

Leptin and metabolic hormones in preterm newborns

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Abstract

Aim—To investigate the inter-relation between leptin and other metabolic hormones in preterm and term infants and to explore whether a functional “adipoinsular axis” might exist in preterm newborns.

Methods—A total of 140 preterm and term newborns were prospectively recruited and categorised according to gestation length. Blood samples were taken at 24 hours (day 1), and on day 4–5 of life.

Results—Serum leptin, cortisol, free thyroxine, and plasma ACTH on day 1 were significantly higher in term than in preterm infants. The relation between serum leptin and gestation followed a non-linear pattern; the slope of the curve began to increase steeply between 33 and 35 weeks gestation. Serum leptin on day 1 was significantly associated with serum insulin, insulin:glucose ratio, and plasma ACTH in infants less than 34 weeks gestation; serum leptin on day 1 and day 4–5 were significantly correlated with insulin:glucose ratio in infants 34 or more weeks gestation. Significant changes in the pattern of metabolic hormones were observed in the first week of life. Serum insulin and plasma glucose were significantly increased between day 1 and day 4–5; serum leptin was significantly decreased.

Conclusions—The circulating leptin concentration increases markedly after 34 weeks gestation and bears a close temporal relation with the exponential accumulation of body fat mass during that period. The inter-relation between serum leptin and insulin or insulin:glucose ratio before and after 34 weeks gestation indicates that the “adipoinsular axis” is likely to be functional in early (<34 weeks gestation) intrauterine life. The rapid decline in the circulating concentrations of leptin after birth may be of physiological advantage to preterm and term newborns by limiting their body energy expenditure and conserving nutritional reserves for subsequent growth and development.

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Keywords: leptin; adipoinsular axis

Leptin, a newly discovered adipostatic hormone, has been found to play an important role in the regulation of body lipid metabolism, feeding behaviour, and energy homeostasis.¹⁻⁴ Recent evidence suggests that circulating leptin in children and adults can be influenced by

metabolic hormones such as corticosteroids and insulin,⁵⁻⁷ systemic infection,⁸ and different stages of physical and pubertal development.⁹⁻¹⁰ Yet little is known concerning the role of leptin in fetal development and the control of body composition in preterm and term infants. Glucose is the principal source of energy for the human fetus but there is an abrupt change in nutrient supply immediately after birth with lipid contributing more than 60% of the total body energy expenditure.¹¹ Failure to increase the adipose tissue mass during gestation causes increased neonatal morbidity.¹²⁻¹³ As fetal growth does not follow a linear pattern throughout the course of pregnancy and fat is predominantly accreted in the last trimester of gestation,¹⁴ the understanding of the interaction of leptin with other metabolic hormones in preterm and term infants may provide valuable insights into this important physiological phenomenon. Our recent study on leptin and metabolic hormones in normal term infants and infants of diabetic mothers suggests that a functional “adipoinsular axis” might exist in term newborns.¹⁵ Whether the axis is active in preterm infants remains to be determined.

This study was undertaken to investigate the inter-relation between leptin and other metabolic hormones including insulin, corticotropin (ACTH), cortisol, thyroid stimulating hormone (TSH), and free thyroxine (FT4) in preterm (less than 37 weeks gestation) and term (37 weeks or more gestation) infants. The change in the pattern of leptin and other metabolic hormones in the first few days life was also determined. The results may provide important information about the ontogeny of leptin in human infants and the understanding of leptin and other metabolic hormones in the regulation of the fetal body weight and composition.

Patients and methods

STUDY POPULATION

A total of 140 newborn infants admitted to the neonatal unit were prospectively recruited between March 1998 and May 1999. Enrolled term (gestational age 37 weeks or more, n = 43) and near term infants (gestational age between 32 and 36 weeks, n = 54) were newborns with increased risk of perinatal infection, but were subsequently proven to be non-infected. Preterm infants with gestational age less than 32 weeks (n = 43) or birth weight below 2300 g were routinely admitted to the neonatal unit for clinical assessment and monitoring. Gestational age was assessed by the mother's last menstrual period, early ultrasound dating, and the new Ballard Score

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Table 1 The clinical characteristics of preterm and term infants

