

# Leptin Is Present in Human Cord Blood

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It has recently been reported that the *ob* gene receptor was expressed on human and murine hematopoietic stem cells and that the *ob* gene product leptin stimulated hemato- and lymphopoiesis at the stem cell level. These findings suggest a role for leptin in hemato- and lymphopoiesis during fetal development. There is at present no evidence, however, that leptin is synthesized and released by the fetus. To investigate this possibility, we have measured plasma leptin concentrations in the cord blood of 78 newborn infants. We found that leptin was present in all 78 infants in concentrations comparable with those found in adults (0.6–55.7 ng/ml). Overall, plasma leptin concentrations in the cord blood of infants correlated with birth weight ( $r = 0.74$ ,  $P < 0.001$ ). These observations show that leptin is synthesized and released by fetal fat cells. In addition, they are compatible with the concept that leptin may play a role in human fetal hematopoiesis. *Diabetes* 46:917–919, 1997

The *ob* gene has recently been identified in mice and humans (1). The association of obesity with abnormalities in this gene has generated a great deal of interest in the *ob* gene product leptin. Leptin, a 16-kDa peptide, is synthesized in and released exclusively from adipose cells (1,2). Leptin has been postulated to be a weight-regulating factor based on the observations that obese *ob/ob* mice (who lacked bioactive leptin) ate less and lost weight when parabiosed to normal mice (who had normal amounts of bioactive leptin) and that the injection of synthetic leptin reduced food intake in *ob/ob* mice and in wild-type diet-induced obese mice (3–5). In contrast to leptin-deficient *ob/ob* mice, obese human subjects have elevated plasma leptin levels (6) and, in contrast to *db/db* mice (7,8), have intact leptin receptors (9). Thus, it remains uncertain what role, if any, leptin plays in the regulation of body weight in humans.

Rather unexpectedly, it has recently been discovered that leptin receptors were expressed in human and murine hematopoietic fetal stem cells (10) and that leptin stimulated hematopoiesis at the progenitor cell level (11). Moreover, lymphoproliferative capacity was markedly compromised in *db/db* mice (11) that expressed a truncated and biologically defective leptin receptor (7,8). These findings suggest the pos-

sibility that leptin may play an important role in fetal hemato- and lymphopoiesis. It is, however, not known whether leptin is produced in the fetus. To investigate the possibility, we measured plasma leptin concentrations in the cord blood of newborn infants. As a second aim, we also investigated the relationship between birth weight and leptin levels.

## RESEARCH DESIGN AND METHODS

**Subjects.** Cord blood was obtained from 78 neonates at the time of delivery and before the separation of the placenta. The neonates were divided into four groups: group 1 (term-AGA [appropriate for gestational age]), which consisted of 43 term infants whose birth weights were within normal limits for gestational age (i.e., between the 10th and 90th percentiles); group 2 (term-LGA [large for gestational age]), which consisted of 10 term infants whose birth weights exceeded the 90th percentile; group 3 (term-SGA [small for gestational age]), which consisted of 4 term infants whose birth weights were below the 10th percentile; and group 4 (preterm-AGA), which consisted of 21 preterm (<37 weeks of gestation) infants whose birth weights were low but appropriate for their gestational age (Table 1). Gestational age at delivery was calculated according to the last menstrual period and confirmed by ultrasound during the first trimester and/or early second trimester (<20 weeks of gestation). Birth weight percentiles were calculated according to Battaglia and Lubchenco (12).

Neonates born to mothers who experienced medical complications other than gestational diabetes mellitus (GDM) during or before pregnancy were excluded. Group 2 contained four infants born to mothers with GDM (diagnosed with a standard 3-h oral glucose tolerance test according to the criteria of Carpenter and Coustan [13]).

The study was approved by the Temple University Hospital Institutional Review Board, and informed consent was obtained from the mothers before the study.

