin and birth weight (Fig 2). There was a significant positive correlation between cord leptin and birth weight (Fig 3) but there was no significant correlation between cord leptin and placental weight (Fig 4). There was no significant correlation between maternal leptin and cord leptin (Fig 5).

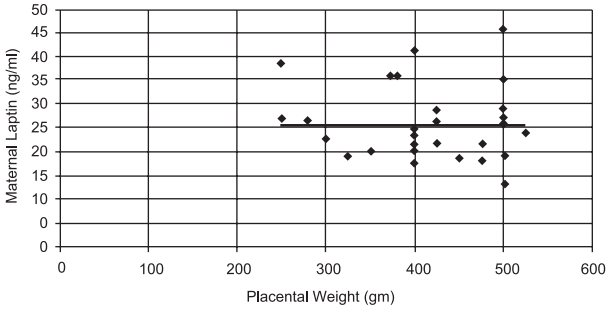

Fig.-1: *Correlation between maternal leptin (ng/ml) & placental weight (gm).*

There was no significant correlation between maternal leptin and placental weight
p(rho) 0.06, p 0.67.

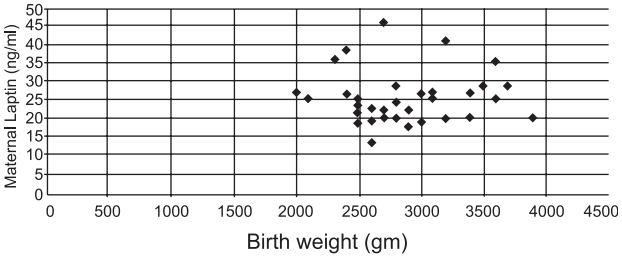

Fig.-2: *Correlation between maternal leptin (ng/ml) & birth weight (gm).*

There was no significant correlation between maternal leptin and birth weight
p(rho) 0.00, p 0.22.

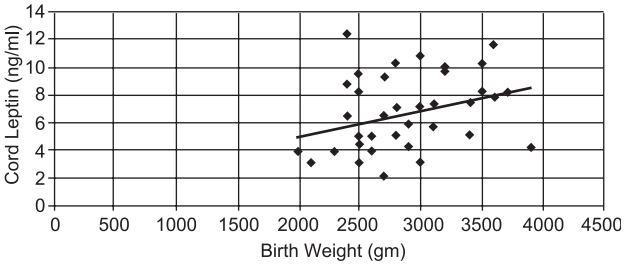

Fig.-3: *Correlation between cord leptin (ng/ml) & birth weight (gm).*

There was a significant positive correlation between cord leptin and birth weight
p(rho) 0.35, p<0.05.

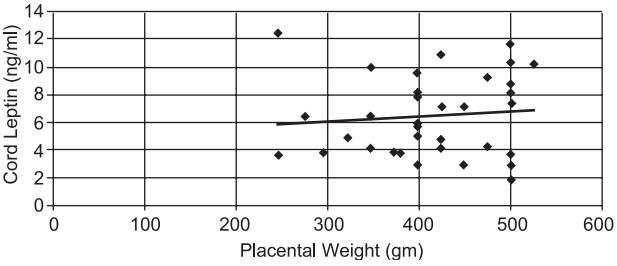

Fig.-4: *Correlation between cord leptin (ng/ml) & placental weight (gm).*

There was a significant correlation between cord leptin and placental weight
p(rho) 0.18, p 0.26.

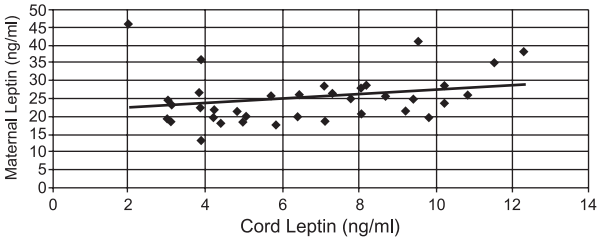

Fig.-4: *Correlation between maternal leptin (ng/ml) and cord leptin (ng/ml).*

There was no significant correlation between maternal leptin and cord leptin.
p(rho) 0.28, p 0.08.

Discussion:

The present study confirms that leptin is present in maternal and placental circulation.

The maternal serum leptin level was 24.50ng/ml (Range-13.15-45.60 ng/ml). Leptin levels in maternal blood in late gestation before delivery measured by Lakhao et al[12] was 27.9±18.1 ng/ml, by Babay et a1[13] was 19.9 ±13.5ng/ml and by Tamura et a1[14] was 22.2± 20 ng/ml. The difference in leptin levels was

most probably due to differences in study population and the method of assay.