	Group 1 (n = 43)	Group 2 (n = 54)	Group 3 (n = 43)	Comparison between the three groups
Gestation (weeks)*	29.6 (28.0–30.4)	34.2 (33.3–35.3)	40.0 (38.7–40.6)	Group 3 > group 2 > group 1
Birth weight (g)*	1180 (970–1410)	1973 (1700–2110)	3300 (2900–3970)	Group 3 > group 2 > group 1
Length (cm)*	37.3 (35.5–40.2)	43.6 (42.1–44.6)	49.9 (47.8–52.1)	Group 3 > group 2 > group 1
BMI (kg/m ²)*	8.2 (7.6–9.4)	10.3 (9.5–11.0)	13.8 (12.8–15.2)	Group 3 > group 2 > group 1
Placental weight (g)*	305 (300–400)	415 (350–495)	550 (500–600)	Group 3 > group 2 > group 1
Male/female (n)	27 : 16	25 : 29	23 : 20	—
Mode of delivery (n)*** (normal : caesarean section : forceps or ventouse)	16 : 26 : 1	25 : 28 : 1	21 : 13 : 9	—
Maternal smoker (n)	1	3	1	—
Rupture of membrane > 24 h (n)	10	12	7	—
Maternal pre-eclampsia (n)	9	9	0	—
Antenatal dexamethasone (doses)	2 (2–4)	2 (0–4)	—	—
Time between last dose of dexamethasone and delivery (h)	40 (17–75)	68 (7–141)	—	—
Apgar scores*				
at 1 min	6 (5–8)	8 (7–9)	9 (8–9)	Groups 2 and 3 > group 1
at 5 min	9 (8–9)	10 (9–10)	10 (9–10)	Groups 2 and 3 > group 1
Arterial cord blood pH	7.29 (7.22 to 7.32)	7.29 (7.24 to 7.33)	7.27 (7.23 to 7.30)	—
Base excess	-5.9 (-8.7 to -3.9)	-5.9 (-7.2 to -3.9)	-6.5 (-7.8 to -3.8)	—
Mechanical ventilation (n)*				
on day 1	38	9	0	—
on day 4–5	26	3	0	—
Oxygen requirement (Fio ₂)*				
on day 1	0.23 (0.21–0.30)	0.21 (0.21–0.21)	0.21 (0.21–0.21)	—
on day 4–5	0.21 (0.21–0.23)	0.21 (0.21–0.21)	0.21 (0.21–0.21)	—

Results expressed as median (interquartile range). *p < 0.05, ***p < 0.001; (> significantly greater).

examination.¹⁶ Exclusion criteria were similar to those of our previous study.¹⁵

FEEDING REGIME

Infants less than 32 weeks gestation were routinely commenced on intravenous dextrose after birth to prevent hypoglycaemia. Very low birth weight infants had enteral feeding introduced between day 5 and 7 of life and the quantity of milk was cautiously stepped up by 0.5–1 ml/hour/day, depending on tolerance. Near term infants had enteral feeding started earlier between day 1 and 5 of life; the rate of milk increment varied between 2 and 10 ml/feed/day, depending on gestation. Term infants were usually commenced on full enteral feeding soon after delivery.

BLOOD SAMPLES AND HORMONAL ASSAYS

The first blood samples were collected when the infants were about 24 hours of age (day 1), and a second sample was obtained on day 4–5 of life. Details of specimen collection, transportation, processing, storage, and methods of hormonal assay have been described previously.¹⁵

DATA COLLECTION AND STATISTICAL ANALYSIS

Demographic and clinical data were prospectively collected (see table 1). Ethical approval of the study was granted by the Clinical Research Ethical Committee of the Chinese University of Hong Kong, and informed

parental consent was obtained before commencement of the test. The statistical tests and computer software used in this study were similar to those described in our previous study.¹⁵ In addition, the Wilcoxon rank sum test was used to compare serum leptin and serum/plasma concentrations of other metabolic hormones between day 1 and day 4–5. Statistically significant or near significant (p < 0.15) parameters associated with leptin were further subjected to the generalised additive models for multivariate analysis,¹⁷ using the S-Plus statistical program (version 4.3, Math-Soft Inc., Seattle, Washington). This non-parametric mathematical technique enables us to develop models which more accurately represent the relation between multivariate predictor variables and the outcome variable.

