Leptin levels at birth and in early postnatal life in small- and appropriate-for-gestational-age infants

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Key words: *small- and appropriate-for-gestational-age newborn; leptin; birth weight; placenta.*

Summary. *The aim of this study was to evaluate leptin concentration at birth and in early postnatal life in small- and appropriate-for-gestational-age infants and to assess its relationship with infants' anthropometry at birth and some characteristics of maternal pregnancy.*

Materials and methods. A total of 367 infants born after 32–42 weeks of gestation were enrolled in the study. Umbilical cord blood samples were collected from 80 small- and 287 appropriate-for-gestational-age newborns. Altogether, 166 venous blood samples were taken from these neonates on days 2–6 of life.

Results. Cord leptin levels were significantly lower in small- compared to appropriate-for-gestational-age infants. We observed a positive correlation between cord leptin and birth weight, all neonatal anthropometric parameters, placental weight, and some maternal nutritional factors. In multivariate analysis, cord leptin concentration explained up to 15% of the variation in sum of newborn's skinfold thickness but only 5% of the variation in birth weight. Postnatally, leptin concentration decreased markedly to the similar low levels in both infant groups and remained so during the first postnatal week.

Conclusions. Significantly lower cord leptin concentration in small-for-gestational-age neonates reflects a lower fat mass content compared to appropriate-for-gestational-age infants. However, an abrupt decrease in leptin levels shortly after birth in both groups suggests that placenta could be an important source of leptin in fetal circulation. The impact of low leptin levels at birth in small-for-gestational-age infants on their postnatal appetite and weight gain remains to be elucidated in future studies.

Introduction

Leptin, product of the *Ob* gene, is produced by adipocytes and, in experimental rodent studies, reduces adiposity by promoting satiety, energy expenditure, and fat oxidation (1–3). Postnatally, it regulates body weight through a negative feedback signal between the adipose tissue and the hypothalamic centers of satiety causing a decrease in food intake and an increase in body temperature and energy expenditure (4). Following leptin discovery in adipose tissue, it has been also detected in the placenta, amniotic fluid, and in fetal plasma as early as week 18 of gestation (5–7). It has been demonstrated that leptin concentration in the cord serum is elevated and independent of maternal serum concentration (6). In children, as in adults, serum leptin concentrations closely correlate with body weight and body fat mass (8, 9). Several recent studies have demonstrated a positive correlation between leptin concentrations in cord blood and birth weight of the newborn infants (8–13). Accordingly, small-for-gestational-age (SGA) newborns have significantly reduced serum leptin concentration (9, 11–14). A gender dimorphism, with higher leptin concentrations in female newborns, was observed in some (9, 15–18), but not all studies (12, 20).

Both placental and fetal adipose tissue production of leptin has been demonstrated (19), but a different contribution of these two compartments to the umbilical cord leptin levels is difficult to evaluate. However, the suggestion that leptin *per se* may play a role in fetal growth is still a matter of debate, since patients with leptin gene mutation have normal birth weight and length (21, 22).

The aim of this study was to evaluate leptin concentration at birth and in early postnatal life in small- and appropriate-for-gestational-age (AGA) infants and

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to assess its relationship with neonatal anthropometry at birth and some maternal pregnancy characteristics (maternal pre-pregnancy weight, pre-pregnancy BMI, weight gain during pregnancy, weight at delivery).

Materials and methods

Study subjects and serum samples

A total of 367 infants, born between April 1998 and November 2000 in Kaunas, mostly at Kaunas University of Medicine Hospital, were enrolled in the study. Mixed venous and arterial umbilical cord blood samples were collected from 80 SGA and 287 AGA infants. Altogether, 166 venous blood samples were taken on postnatal days 2–6 from 56 SGA and 94 AGA neonates. Neonatal venous blood samples were obtained by puncture of the antecubital vein for the purpose of the neonatal screening on days 2–3 of life in 94 cases (30 SGA and 64 AGA), on days 4–5 – in 43 cases (18 SGA and 25 AGA), and on day 6 – in 8 SGA and 5 AGA infants. The obtained cord and neonatal blood samples were centrifuged, and serum was separated and stored at –20°C until assays.