Serum leptin values recorded in nonpregnant state by Liu et al[15] was 7.98ng/ml, in early pregnancy by Gearly et al[3] was 11.8ng/ml and on third day post partum by Schering et al[16] was 10.6 ng/ml. So values at birth are higher than those recorded in non pregnant state, early pregnancy and post partum. The finding suggests that factors other than adipose tissue mass may regulate leptin levels during gestation.

There was no significant correlation between maternal serum leptin and placental weight, a finding supported by Tamura et al[14]. Schubring et al[6] found that a significant negative correlation exists between maternal leptin and placental weight. They measured serum leptin levels by radiommunoassay in maternal blood sampled directly after delivery. Maternal leptin did not have any significant relation to birth weight and the finding is consistent with the studies of Babay et al[13] and Tamura et al[14].

In present study median leptin concentration in cord blood was 6.4ng/ml (Range 2.021-12.30 ng/ml). Different studies[3,6,13,14,17,18] showed leptin concentrations in cord blood of the newborns between 4 and 10 ng/ml. The exception was Matsuda et a1[14] who reported cord leptin concentration 14.4ng/ml. This was a relatively early study done in 1997 using radioimmunoassay for leptin assessment. Median leptin level in intrauterine growth restricted babies were 2.3ng/ml and 3.7ng/ml according to Jaquet et al[17] and Varvarigou et al[18] .These values are lower than that in our study. This finding supports the positive correlation of cord leptin with neonatal fat mass.

This study shows that cord leptin levels are significantly lower than maternal leptin levels($p<0.001$).The relatively large gradient of serum leptin level between maternal and venous blood supports the fact that placenta acts as a barrier against the large (16KD) molecules of leptin from maternal to fetal circulation.

There was a significant positive correlation ($p<0.05$) between cord blood leptin and birth weight. A similar positive correlation between cord leptin and birth weight is found by all other studies[2,3,6,9,13-18]. Leptin is synthesized in adipocytes and acts as a satiety signal from adipose tissue mass of the body to hypothalamus. In view of the significant correlation of cord serum leptin and birth weight, it can be speculated that fetal adipose tissue is a major source of leptin in feto placental circulation and leptin is involved in fetal growth in last trimester, when maximum fetal fat mass is laid down. Because energy balance in a growing fetus must be positive, a low concentration of serum leptin in low birth weight babies is physiologically suitable for fetal growth.

Most of the previous studies[12,13,17,18] found significant positive correlation between cord blood leptin and placental weight. But Matsuda et a1(n=82)[19] and our study found no significant correlation between cord serum leptin and placental weight. One reason for the lack of correlation in this study may have been the difference in study population and sample size. Otherwise it may be possible that neonatal fat mass, not the placenta is the major source of leptin in feto placental circulation.

There was no significant correlation between maternal leptin and cord leptin concentrations. This finding is similar to the findings of Yilditz et al[20] Oktem et al[21] and Laml et al[22]. Absence of correlation between maternal and cord leptin indicates that leptin in feto-placental circulation is independent of material leptin production and may be derived from fetus and/or placental tissue. Several studies[13,14,18] found significant correlation between maternal and cord leptin. All of them had large sample sizes and used radio immunoassay for leptin estimation.

Our study did not find any significant difference in leptin concentration of female and male newborns. This finding is in compliance with the findings of Geary et al[3], Shekhawat et al[2] and Tamura et al[14]. However Matsuda et al[19] and Babay et al[13] demonstrated significantly higher level of leptin in the female newborns than in the male newborns. The discrepant findings are difficult to explain. It may be the result of small number of studied women, gestation at which cord leptin assessment was done and the method of assay used when measuring leptin.

We acknowledge that the relatively small number of women in our study may affect the reliability of correlation attributed. The small sample size was due to limited availability of the expensive EIA (enzyme-linked immunometric assay) kit for leptin assay. Further studies are needed to define the role of leptin more clearly and to decide whether leptin might serve as a diagnostic or therapeutic tool in obstertrics.