Results

SUBGROUP ANALYSIS

Groups 1 (preterm), 2 (near term), and 3 (term) represented infants who were less than 32, 32–36, and 37 or more weeks gestation, respectively. Table 1 summarises the clinical characteristics of these infants. Gestational age, birth weight, body length, body mass index (BMI), and placental weight were significantly higher in older gestation infants, whereas Apgar scores at 1 and 5 minutes were significantly lower in preterm infants. In addition, significantly more preterm infants were born by caesarean section and required

Table 2 Blood hormone and plasma glucose concentrations on day 1 of life

	Group 1 (n = 43)	Group 2 (n = 54)	Group 3 (n = 43)	Comparison between the three groups
Leptin (ng/ml)*	0.05 (0.05–0.25)	0.23 (0.07–0.46)	1.7 (0.48–6.33)	Group 3 > groups 1 and 2
ACTH (pmol/l)*	3.3 (2.7–3.9)	5.4 (3.9–9.5)	7.8 (4.9–18.3)	Group 3 > group 1; group 2 > group 1
Cortisol (nmol/l)†	145 (89–311)	228 (142–354)	298 (205–415)	Group 3 > group 1
Insulin (pmol/ml)	30.1 (13.9–52.4)	27.7 (12.9–51.7)	23.0 (7.2–53.1)	—
Glucose (mmol/l)†	5.3 (3.8–7.4)	4.5 (4.1–5.4)	4.1 (3.7–4.7)	Group 1 > group 3
Insulin:glucose ratio	4.7 (2.6–9.2)	6.0 (2.8–10.6)	5.5 (2.2–10.8)	—
FT4 (pmol/l)*	10.9 (6.7–15.6)	22.5 (16.7–27.9)	28.6 (23.7–33.3)	Group 3 > group 2 > group 1
Cord TSH (mIU/l)	5.2 (3.0–8.2)	6.4 (4.8–7.6)	4.9 (3.9–7.2)	—

Results expressed as median (interquartile range); *p < 0.05, †p < 0.005; (> significantly greater).

Table 3 Blood hormone and plasma glucose concentration on day 4–5 of life

	Group 1 (n = 43)	Group 2 (n = 54)	Group 3 (n = 43)	Comparison between the three groups
Leptin (ng/ml)*	0.11 (0.05–0.24)	0.13 (0.05–0.35)	0.77 (0.25–2.33)	Group 3 > groups 1 and 2
ACTH (pmol/l)	3.9 (3.2–6.5)	5.4 (3.2–8.1)	6.1 (4.0–9.4)	—
Cortisol (nmol/l)*	201 (99–322)	243 (152–349)	134 (90–260)	Group 2 > group 3
Insulin (pmol/ml)	42.4 (15.1–73.9)	35.6 (19.9–56.0)	49.5 (26.5–92.6)	—
Glucose (mmol/l)***	6.1 (5.1–7.2)	5.2 (4.4–6.1)	4.9 (4.3–5.4)	Group 1 > groups 2 and 3
Insulin:glucose ratio	6.1 (3.3–11.6)	7.2 (4.9–11.0)	10.4 (5.6–18.3)	—
FT4 (pmol/l)*	11.5 (6.6–16.7)	18.6 (15.7–22.2)	24.0 (18.9–27.3)	Group 3 > group 2 > group 1

Results expressed as median (interquartile range); *p < 0.05, ***p < 0.001; (> significantly greater).

mechanical ventilation or oxygen supplementation on day 1 and day 4–5.

Table 2 summarises the blood hormone and plasma glucose concentrations on day 1. Serum leptin, cortisol, FT4, and plasma ACTH were significantly higher in older gestation infants, whereas plasma glucose was significantly lower in group 3 than in group 1.

Table 3 summarises the blood hormone and plasma glucose concentrations on day 4–5. Serum leptin and FT4 remained significantly

higher in older gestation infants, whereas plasma glucose was significantly lower in groups 2 and 3 than in group 1. Serum cortisol was significantly higher in group 2 than in group 3 on day 4–5.