All infants were born after 37–42 weeks of gestation from singleton pregnancies and had no obvious malformations. Because the present study is part of a joint Swedish-Brazilian-Lithuanian research project and in order to be able to make comparisons among countries, SGA infants in this study were defined on the basis of a birth weight and/or length more than –2 SD below the mean, and AGA infants, as having, birth weight and birth length within ±2 SD for a given gestational age and gender according to Swedish reference data (23).

Obstetrical data were recorded from standard medical files with structured form used in all antenatal clinics in Lithuania. Gestational age was defined based on the date of the last menstrual period.

Informed parental consent was obtained, and the study protocol was approved by the local Ethical Committee of Kaunas University of Medicine.

Measurements of the newborn infants

Birth weight was recorded within 10 g by midwives using an electronic scale. Placental weights were recorded wet without separating the membranes and cord. Within 24 hours after birth, study children were measured by trained medical personnel (two nurses and one pediatrician). Birth length was measured on a wooden measuring board and recorded to the nearest mm. Head (maximal fronto-occipital circumference), thoracic and calf circumferences were measured with non-stretchable measuring tapes, checked against a metallic reference. Skinfold thickness was measured using Harpenden caliper at three sites: in the middle third of the quadriceps and triceps muscles and in the subscapular region. Each measurement was repeated twice, and the mean value was used for analysis. Ponderal index was calculated as neonatal weight/length^3 ratio. Parental heights were measured by the same personnel with a standard measuring scale.

Hormonal analysis

Serum leptin concentrations were determined in duplicate by RIA (human leptin RIA kit, Linco Research, Inc., St Charles, MO). The assay has a detection range of 0.2–100 µg/L with an intra-assay CV of 5.5% and interassay – 9.8% at 2.5 µg/L; at 15.2 µg/L the intra-assay CV was 5.4 % and interassay CV – 6.8%.

Leptin analysis was performed at the laboratory of Pediatric Growth Research Center of Göteborg University (Sweden).

Statistical analysis

Results are presented as mean ± SD or mean ± SE. Kolmogorov-Smirnov goodness-of-fit test was performed in order to assess the normality of distribution of leptin.

The means of continuous variables were compared using Student's t test for independent samples. Correlation analyses were performed using Pearson's coefficient. Leptin concentrations at birth and postnatally in SGA and AGA infants were compared using Mann-Whitney U and Wilcoxon tests for independent and paired samples, respectively. The relationship of birth weight with cord leptin, some maternal pregnancy factors, placental weight, and gestational age was assessed by the multiple stepwise regression analysis.

All calculations were made using the SPSS program (for Windows, version 10). Probability values of less than 0.05 were considered significant.

Results

Clinical characteristics of the SGA and AGA newborns are summarized in Table 1. As expected, all neonatal anthropometric measurements and placental weight were higher in the AGA *vs.* SGA group.

Cord leptin levels were significantly lower in SGA compared to AGA infants. However, after adjustment for birth weight SDS (BWSDS), cord leptin levels were even higher in SGA than in AGA infants, although the difference did not reach statistical significance (Table 2).

Table 1. **Means (SD) of anthropometric measurements of SGA and AGA newborns**

Charakteristic	SGA, n=80	AGA, n=287	P value
Gestational age, weeks	38.8 (1.6)	39.16 (1.8)	NS
Male/female ratio	40/40	143/144	NS
Birth weight, g	2398 (374)	3507 (501)	<0.001
Birth weight SDS	–2.4 (0.5)	0.1 (0.9)	<0.001
Birth length, cm	46.8 (2.8)	50.7 (2.06)	<0.001
Birth length SDS	–1.6 (0.8)	0.4 (0.8)	<0.001
Head circumference, cm	32.36 (1.64)	34.95 (1.7)	<0.001
Thoracic circumference, cm	29.95 (2.26)	33.78 (2.06)	<0.001
Ponderal index, g/cm^3	2.33 (0.24)	2.65 (0.23)	<0.001
Placental weight, g	423.55 (97.08)	533.73 (82.90)	<0.001
Skinfold thickness, mm			
triceps	4.71 (1.13)	5.93 (1.64)	<0.001
quadriceps	5.03 (1.28)	7.13 (1.76)	<0.001
subscapular	3.94 (0.95)	5.24 (1.32)	<0.001
Sum of skinfold thickness, mm	13.65 (2.8)	18.26 (3.8)	<0.001

AGA – appropriate for gestational age; NS – not significant; SGA – small for gestational age; SD – standard deviation; SDS – standard deviation score.

