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Key Words
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Changes of Maternal Serum Leptin Levels during Pregnancy

Abstract

Maternal leptin levels in serum and urine, their relations to maternal weight and body mass index, were examined in 9 healthy pregnant women from the 12th week of gestation until term. Serum leptin concentration was found to increase progressively during the first two trimesters followed by a slight decline thereafter. The peak value of 27.6 ± 15.3 ng/ml (mean ± SD) concentration was reached at the 28th week. Serum leptin levels during the first two trimesters correlated significantly with maternal weight ($p = 0.002$) and body mass index ($p = 0.002$) but such a relationship was absent during the third trimester. Leptin could be detected only in about half of urine samples; its concentrations proved to be independent of serum values. No correlation was found between maternal serum leptin levels and the birth weight of neonates. Maternal leptin levels appear to refer to alterations in maternal fat tissue mass that occur during pregnancy.

Introduction

The *ob* gene product leptin, a 16-kD peptide, was originally found to be synthetized and released from adipocytes [1]. Leptin has been postulated to be a weight-regulating factor because it suppresses appetite and augments energy expenditure [2]. In the human a strong positive correlation has been shown between percentage of body fat and plasma leptin concentrations [2]. Leptin appears to regulate its own gene expression through a feedback mechanism involving the hypothalamic-pituitary axis [3]; glucocorticoids and insulin are known to enhance directly its synthesis by increasing leptin mRNA [3, 4].

In accordance with increased maternal body fat mass, Schubring et al. [5] found significantly higher maternal leptin levels at term as compared with nonpregnant sera. Butte et al. [6] reported a significantly higher serum leptin at the 36th week than postpartum, and similarly elevated maternal leptin levels were detected at term by Hassink et al. [7]. However, longitudinal examination of leptin levels throughout pregnancy has not been performed.

The purpose of our study was to determine sequential changes of leptin concentrations in maternal serum and urine during pregnancy, and to examine their relations to maternal weight gain and neonatal birth weight.

Patients and Methods

In cases of 9 healthy pregnant women, samples of venous blood and those of 24-hour urine collections were taken at 4-week intervals from the 12th gestational week up to delivery. At the same time, maternal weight, body mass index (BMI) and the volume of daily urine excretion were also recorded. At the 12th week, maternal weight and BMI was 59.5 ± 10.47 (mean ± SD) kg and 26.15 ± 3.91 kg/m^2, respectively. After uneventful pregnancies, patients gave birth at term. Women who delivered before the 40th week (3 cases) were lost for the final 40th week sampling. Newborns' weight processed as 'corrected' birth weight (expressed as birth weight in grams/gestational age in weeks), ranged between 70.5 and 100 g/week.

Sera for leptin examinations were separated by refrigerated centrifuge at 4 °C, and stored together with urine samples at –20 °C until assayed. Serum leptin was measured by radioimmunoassay as described previously [8]. For leptin measurement in urine an ultrasensitive version was applied under nonequilibrium conditions. In brief, 100 µl urine was incubated with 25 µl 1st antibody at room tempera-

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ture. After 24 h, 25 µl tracer (200,000 cpm/ml) was added and incubation was continued overnight. Separation of bound and free tracer was achieved as described previously [8]. Maximum binding of tracer was about 35%. Half-maximum binding occurred at 0.05 ng/ml and sensitivity with undiluted samples was 0.003 ng/ml. The intra- and interassay coefficients of variation were 3.3 and 9.4% respectively.

The study was approved by the Ethical Committee of the Medical University School of Pécs and written informed consent was obtained in each case. Statistical analysis was performed by paired t-test and linear regression analysis. Significant difference and correlation was considered at $p < 0.05$.

Results

Maternal serum leptin concentration obtained serially in 4-week periods is depicted in figure 1. From the 12th to the 28th week its concentration increased significantly ($p = 0.009$), the maximum value of 27.61 ± 15.37 ng/ml (mean ± SD) was detected at the 28th week. No further significant change of leptin concentration occurred during the third trimester.

Initial (obtained at the 12th week) serum leptin concentrations varied in a wide range (6.06–23.45 ng/ml) but correlated significantly to initial maternal weight ($r = 0.437$, $p = 0.001$) and BMI ($r = 0.428$, $p = 0.002$). When all individual leptin levels were considered and related to the corresponding weight gain parameters during the whole period of pregnancy, serum leptin levels appeared to marginally correlate with maternal weight ($r = 0.246$, $p = 0.056$) but strongly with BMI ($r = 0.333$, $p = 0.009$). Separated evaluation of data prior to and following the 28th week revealed that from the 12th to 28th gestational week serum leptin correlated strongly with maternal weight ($r = 0.473$, $p = 0.002$) and BMI ($r = 0.470$, $p = 0.002$) (fig. 2) but no such relationships were found after the 28th week.

Leptin was detectable in about half of urine samples. Its concentrations ranged between 1 and 108 pg/ml; the highest daily leptin excretion was 173 ng. Urinary leptin concentrations or daily excretions were independent of serum values.