OVERALL ANALYSIS

When the results were pooled and analysed, serum leptin on day 1 was significantly correlated with gestation, birth weight, body length, BMI, and placental weight (p < 0.001, r > 0.36). However, when these parameters were subjected to the generalised additive models for multivariate analysis, only female sex and gestation (p < 0.01), birth weight (p < 0.001), or BMI (p < 0.02) were found to be significantly associated with serum leptin. Plasma ACTH, serum cortisol, and FT4 on day 1 were also significantly correlated with gestation (p < 0.01, r > 0.25), placental weight (p < 0.01, r > 0.24) and the aforementioned anthropometric parameters (p < 0.05, r > 0.20). In addition, serum cortisol on day 1 was significantly higher in infants born by normal or instrumental delivery than by caesarean section (p < 0.05), and in those whose mother had rupture of membranes longer than 24 hours (p < 0.05).

Similarly, gestation, birth weight, body length, BMI, and placental weight on day 4–5 were significantly correlated with serum leptin (p < 0.001, r > 0.41) and FT4 (p < 0.001, r > 0.41). When these parameters were subjected to the generalised additive models for multivariate analysis, only female sex and gestation (p < 0.005), birth weight (p < 0.02), or BMI (p < 0.002) were significantly associated with serum leptin. Both plasma ACTH and serum cortisol on day 4–5 were significantly higher in infants whose mother had rupture of membranes longer than 24 hours (p < 0.05 and p < 0.01, respectively).

As the relation between serum leptin and gestation followed a non-linear pattern (fig 1) and the slope of the curve began to increase steeply between 33 and 35 weeks gestation, we assessed the inter-relation between serum leptin and other metabolic hormones before and after 34 weeks gestation. Serum leptin on day 1 was significantly associated with serum insulin, insulin:glucose ratio, and plasma ACTH in infants less than 34 weeks gestation, whereas serum leptin on day 1 and day 4–5 was significantly correlated with insulin:glucose ratio in infants 34 or more weeks gestation (table 4). Similarly, serum leptin and BMI showed a non-linear relation (fig 2).

Table 4 Significant correlations between serum leptin and other metabolic hormones before and after 34 weeks of gestation

	<34 weeks gestation (n = 65)		≥34 weeks gestation (n = 75)	
	Correlation (r)	p value	Correlation (r)	p value
<i>Day 1</i>				
Leptin				
Insulin	0.28	<0.05	—	—
Insulin:glucose ratio	0.32	<0.05	0.24	<0.05
ACTH	0.26	<0.05	—	—
Insulin				
Leptin	0.28	<0.05	—	—
Insulin:glucose ratio	0.94	<0.001	0.96	<0.001
Glucose	—	—	0.36	<0.005
FT4	—	—	-0.26	<0.05
ACTH				
Leptin	0.26	<0.05	—	—
Cortisol	—	—	0.55	<0.001
FT4				
Insulin	—	—	-0.26	<0.05
Insulin:glucose ratio	—	—	-0.23	<0.05
<i>Day 4–5</i>				
Leptin				
Insulin:glucose ratio	—	—	0.27	<0.05
Insulin				
Insulin:glucose ratio	0.89	<0.001	0.94	<0.001
ACTH				
Cortisol	—	—	0.55	<0.001

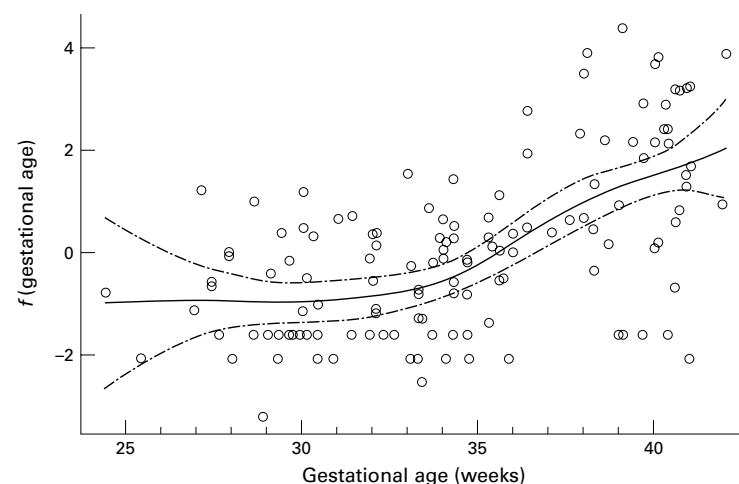


Figure 1 The non-linear relation between serum leptin on day 1 and gestational age, after adjustment for sex. Serum leptin is expressed as a fitted function for gestational age. The dotted lines represent twice the pointwise asymptotic standard errors of the estimated curve. The points are partial residuals (the fitted values for each function plus the overall residuals from the generalised additive model).