Table 2. **Cord leptin levels (means (SE)) of SGA and AGA newborns, crude and adjusted for BWSDS (birth weight SDS)**

Cord leptin level, ng/mL	SGA, n=80	AGA, n=287	P value
Unadjusted	4.3 (0.66)	7.1 (0.48)	0.001
Adjusted for BWSDS	6.95 (0.93)	5.84 (0.56)	NS

AGA – appropriate for gestational age; NS – not significant; SGA – small for gestational age; SE – standard error; SDS – standard deviation score.

When two groups of newborns were taken combined in the analysis, we observed significantly positive correlations between cord leptin levels and birth weight, all newborns' anthropometric parameters, ponderal index, placental weight, and some maternal pregnancy factors (Table 3). The relationship of cord leptin concentration to sum of skinfold thickness is depicted in Fig. 1.

A week positive correlation was found between cord leptin levels and gestational age in the total group (Table 3). A positive correlation was also observed between cord leptin levels and some factors of maternal pregnancy (maternal pre-pregnancy weight, pre-pregnancy BMI, weight gain during pregnancy, weight at delivery) (Table 3).

When the newborns were grouped according to birth weight, positive correlations between cord serum leptin levels and anthropometric parameters in the AGA group remained at the similar order of significance. In contrast, cord leptin concentration in the SGA group was significantly related only to skinfold thickness measurements (triceps: r=0.388, P<0.001, quadriceps: r=0.436, P<0.001, subscapular: r=0.425, P<0.001) and inversely associated with birth length and head circumference (r=–0.235, P<0.05, r=–0.276, P<0.05).

Looking separately at cord leptin levels by gender in the whole cohort, significant differences were observed, girls having higher values of leptin than boys (7.8±7 *vs.* 4.5±2.6 ng/mL in girls and boys, respectively, P<0.001).

Leptin concentration, being significantly different at birth, postnatally decreased markedly to the similar low levels in SGA and AGA newborns. During the first postnatal week, leptin levels remained low in both groups of newborns (Fig. 2).

Table 3. **Pearson's correlation coefficients (r) between cord leptin level and gestational age, neonatal measurements, placental weight and parental auxology in SGA and AGA groups (leptin levels were log-transformed before analysis)**

Charakteristic	Pearson's correlation coefficient	P value
Gestational age, weeks	0.22	<0.05
Placental weight, g	0.33	0.001
Birth weight, g	0.5	<0.001
Birth weight SDS	0.553	<0.001
Birth length, cm	0.316	<0.001
Birth length SDS	0.437	<0.001
Ponderal index	0.418	<0.001
Head circumference, cm	0.346	<0.001
Thoracic circumference, cm	0.413	<0.001
Calf circumference, cm	0.499	<0.001
Skinfold thickness, mm, site		
triceps	0.336	<0.001
quadriceps	0.528	<0.001
subscapular	0.5	<0.001
Sum of skinfold thickness	0.55	<0.001
Maternal height, cm	0.09	NS
Midparental height, cm	–0.126	NS
Maternal pregnancy characteristics:		
Maternal pre-pregnancy weight, kg	0.13	<0.05
Pre-pregnancy BMI	0.1	NS
Weight at delivery, kg	0.236	<0.01
Weight gain during pregnancy, kg	0.2	<0.01

AGA – appropriate for gestational age; BMI – body mass index; NS – not significant; SGA – small for gestational age; SDS – standard deviation score.