No correlation was observed between maternal leptin concentrations or their relative increase and 'corrected' birth weights.

Discussion

Our study demonstrates that maternal serum leptin concentration increases during the first two but not during the third trimester of pregnancy, the maximum value appears to be between the 24th and 32th week of gestation.

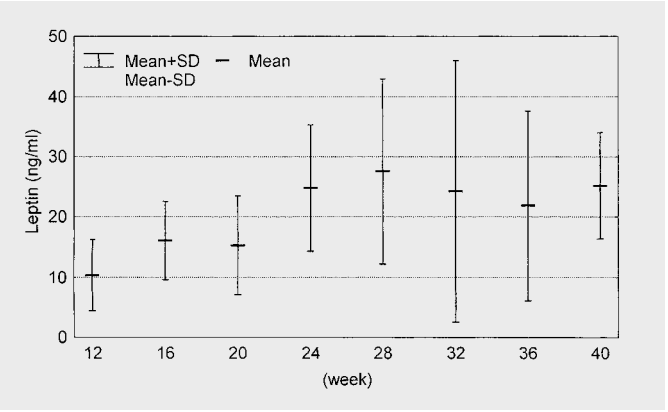

Fig. 1. Sequential changes of serum leptin concentrations (mean ± SD) during pregnancy by longitudinal examination of 9 cases.

Maternal weight gain during pregnancy is accounted for by the combined effects of increasing weight of the uterus with its content, extracellular fluid accumulation, and increasing maternal fat mass. Since the contribution of factors accounting for gestational weight gain varies as the pregnancy advances [9], maternal weight gain cannot be considered as a relative estimate of fat accretion, consequently, it is not proportional to adipocyte-derived leptin levels. During the first part of pregnancy the fat accumulation, caused by the combined effects of hyperphagia, enhanced lipogenesis, and unchanged or increased extrahepatic lipoprotein lipase activity, increases. On the contrary, in late gestation, by the change of maternal lipid metabolism to a catabolic condition, no further fat accumulation occurs [10]. Thus, changes of maternal serum leptin follows the pattern of gestational alterations of maternal fat tissue mass.

Leptin is expected to be involved in a complex metabolic and neuroendocrine regulatory system [11]; insulin, cortisol, sex steroids, and catecholamines might be expected to directly influence its release in pregnancy too. Definitive effects of higher insulin and glucocorticoid secretion on leptin production are unlikely in the first two trimesters because insulin level increases only in late pregnancy [12], and the effects of rising corticosteroids are antagonized by the increasing concentration of the binding protein transcortin [13]. The suspected effects of sex steroids and catecholamines on leptin production in pregnancy have not yet been elucidated. Leptin production by the placenta [7] possibly contributes to maternal levels. However, it is tempting to assume that in pregnant women changes of leptin concentration may refer basically to the alteration of maternal fat mass.

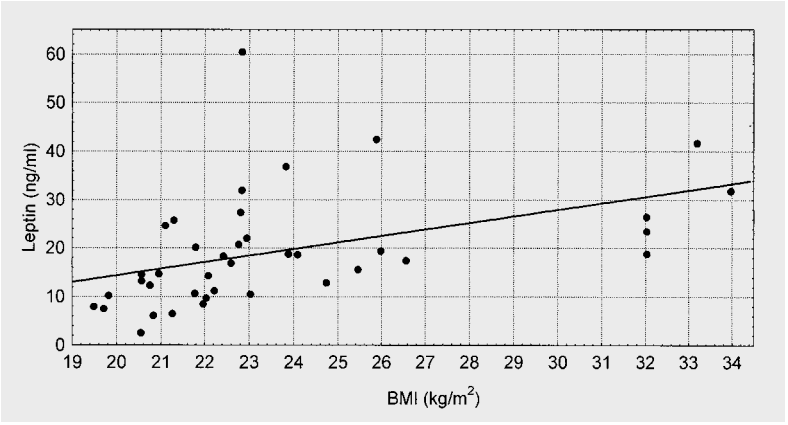

Fig. 2. Correlation of maternal serum leptin and BMI from the 12th to 28th gestational weeks by longitudinal examination of 9 cases.

As maternal weight increases up to term but serum leptin levels slightly decline after the 28th week, it is not surprising that serum leptin correlated with maternal weight and BMI in the first two trimesters but not later; however, serum leptin showed a statistically significant correlation with parameters of maternal weight gain when all data were compiled from the 12th week to term. This result may explain the previous conflicting findings on the correlation of maternal leptin and weight/BMI found near term [5–7].

In about half of the cases, leptin concentrations in urine were below the sensitivity of the method (0.003 ng/ml) but it seems that both urine concentration and daily excretion are independent of the serum level throughout pregnancy.

In accordance with previous observations [5–7], maternal serum leptin concentration or its relative increase did not correlate with neonatal birth weight. Since fetal weight can be normal even if maternal weight decreases [9], it appears to be reasonable to assume that fetal weight should be independent of maternal fat mass and maternal leptin.

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