

Increased leptin concentration in preterm infants of pre-eclamptic mothers

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Abstract

Aim—To study the effect of maternal pre-eclampsia on cord plasma leptin concentrations in preterm infants.

Methods—Leptin concentration was analysed in cord plasma of 74 preterm infants, gestational age 24 to 32 weeks. Of these, 14 were born to pre-eclamptic mothers, in 10 intrauterine growth retardation (IUGR) was present, and 59 had been exposed antenatally to corticosteroids.

Results—The mean (SD) concentration of cord plasma leptin was 1.31 (0.88) µg/l. A significant correlation was found between leptin concentration and gestational age ($r = 0.336$; $p = 0.0037$). Leptin levels were higher in infants of pre-eclamptic mothers ($p = 0.0007$), in those with IUGR ($p = 0.0005$), and in infants exposed antenatally to corticosteroids ($p = 0.02$). In multiple regression analysis, leptin was associated with gestational age and maternal pre-eclampsia (both $p < 0.05$), but not with antenatal corticosteroids.

Conclusions—Increased fetal leptin in maternal pre-eclampsia may reflect a physiological adaptation to fetal stress such as hypoxia.

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Keywords: leptin; preterm infants; pre-eclampsia; hypoxia

Leptin is a recently discovered primarily adipose tissue derived hormone, first recognised for its anti-obesity action in experimental animals.¹⁻⁴ Leptin receptors are expressed in numerous fetal tissues and the leptin gene is expressed in a number of mouse fetal tissues, suggesting a role for leptin in fetal development.⁵⁻⁷ In humans, immunoreactive leptin is already present in the fetoplacental circulation at 18 weeks of gestation and its concentration increases appreciably after 34 weeks of gestation.⁸ At birth, leptin concentrations in cord blood correlate closely with birth weight in term newborn infants; infants who are large for dates have high concentrations of leptin, and infants with intrauterine growth retardation (IUGR) have low concentrations of leptin, suggesting that fat mass may be a major determinant of leptin secretion in utero.⁸⁻¹¹

Data on the physiology of leptin in prematurity are sparse. Antenatal exposure to corticosteroids has been reported to be associated with increased leptin levels in cord blood in premature infants in some studies,¹² and no effect of the type of fetal growth on cord blood

leptin concentrations was observed by others.⁸ In pre-eclampsia, maternal plasma leptin concentrations are increased, possibly because of placental production of the hormone under hypoxic conditions.¹³ The effects of pre-eclampsia on fetal concentrations of leptin are not known.

Given the putative role of leptin as a regulator of fetal development, it is important to identify factors regulating leptin metabolism in utero.¹⁴ In the present study, we measured leptin concentrations in cord plasma of 74 small preterm infants, gestational age below 32 weeks, to find out which factors are associated with leptin levels. Specifically, we examined whether leptin concentrations are associated with gestational age and birth weight of the infant, and whether maternal pre-eclampsia results in altered leptin levels in preterm infants.

Patients and methods

PATIENTS

We studied 74 preterm infants, born from consecutive preterm deliveries in the Department of Obstetrics and Gynaecology of Helsinki University Central Hospital, at gestational age 24.1–32 weeks and birth weight 385–2100 g (table 1). The upper limit of gestational age was chosen to minimise the effect of accumulating fetal fat mass as a source of leptin.¹⁵ Gestational age was determined by ultrasound during the first trimester. Relative birth weight (weight SD) was determined by reference to a Finnish newborn population of 74 766 singletons born in 1978–1982.¹⁶ Fourteen of the infants were born to mothers who had established proteinuric pre-eclampsia (table 2). IUGR (weight < -2 SD) was present in 10 infants (table 2); of the infants with IUGR, five were born to pre-eclamptic mothers and two each from two triplet pregnancies without pre-eclampsia. Four pairs of twins and six infants from triplet pregnancies were included in the study. In 59 cases the mother had received antenatal treatment with corticosteroids, in the form of two doses of 12 mg betamethasone with a 12 hour interval, more than 12 hours before delivery (mean four days seven hours, SD three days 17 hours, range 12 hours to 16 days) (table 2). Body mass index (BMI) was determined as weight (kg)/length (m)². Of the infants studied, 32 were delivered vaginally and 42 by caesarean section. Twelve mothers smoked at least five cigarettes a day. Infants of diabetic mothers and infants with malformations were excluded.