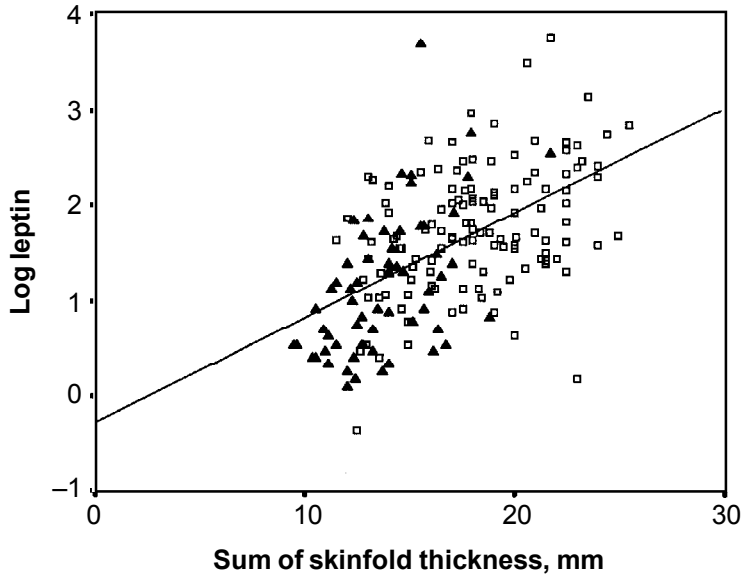

Fig. 1. **Relationship between cord log leptin and sum of skinfold thickness in SGA (▲) and AGA (□) infants (r^2=0.3 for the total group, P<0.001)**
AGA – appropriate for gestational age; SGA – small for gestational age.

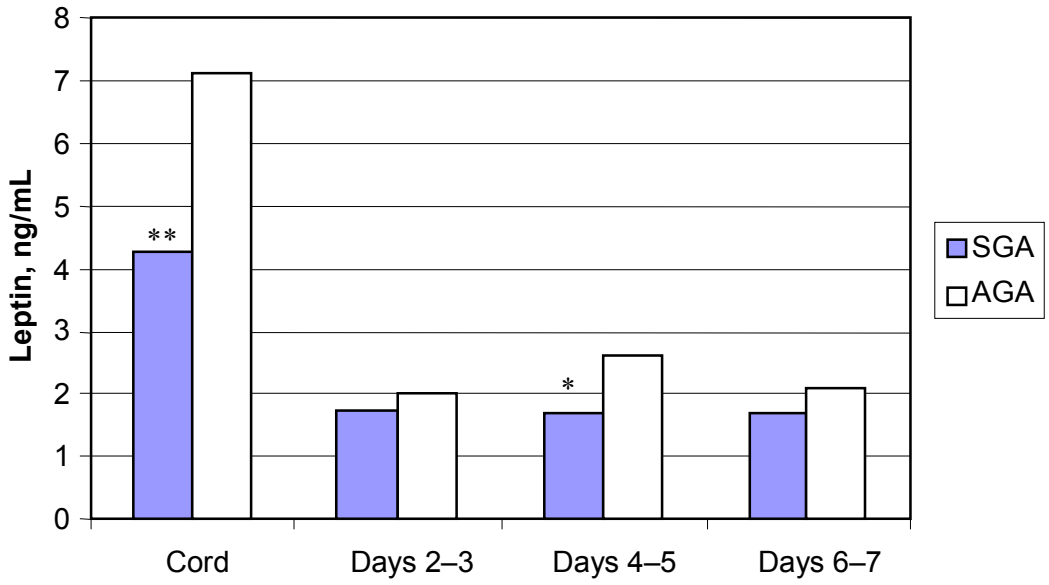

Fig. 2. **Postnatal change in leptin levels in SGA and AGA infants (assessed by Mann-Whitney U test)**
AGA – appropriate for gestational age; SGA – small for gestational age.
**P<0.001 between SGA and AGA groups of newborns;
*P<0.05 between SGA and AGA groups on days 4–5; on days 2–3 and 6–7 the difference was insignificant.

A strong inverse relationship was found between leptin levels at birth and its postnatal decrease (r^2=0.97, P<0.001). Changes in leptin levels after birth were not related to postnatal weight change of the neonates (r=0.73, P=0.43).

The relationship of birth weight with placental weight, cord leptin, gestational age, and maternal weight gain during pregnancy was assessed by the multiple stepwise regression analysis (Table 4A). These factors together explained up to 54% of the variation in birth weight. Variation in the placental weight alone was associated with the variation in birth weight in approximately 36%, while only 5% of the variation in birth weight was explained by that of cord leptin concentration. In contrast, cord leptin concentration explained up to 15% of the variation in sum of skinfold thickness (Table 4B).