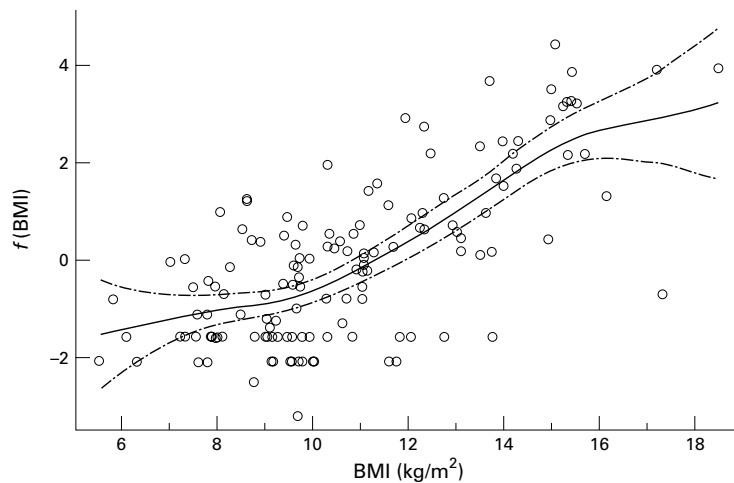


Figure 2 The non-linear relation between serum leptin on day 1 and BMI, after adjustment for sex. Serum leptin is expressed as a fitted function for BMI. The dotted lines represent twice the pointwise asymptotic standard errors of the estimated curve. The points are partial residuals (the fitted values for each function plus the overall residuals from the generalised additive model).

CHANGES IN THE PATTERN OF METABOLIC HORMONES BETWEEN DAY 1 AND DAY 4–5
Significant changes in the pattern of metabolic hormones were observed in the first week of life. There was a significant increase in serum insulin (median 5.8 pmol/l, $p < 0.05$) and plasma glucose (median 0.70 mmol/l, $p < 0.0001$) between day 1 and day 4–5. In contrast, serum leptin (median -0.02 ng/ml, $p < 0.0001$) and FT4 (median -2.0 pmol/l, $p < 0.001$) were significantly decreased during this period.

Discussion

The association between serum leptin and birth weight or BMI in this and other studies^{9 15 18–22} suggests a pivotal role of leptin in regulating fetal growth and development. Serum leptin is significantly higher in older gestation infants^{18 19 22} and our results further indicate that this phenomenon appears to be most prominent after 34 weeks gestation as shown by the rapid change in slope of the curve during this period (fig 1). It has been well documented that the accumulation of fetal adipose tissue increases exponentially during the latter half of the third trimester.¹⁴ The corresponding increase in serum leptin during the same period may thus provide an explanation of a close temporal relation between the two events. A similar rapid increase in serum leptin at around 32–34 weeks gestation was also observed by Jaquet and Matsuda and their coworkers using umbilical cord blood samples.^{18 22} However, an association between serum leptin and insulin has not been established at early preterm gestations. Hence, this study is also designed to investigate this relation by concurrently measuring serum leptin and insulin in these infants. Our results show a significant correlation between serum leptin and insulin or insulin:glucose ratio before and after 34 weeks gestation and lends further support to the hypothesis that the “adiposinsular axis” is likely to be active in early intrauterine life. Although our data do not establish precisely when in gestation the

Key message

Serum leptin increases considerably after 34 weeks gestation and bears a close temporal relation with the rapid accumulation of body fat mass during late gestation. The association between serum leptin and insulin or insulin:glucose ratio suggests that the “adiposinsular axis” is likely to be functional in early (less than 34 weeks gestation) intrauterine life

adiposinsular axis becomes fully matured, recent studies reported the presence of leptin in fetal cord blood as early as 18–26 weeks gestation.^{9 18 19 22} Thus, in view of the dramatic increase in serum leptin after 34 weeks gestation and the rapid accumulation of fetal fat mass during this period, we postulate that the adiposinsular axis is likely to be active and functional before 34 weeks gestation.