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Table 1 Data on 74 preterm infants

Male/female	37/37
Gestational age (weeks)	28.7 (2.4)
Weight (g)	1180 (396)
Length (cm)	37.5 (4.0)
BMI (kg/m ²)	8.5 (1.3)
Placenta (g)	451 (180)

Where applicable, values are mean (SD).
BMI, body mass index.

METHODS

Blood samples from the umbilical vein were taken at birth into EDTA tubes. The tubes were centrifuged at 1000 *g* for five minutes, and plasma was stored at -20°C until analysis. Leptin was determined by radioimmunoassay (Linco Research, St Charles, Missouri, USA).¹⁷ The detection limit of this assay is 0.26 $\mu\text{g/l}$ in our laboratory as determined by calculating 2 standard deviations (mean of 13 assays) from the zero reference point, and the intra-assay and interassay coefficients of variation at low concentration (2.8 $\mu\text{g/l}$) are 4.7% and 2.6% and at medium concentration (15.6 $\mu\text{g/l}$) 3.8% and 2.2% respectively.

STATISTICAL ANALYSIS

Comparisons between grouped items were performed using an unpaired *t* test. Grouped items (pre-eclampsia, antenatal steroids, smoking, etc) were categorised as either no = 0 or yes = 1. Leptin concentrations were logarithmically transformed to normalise the distribution. Simple and multiple regression analysis were used. $p < 0.05$ was considered statistically significant. The results are given as mean (SD) and as median and interquartile range. All calculations were carried out with StatView 4.1 (Abacus Concepts Inc, Berkeley, California, USA).

ETHICS

The study was approved by the ethics committee of the Department of Obstetrics and Gynaecology, Helsinki University Central Hospital.

Results

Immunoreactive leptin was detectable in cord plasma samples from all preterm infants. Median leptin concentration was 1.01 (interquartile range 0.81–1.43) $\mu\text{g/l}$. A significant correlation was found between cord blood leptin and gestational age ($r = 0.336$, $p = 0.0037$), but not with birth weight ($r = 0.155$), relative

birth weight ($r = 0.211$), BMI ($r = 0.186$), placental weight ($r = -0.108$), Apgar score ($r = 0.197$), or cord artery pH ($r = -0.104$).

Significantly higher leptin levels were found in infants of pre-eclamptic mothers (median 1.80 (1.11–2.08) *v* median 0.93 (0.79–1.29) $\mu\text{g/l}$; $p = 0.0007$), in infants with IUGR (median 1.80 (1.34–3.04) *v* median 0.93 (0.74–1.03) $\mu\text{g/l}$; $p = 0.0005$) and in those exposed to antenatal steroids (median 1.18 (0.85–1.73) *v* median 0.76 (0.66–0.95) $\mu\text{g/l}$; $p = 0.02$). Maternal smoking was not observed to affect cord blood leptin concentrations. Infants of pre-eclamptic mothers had significantly smaller placentas than other infants (322 (118) *v* 451 (180) g; $p < 0.05$).

When gestational age, presence of pre-eclampsia, and exposure to antenatal steroids were included as independent determinants of leptin concentration in multiple regression analysis, gestational age (partial $r = 0.257$, $p = 0.02$) and pre-eclampsia (partial $r = 0.32$, $p = 0.004$) were significantly and independently associated with leptin, whereas exposure to steroids remained non-significant (partial $r = 0.103$, $p = 0.39$).