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References :

1. Zang Y, Proenca R, Maffei M, Barone M, Leapold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994; 372:425-432.
2. Shekhawat PS, Garland JS, Sheepuri C, Mich GJ, Shoshidharan P, Petz CS et a1. Neonatal cord blood leptin : its relationship to birth weight, body mass index, maternal diabetes and steroids. Pediatr Res, 1998;43:338-343.
3. Geary M, Pringle PS, Persaud M, Wilshin J, Handmarsh PS, Rodek CH et a1. Leptin concentrarion in maternal serum and cord blood: relationship to maternal anthropometry and fetal growth. Br J Obstet Gynaecol, 1999;106:1054-1060
4. Rosenbaum M, Leibel RL. The role of leptin in human physiology. N Engl J Med 1999; 341:913-914.
5. Butt NF, Hopkinson JM, Nicolson MA. Leptin in human reproduction: serum leptin levels in pregnant and lactating women. J Clin Endocrinol Metab, 1997; 82:585-589.
6. Schubring C, Kiess W, Englaro P, Roscher W, Dotsch J, Hanitsch S et a1. Levels of leptin in maternal serum, amniotic fluid and arterial and venous cord blood: relation to neonatal and placental weight. J Clin Endocrinol Metab, 1997;82:1480-1483.
7. Teppa RJ, Ness RB, Crombleholm WR, Robertson JM. Free leptin is increased in pregnancy and further increased in pre-eclampsia. Metabolism, 2000;49:1043-1048.
8. Yura S, Sagawa N, Mise H, Mari T, Masuzaki H, Ogawa Y et a1. A positive umbilical venous arterial difference of leptin level land its rapid decline after birth. Am J Obstet Gynecol, 1998;178:926-930
9. Martinez- Abundis E, Gonzaliz-Ortez M, Gonzales-Pascel S. Serum leptin levels and the severity of preeclampsia. Arch Gynecol Obstet, 2000;264:1-73
10. Principles of Nutritional Assessment. In Nutritional Science. Gibson RS. Oxford, London. Oxford University press 1990, pp 155-208.
11. Lage EM, Driscoll SG, Murro H. Qualitative studies of human placenta. Biol Neonat, 1973;23:231-257
12. Lakhao GR, Nazir K, Chundrigar T, Zabeen N, Qureshi MA. Serum leptin levels in pregnant Pakistani females: relationship with body mass index and placental weight. J Pak Med Assocs, 2001;51-32-36
13. Babay ZA, Warsy AS, E1 Hazmi MA, Adder MH. Leptin level in pregnant mothers at term and cord blood and the effect of newborn gender. Saudi Med J; 2004:25:212-214
14. Tamura T, Goldenberg RL, Johnston KE, Clever SP. Serum Leptin concentration during pregnancy and their relationship to fetal growth. Obstet Gynecol 1998;91:389-95
15. Liu Y, Wang W, Helomi M. Serum leptin levels in normal pregnant women and their babies. Zhonghua Fu Chan Ki Zhi 2000;35:392-395
16. Schubring C, Englaro P, Siebler T, Bluin WF, Demirakca T Kratch J et a1. Longitudinal analysis of maternal serum leptin level during pregnancy, at birth and upto six weeks after birth: relation to body mass index, skinfolds, sex steroids and umbilical cord leptin levels.Horm Res 1998;50:276-283
17. Jaquet D, Leger J, Levy Marchal C, Oury JF, Czerichow P. Ontogeny of leptin in human fetus and newborns: Effect of intrauterine growth retardation on serum leptin concentration. J Clin Endocrinol 1999;50:177-183
18. Varvarigou A, Mantzoros CS, Barbatis NG. Cord blood leptin concentration in relation to intrauterine growth. Clin Endocrinol 1999;50:177-183
19. Matsuda J, Yokota I, Iida M, Murakami T, Naito E, Ito M et a1. Serum leptin concentration in cord blood: relationship to birth weight and gender. J Clin Endocrinol Metab, 1997;82:1682-1644
20. Yilditz L, Avci B, Ingee M. Umbilical cord and maternal blood leptin concentrations in intrauterine growth retardation. Clin Chem Lab Med, 2002;40:1114-1117
21. Oktem O, Dedeoglu N, Oymuk Y, Sezen D, Koksal L, Peken T et al. Materenal serum, amniotic fluid and cord leptin levels at term: their correlation with fetal weight. J Perinatal Med, 2004;32:266-277
22. Laml T, Hartmann BW, Rucklinger E, Preyer O, Sorgi G, Wagenbicher P. Maternal serum leptin concentration do not correlate with cord blood leptin concentrations in normal pregnancy. J Soc Gynecol Invest, 2001;8:43-47