Discussion

A considerable number of previous reports have shown that leptin is present in the cord blood and that these levels are not related to levels in maternal serum, but correlate closely with size at birth, suggesting that cord levels reflect fetal leptin production (9–13, 19, 20). The results of the present study confirm and expand previous observations that leptin is significantly and directly related to fetal weight. Leptin concentration in the cord blood was significantly increasing with progressing gestational age, which is probably related to the corresponding increase in fetal adipose tissue from 32 weeks to term. In addition, SGA infants had significantly lower levels of cord leptin compared with AGA infants. The total amount of body fat is less in SGA than in AGA infants, as it could be demonstrated with higher ponderal index and overall skinfold thickness in the latter group. Furthermore, a significant positive correlation between ponderal index as well as skinfold thickness and leptin values at birth was found, indicating that the concentration of cord leptin levels is closely related to the amount of adipose tissue in infants.

Interestingly, after adjustment for birth weight, leptin levels at birth were higher in SGA than in AGA infants. Although the reported differences did not reach statistical significance, these observations are suggestive of possible relative leptin resistance in SGA infants, present already in uterus.

In the multivariate regression analysis, the highest proportion of variation in infants birth weight could be explained by the variation in placental weight (up to 36%) and only minor – by that in cord leptin concentration (up to 5%), suggesting that leptin levels passively reflect rather than determine fetal weight gain. These observations are compatible with findings that infants with congenital leptin deficiency or leptin receptor gene mutation have normal birth weights (15, 16). On the contrary, cord leptin concentration explained up to 15% of the variance in infants' skinfold

***Table 4A*. The influence of placental weight, gestational age, cord leptin level, and maternal weight gain during pregnancy on the variation of birth weight**

A

Dependent variable	Independent variable in the model	Adj. $R^2 \times 100$ (%), cumulative	P value
Birth weight, g	Placental weight	36	<0.001
	Gestational age	48	<0.001
	Cord leptin	53	<0.001
	Maternal weight gain during pregnancy	54	0.031

***Table 4B*. The influence of cord leptin, gestational age, and placental weight on the variation of sum of skinfold thickness as assessed by stepwise multiple regression analysis (leptin values were log-transformed before analysis)**

B

Dependent variable	Independent variable in the model	Adj. $R^2 \times 100$ (%), cumulative	P value
Sum of thickness skinfold, mm	Cord leptin	15	<0.001
	Gestational age	20	0.001
	Placental weight	22	0.013

thickness, indicating again a strong association of leptin levels with adiposity.

In this study, cord leptin levels were markedly higher in female than in male infants, and this difference was independent of birth weight and gestational age. Although the sexual dimorphism in leptin levels becomes most apparent at the onset of puberty, a significant gender difference in leptin levels at birth has previously been reported by some (9, 15–18), but not all studies (12, 20). It is discussed that these gender differences might reflect the transient perinatal elevation in sex steroids, as estrogens are associated with higher leptin concentrations, while androgens are inversely related to leptin levels (18). Not consistent with these observations, Matsuda *et al.* (12) reported that serum concentrations of estradiol and testosterone did not differ between male and female neonates and did not correlate with leptin concentration suggesting that the existence of this gender difference in the fetus might also depend on genetic factors.

Within 2–3 days after birth, serum leptin concentration in AGA infants decreased dramatically to the low levels observed in SGA infants. One possible explanation is that leptin levels reflect the nutritional status of the neonate, as insulin has been shown to be a potent physiological regulator of leptin expression in human adipose tissue (24), and a markedly elevated plasma leptin in large for gestational age full-term neonates was significantly related to hyperinsulinemia (10). Thus, the rapid decrease in leptin levels after birth could be mediated by the period of starvation after birth, weight reduction, hormonal changes after birth, for instance the fall in insulin levels. However, in our study, postnatal change in leptin levels was not related to neonatal weight change.

Several lines of evidence are compatible with the contention that fetal leptin derives, at least in part, from the placenta. In a study by Hassink *et al.* (19), leptin concentrations in the cord blood were independent of insulin and glucose levels, and leptin mRNA expression in the placental tissue has been demonstrated. Furthermore, in a study by Yura *et al.* (25) higher leptin levels in the umbilical veins than in umbilical arteries were found, which is consistent with leptin secretion from placenta to the fetal circulation. This notion is further supported by a significant positive correlation of cord leptin levels and placental weight in our as well as other studies (12, 24). Thus, one possible reason of rapid decline of leptin concentration in the neonatal circulation after birth could be due to the sudden removal of the placenta.