When infants with IUGR and infants born to pre-eclamptic mothers were excluded, simple regression analysis of the 55 remaining infants showed significant correlations between cord leptin levels and gestational age ($r = 0.360$, $p = 0.0069$), BMI ($r = 0.424$, $p = 0.0033$), and birth weight ($r = 0.487$, $p = 0.0002$). In these 55 infants, cord plasma leptin concentration of those exposed to antenatal steroids ($n = 41$) did not differ from those not exposed (median 0.94 (0.81–1.30) *v* median 0.75 (0.65–0.86) $\mu\text{g/l}$, $p = 0.09$).

Discussion

Our data show that, in preterm infants, maternal pre-eclampsia is associated with increased leptin concentration and that pre-eclampsia is an independent determinant of leptin levels. Pre-eclampsia has recently been shown to increase maternal leptin levels, but no such association has yet been reported in the fetus.¹³ Reduced uteroplacental blood flow leading to fetoplacental hypoxia is important in the pathogenesis of IUGR—for example, in pre-eclampsia.¹⁸ Mise *et al*¹³ postulate that elevated maternal plasma leptin concentration in pre-eclampsia is caused mostly by the augmentation of placental production of leptin in response to hypoxia. However, in our study,

Table 2 Infants with and without maternal pre-eclampsia, intrauterine growth retardation (IUGR), and exposure to betamethasone

	Pre-eclampsia		IUGR		Betamethasone	
	Yes ($n = 14$)	No ($n = 60$)	Yes ($n = 10$)	No ($n = 64$)	Yes ($n = 59$)	No ($n = 15$)
Male/female	10/4	27/33	5/5	32/32	29/30	8/7
Gestational age (weeks)	29.4 (1.5)	28.5 (2.5)	29.6 (2.6)	28.5 (2.3)	29.1 (2.1)‡	27.0 (2.7)
Weight (g)	1048 (221)	1211 (421)	940 (367)†	1218 (389)	1211 (379)	1060 (450)
Length (cm)	36.5 (2.5)	37.5 (3.9)	36.0 (4.0)	37.5 (3.7)	38.0 (3.5)‡	35.0 (4.0)
BMI (kg/m ²)	7.7 (0.4)*	8.6 (1.4)	7.2 (0.7)†	8.6 (1.3)	8.7 (1.2)‡	7.7 (1.4)
Placenta (g)	322 (118)*	481 (179)	358 (157)	465 (180)	456 (191)	429 (130)

Where applicable, values are mean (SD).

* $p < 0.05$ *v* infants without maternal pre-eclampsia; † $p < 0.05$ *v* infants without IUGR; ‡ $p < 0.05$ *v* infants without exposure to antenatal steroids.

BMI, body mass index.

there was no correlation between cord plasma leptin concentration and Apgar score or cord artery pH. In accordance with this, *in vitro* data indicate that a significant increase in leptin secretion does not occur until 72 hours of hypoxia.¹³

In our study, preterm infants with IUGR, with or without pre-eclampsia, had higher cord leptin levels than those with normal growth. This is in contrast with that observed in most, but not all, studies on full term infants.⁹⁻¹² Interestingly, in our study, when infants with IUGR and infants of pre-eclamptic mothers are excluded from the analysis, there is a correlation between birth weight and leptin concentration similar to that observed in term infants. Thus, it is possible that pre-eclampsia, IUGR, and the concomitant increase in leptin concentration may interfere with the association between leptin and birth weight. The overlap between groups of infants with IUGR and maternal pre-eclampsia makes it difficult to differentiate the effects of these two clinical conditions on leptin metabolism. Our finding of preterm infants with IUGR having higher leptin concentrations agrees with the study of Shekhawat *et al.*,¹² whereas no such relation was found in a study by Jaquet *et al.*⁸ However, the possible connection of pre-eclampsia with fetal leptin concentrations was not examined in those studies.⁸⁻¹² Moreover, in term infants, maturity and fetal fat mass may interfere with the effects of pre-eclampsia on fetal leptin.

