Leptin and metabolic hormones in preterm newborns

P C Ng, C W K Lam, C H Lee, G W K Wong, T F Fok, I H S Chan, K C Ma, E Wong

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 infants 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.

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.9–11 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.12 Failure to increase the adipose tissue mass during gestation causes increased neonatal morbidity.13–15 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,16 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.17 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
Table 1 The clinical characteristics of preterm and term infants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 43)</th>
<th>Group 2 (n = 54)</th>
<th>Group 3 (n = 43)</th>
<th>Comparison between the three groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation (weeks)*</td>
<td>29.6 (28.0–30.4)</td>
<td>34.2 (33.3–35.3)</td>
<td>40.0 (38.7–40.6)</td>
<td>Group 3 &gt; group 2 &gt; group 1</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>1180 (970–1410)</td>
<td>1973 (1700–2110)</td>
<td>3300 (2900–3970)</td>
<td>Group 3 &gt; group 2 &gt; group 1</td>
</tr>
<tr>
<td>Length (cm)*</td>
<td>37.3 (35.5–40.2)</td>
<td>43.6 (42.1–44.6)</td>
<td>49.9 (47.8–52.1)</td>
<td>Group 3 &gt; group 2 &gt; group 1</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>8.2 (7.6–9.4)</td>
<td>10.3 (9.5–11.0)</td>
<td>13.8 (12.8–15.2)</td>
<td>Group 3 &gt; group 2 &gt; group 1</td>
</tr>
<tr>
<td>Placental weight (g)*</td>
<td>305 (300–400)</td>
<td>415 (380–495)</td>
<td>550 (500–660)</td>
<td>Group 3 &gt; group 2 &gt; group 1</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>27 : 16</td>
<td>25 : 29</td>
<td>23 : 20</td>
<td>—</td>
</tr>
<tr>
<td>Mode of delivery (n)*** (normal : caesarean section : forceps or ventouse)</td>
<td>16 : 26 : 1</td>
<td>25 : 28 : 1</td>
<td>21 : 13 : 9</td>
<td>—</td>
</tr>
<tr>
<td>Maternal smoker (n)</td>
<td>13</td>
<td>1</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Rupture of membrane &gt; 24 h (n)</td>
<td>10</td>
<td>12</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Maternal pre-eclampsia (n)</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Antenatal dexamethasone (doses)</td>
<td>2 (2–4)</td>
<td>2 (0–4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Time between last dose of dexamethasone and delivery (h)</td>
<td>40 (17–75)</td>
<td>68 (7–141)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Leptin (ng/ml)*</td>
<td>0.05 (0.05–0.25)</td>
<td>0.23 (0.07–0.46)</td>
<td>1.7 (0.48–6.33)</td>
<td>Group 3 &gt; groups 1 and 2</td>
</tr>
<tr>
<td>ACTH (pmol/l)*</td>
<td>3.3 (2.7–3.9)</td>
<td>5.4 (3.9–9.5)</td>
<td>7.8 (4.9–18.3)</td>
<td>Group 3 &gt; group 1; group 2 &gt; group 1</td>
</tr>
<tr>
<td>Cortisol (mmol/l)*</td>
<td>145 (99–311)</td>
<td>228 (142–354)</td>
<td>298 (205–415)</td>
<td>Group 3 &gt; group 1</td>
</tr>
<tr>
<td>Insulin (pmol/ml)†</td>
<td>30.1 (13.9–52.4)</td>
<td>27.7 (12.9–51.7)</td>
<td>23.0 (7.2–53.1)</td>
<td>—</td>
</tr>
<tr>
<td>Glucose (mmol/l)†</td>
<td>5.3 (3.8–7.4)</td>
<td>4.5 (4.1–5.4)</td>
<td>4.1 (3.7–4.7)</td>
<td>Group 1 &gt; group 3</td>
</tr>
<tr>
<td>Insulin/glucose ratio</td>
<td>4.7 (2.6–9.2)</td>
<td>6.0 (2.8–10.6)</td>
<td>5.5 (2.2–10.8)</td>
<td>—</td>
</tr>
<tr>
<td>FT4 (pmol/l)*</td>
<td>5.2 (3.0–8.2)</td>
<td>6.4 (4.8–7.6)</td>
<td>4.9 (3.9–7.2)</td>
<td>—</td>
</tr>
<tr>
<td>Cord TSH (mIU/l)</td>
<td>5.2 (3.0–8.2)</td>
<td>6.4 (4.8–7.6)</td>
<td>4.9 (3.9–7.2)</td>
<td>—</td>
</tr>
</tbody>
</table>

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

The points are partial residuals (the fitted values for each function plus the overall residuals dotted lines represent twice the pointwise asymptotic standard errors of the estimated curve.

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).

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).
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 mg/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 suggests a pivotal role of leptin in regulating fetal growth and development. Serum leptin is significantly higher in older gestation infants and the relationship with the rapid accumulation of fetal fat mass 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. 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. 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:glucose ratio before and after 34 weeks gestation and lends further support to the hypothesis that the “adipoinsular axis” is likely to be active in early intrauterine life. Although our data do not establish precisely when in gestation the adipoinsular axis becomes fully matured, recent studies reported the presence of leptin in fetal cord blood as early as 18–26 weeks gestation. 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 adipoinsular 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 maturating and become increasingly active with advancing gestations. Similar to our previous study, 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, and insulin has also been shown in vitro to block corticosteroid stimulated release of leptin, it is possible that hormones of the HPA and adipoinsular 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 homoeostasis 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 normal or instrumental delivery than 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). 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.

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. 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. Low circulating concentrations of leptin and FT4 may, therefore, be a physiological advantage to newborn infants. A rapid decline in the circulating concentrations between day 1 and day 4–5 is expected. It is likely that the hormonal concentrations are influenced by the degree of stress experienced by preterm infants. 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. Low circulating concentrations of leptin and FT4 may, therefore, be a physiological advantage to newborn infants. A rapid decline in the circulating concentrations between day 1 and day 4–5 is expected.

Our previous study illustrates that the “adipoinsular axis” is likely an important link between the human stress response and metabolism, thereby determining postnatal weight gain. Low circulating concentrations correlated inversely with postnatal weight gain. Low circulating concentrations of leptin and FT4 show a rapid decline in their circulating concentrations after 34 weeks gestation and coincides with the rapid accumulation of adipose tissue during late gestations. The association between serum leptin levels are increased in survivors of acute sepsis: associated loss of diurnal rhythm in cortisol and leptin secretion. J Clin Endocrinol Metab 1998;83:280–3.

Our results, as in others, 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. 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 “adipoinsular axis” is likely to be active in early (less than 34 weeks gestation) intrauterine life. The results in this and in our previous study 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.