Like leptin, other metabolic hormones including ACTH, cortisol, and FT4 are also positively correlated with gestation, birth weight, and BMI. The pattern indicates that these endocrine axes are also maturing and become increasingly active with advancing gestations. Similar to our previous study,¹⁵ a significant association between serum leptin and hormones of the hypothalamic–pituitary–adrenal (HPA) axis is observed (table 4). As corticosteroids have the ability to increase leptin production,^{5 6 19} and insulin has also been shown in vitro to block corticosteroid stimulated release of leptin,⁷ it is possible that hormones of the HPA and adiposinsular axes may be inter-related with each other. We speculate that this may be one of the mechanisms in which the level of stress may influence body energy homeostasis and consequently affects the body weight and fat regulation. An anticipated association between serum leptin and plasma ACTH in infants beyond 34 weeks gestation was not found. Whether the use of antenatal dexamethasone in preterm infants influences the relation between the two axes requires further investigation. Moreover, our results confirm the observations that higher plasma ACTH or serum cortisol concentrations are found in infants born by caesarean section, in infants whose mothers had prolonged rupture of membranes, and in those who suffered from perinatal stress with suboptimal Apgar scores or adverse arterial cord blood parameters (data not shown).^{23–25} Nonetheless, in contrast to other metabolic hormones, serum cortisol concentrations on day 4–5 in preterm infants (groups 1 and 2) are higher than those of older gestation infants (group 3). This finding can be explained by the fact that many preterm infants are still under severe stress, requiring mechanical ventilation and intensive care treatment at this stage. Hence, they have higher circulating concentrations of stress hormones.²³

The hormonal patterns of leptin, insulin, and FT4 show significant changes between day 1

and day 4–5. ACTH and cortisol reveal a sharp decline in blood concentration in the term newborns (group 3), but their overall concentrations between day 1 and day 4–5 are unaffected. It is likely that the hormonal concentrations are influenced by the degree of stress experienced by preterm infants.²³ Insulin, an anabolic hormone, shows an increase in serum concentration after birth, whereas leptin and FT4 show a rapid decline in their circulating concentrations. Ong and Matsuda and their coworkers suggested that cord serum leptin concentrations correlated inversely with postnatal weight gain.^{22 26} Low circulating concentrations of leptin and FT4 may, therefore, be a physiological advantage to newborn infants as body energy expenditure can be minimised and nutritional reserves conserved for subsequent growth and development.⁹ Thus, it is possible that the fetal adiposinsular axis and the concentration of serum leptin at birth may influence the “programming” of satiety and body metabolism, thereby determining postnatal weight gain and adiposity.²⁶

Our results, as in previous studies,^{18 21 26} reveal a sex difference with higher serum leptin in female than in male infants. This difference in serum leptin is most apparent after 34 weeks gestation when the rate of intrauterine fat deposition is at its peak.¹⁸ Whether this phenomenon of sexual dimorphism represents a sex difference in body fat distribution or is a result of the gonadal steroid status in utero remains to be determined.

In summary, we have shown that circulating leptin concentration increases considerably after 34 weeks gestation and coincides with the rapid accumulation of adipose tissue during late gestations. The association between serum leptin and insulin or insulin:glucose ratio before and after 34 weeks gestation further illustrates that the “adiposinsular axis” is likely to be active in early (less than 34 weeks gestation) intrauterine life. The results in this and in our previous study¹⁵ both show a significant association between leptin and hormones of the HPA axis, and suggest that there may be an important link between the human stress response and body weight or fat regulation. Again, female infants have significantly higher circulating leptin concentrations than male infants. A rapid decline in the circulating concentrations of leptin and FT4 after birth may be of physiological advantage to newborn infants by limiting body energy expenditure and conserving nutritional reserves for growth and development.

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