In this study, the weight of the placenta did not correlate with leptin concentration as in term infants.⁹ In fact, infants of pre-eclamptic mothers had smaller placentas and increased leptin concentration. This finding may be explained by the hypothesis that hypoxia augments placental production of leptin.¹³

Hypoxia and IUGR, the fetal hallmarks of pre-eclampsia, are associated with increased morbidity.¹⁸⁻¹⁹ The roles of leptin in haematopoiesis, fetal erythroid development, and angiogenesis raise the possibility that relative hyperleptinaemia is a part of the fetal adaptation to hypoxia.⁵⁻²⁰⁻²² In adults, plasma leptin levels are increased in survivors of acute sepsis, and leptin has been claimed to be a stress related hormone.²³ Thus it may also play a role in response to severe stress states in the fetus, such as pre-eclampsia.

Shekhawat and co-workers¹² found that the use of antenatal steroids was associated with increased cord plasma leptin levels in preterm infants. The mean gestational age in their study was 32 weeks, and infants of diabetic mothers were included. Unfortunately, no weight data were available on the infants exposed to antenatal steroids, making the interpretation of their results difficult. In our infants, we also found an association between the use of antenatal steroids and high cord plasma leptin. However, this correlation disappeared when infants with IUGR and infants born to mothers with pre-eclampsia were excluded. Moreover, in multiple regression analysis, antenatal exposure to steroids was not an independent determinant of leptin lev-

els. Therefore it is possible that the effect of antenatal steroids on leptin production is primarily dependent on maturity. So far, in adults also the effects of corticosteroids on leptin levels are disputed.²⁴⁻²⁵

We found that maturity, defined by gestational age, is a significant determinant of cord plasma leptin levels in preterm infants. This is in accordance with previous studies performed in preterm and term infants.⁸⁻¹² This may be related to the accumulation of adipose tissue in the fetus during late gestation.¹⁵ Given the presence of mRNA for leptin receptor isoforms in the lung, liver, kidneys, and haematopoietic cell lines of human fetuses, these data suggest that leptin may participate in the regulation of fetal growth and development.⁵

In conclusion, gestational age is an important determinant of cord plasma leptin levels in preterm infants. Leptin levels are increased in pre-eclampsia and IUGR, which may be part of the physiological adaptation to stress during the fetal period.

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Neonatal jaundice in antiquity

Since antiquity, jaundice was considered by Jewish sages, as can be seen from their discussions in the Talmud on the Biblical commandment to circumcise every male Jewish infant at 8 days of age, provided that he is medically fit. They were very concerned about jaundice. Today it is recognised that considerably elevated plasma bilirubin levels can have toxic effects on the brain, as well as other organs, and raised levels may indicate septicaemia, urinary infection, or hepatitis.

“Yerakon” is the classical Hebrew word for jaundice in newborn infants. In the Talmud’s commentaries, it is suggested that the word is derived from “yarok” which means green in Aramaic but can also be translated as yellow or pallor in both humans and vegetables. In the warnings on punishment for sin in Deuteronomy, “yerakon” (or yellow blight) is one among several punishments that afflict man.

In the Greek translation of the Bible (the Septuagint), written in Alexandria in the 2nd and 3rd centuries BC, the word “yerakon” has been written as “ochre” and sometimes as “ikterus”. In the Vulgate Latin translation can be found the term “aerugo” which means the colour of gold, and in modern Hebrew it is called “zahavit” from “zahav” which means gold. In modern Arabic, it is called “warrak”, equivalent to the Hebrew term “yarok”.

Circumcision is among the oldest surgical procedures practised by Jews and Moslems for religious reasons. Moses Maimonides (1138–1204) and Joseph Caro (1488–1575) codified the procedure of circumcision based on the Talmudic ruling. It was established that under normal conditions the operation was performed on the eighth day of life, but was postponed until full recovery if there was any evidence of illness, such as jaundice.

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