The physiologic role of leptin in fetal and neonatal development is unknown at present. It has been suggested that satiety in babies may be predetermined in

uterus and leptin therefore may be one example of "programming" (26). Postnatally, fasting, cold exposure, and elevated levels of free fatty acids are associated with a decrease in both the leptin levels and the *ob* gene expression in humans and rodents (27). Leptin may interact with appetite-regulating systems in the ventromedial hypothalamic arcuate nucleus by decreasing biosynthesis and secretion of neuropeptide Y, which is a potent stimulator of appetite (4). Thus, a rapid fall in leptin levels after birth might be an important stimulation for feeding behavior and energy uptake that is necessary for rapid neonatal growth.

The effect of intrauterine programming on postnatal leptin secretion in humans has also been demonstrated. While growth-retarded newborn infants have lower than normal leptin concentrations, by 12 months of age they have higher than normal plasma leptin levels (9). In the study by Ong *et al.*, low leptin levels in cord blood strongly predicted high rates of weight gain in infancy and catch-up growth (8). It is suggested that leptin could represent the mechanism whereby intrauterine factors, which affect weight and adiposity at birth, could influence postnatal levels of satiety, peripheral metabolism, and weight gain. Infancy appears to be a critical period for the development of obesity and metabolic complications: higher rates of infancy weight gain are seen in children who subsequently develop obesity and have also been linked with risks for type 2 diabetes and cardiovascular disease in adulthood (8).

In summary, results of this study indicate fetal leptin production by adipose tissue, but an abrupt decrease in leptin levels shortly after birth suggests placenta as an important source of leptin in fetal circulation. Significantly lower cord leptin concentration in SGA neonates reflects a lower fat mass content compared to AGA infants. Further prospective follow-up studies are needed to explore whether low leptin levels at birth are able to program the susceptibility of these SGA individuals to long-term metabolic abnormalities associated with increased appetite and excessive weight gain.

Mažų ir gestacijos amžių atitinkančių naujagimių leptino kiekis gimus ir ankstyvuoju ponataliniu laikotarpiu

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Raktažodžiai: maži ir gestacijos amžių atitinkantys naujagimiai, leptinas, gimimo svoris, placenta.

Santrauka. *Tyrimo tikslas.* Nustatyti leptino kiekį gimusiam naujagimiui ir ankstyvuoju ponataliniu laikotarpiu mažiems ir gestacijos amžių atitinkantiems naujagimiams bei įvertinti ryšį su naujagimių antropometriniais parametrais, motinos nėštumo rodikliais.

Tyrimo medžiaga ir metodai. Į studiją įtraukti 367 naujagimiai, gimę 32–42 gestacijos savaitę. 80 mažiems ir 287 gestacijos amžių atitinkantiems naujagimiams buvo paimta virkštelės kraujo. 2–6 gyvenimo dieną buvo pakartotinai paimti kraujo pavyzdžiai (56 mažiems ir 94 gestacijos amžių atitinkantiems naujagimiams).

Rezultatai. Virkštelės leptino kiekis reikšmingai mažesnis buvo mažų naujagimių lyginant su gestacijos amžių atitinkančiais naujagimiais. Rasta teigiama koreliacija tarp virkštelės leptino kiekio ir gimimo svorio, naujagimių antropometrinių parametrų, placentos svorio, motinos mitybos rodiklių. Taikant dauginės regresijos metodą, leptino kiekis turi įtakos 15 proc. naujagimių poodinio riebalinio audinio sumos ir tik 5 proc. gimimo svoriui. Ponataliniu laikotarpiu leptino kiekis žymiai sumažėjo abiejuose naujagimių grupėse ir išliko mažas pirmąją ponatalinę savaitę.

Išvados. Pagal gestacijos amžių mažiems naujagimiams mažas leptino kiekis yra sąlygotas mažo riebalinio audinio kiekio lyginant su gestacijos amžių atitinkančiais naujagimiais. Ryškus leptino kiekio sumažėjimas po gimimo abiejose grupėse sąlygoja, kad placenta galėtų būti vienas pagrindinių leptino šaltinių vaisiui nėštumo metu. Mažas leptino kiekis gimus pagal gestacijos amžių mažiems naujagimiams, jos galimas ryšys su apetitu ponataliniu laikotarpiu, svorio augimo tempu gali būti kitų studijų objektas.

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