**Methods.** Blood was collected at birth from the umbilical cords of 78 infants delivered at Temple University Hospital. The blood was immediately centrifuged, and the plasma was separated and stored at  $-70^{\circ}\text{C}$ .

Plasma glucose was measured with a glucose analyzer (Beckman Instruments, Palo Alto, CA). Plasma free insulin was determined by radioimmunoassays (RIAs), using an antiserum with minimal (<0.2%) crossreactivity with proinsulin (Linco Research, St. Charles, MO). Leptin levels were measured by RIA with an antiserum that did not crossreact with human insulin, proinsulin, glucagon, pancreatic polypeptide, or somatostatin (Linco Research, St. Charles, MO). The lowest concentration of plasma leptin detectable was 0.5 ng/ml. The intra- and interassay coefficients of variation were <8%.

**Statistical analysis.** The data are expressed as means  $\pm$  SE. Mean plasma leptin values and other measures of the groups were compared by Kruskal-Wallis one-way analysis of variance on ranks. Pearson's correlation coefficient was used to determine the relationship between continuous variables.

## RESULTS

**Plasma leptin levels.** Plasma immunoreactive leptin was detectable in the cord blood of all 78 neonates in concentrations ranging from 0.6 to 55.7 ng/ml. Mean plasma leptin concentrations were  $3.0 \pm 0.6$ ,  $3.5 \pm 0.8$ ,  $8.0 \pm 0.7$ , and  $31.1 \pm 5.1$  ng/ml in preterm-AGA, term-SGA, term-AGA, and term-LGA newborn infants, respectively (Fig. 1). Plasma leptin concentrations in term-AGA infants were significantly higher than in preterm-AGA neonates ( $P < 0.05$ ), but significantly lower than in term-LGA infants ( $P < 0.05$ ).

There was a positive correlation between cord plasma leptin levels and birth weights for all 78 infants ( $r = 0.74$ ,  $P <$

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AGA, appropriate for gestational age; GDM, gestational diabetes mellitus; LGA, large for gestational age; RIA, radioimmunoassay; SGA, small for gestational age.

TABLE 1  
Study population

Group	<i>n</i>	Gestational age at delivery (weeks)	Birth weight (g)
Group 1 (term-AGA infants)	43	39.2 ± 1.3	3,136 ± 384.5
Group 2 (term-LGA infants)	10	38.7 ± 1.2	4,163 ± 383.5
Group 3 (term-SGA infants)	4	38.6 ± 0.6	2,280 ± 149.5
Group 4 (preterm-AGA infants)	21	32.4 ± 2.8	1,897 ± 601.4

Data are means ± SE.

0.001; Fig. 2). There were, however, large differences among the four groups. For instance, there was no significant correlation between plasma leptin and birth weight in preterm-AGA infants, a weak correlation in term-AGA infants ( $r = 0.34$ ,  $P < 0.03$ ), and a strong correlation in term-LGA infants ( $r = 0.92$ ,  $P < 0.001$ ).

**Plasma glucose and insulin levels.** Mean plasma glucose concentration in all infants was  $79.2 \pm 5.8$  mg/dl and did not differ significantly among the four groups. Insulin concentrations were significantly higher in term-LGA infants than in term AGA and SGA infants ( $25.4 \pm 8.0$  vs.  $8.5 \pm 1.5$  vs.  $6.7 \pm 3.1$   $\mu$ U/ml, respectively;  $P < 0.01$ ). Plasma leptin levels did not correlate with plasma insulin levels, except in the term-LGA group ( $r = 0.72$ ,  $P = 0.02$ ).

## DISCUSSION

The main finding of this study was that leptin was present in the cord blood of all 78 newborn infants tested, indicating the fetal synthesis and secretion of leptin. The leptin concentrations in these infants were comparable with those found in adults. Plasma leptin concentrations correlated closely with birth weight in the larger infants (term-LGA group,  $r = 0.92$ ;  $P < 0.001$ ). The correlation was weaker in normal weight infants (term-AGA,  $r = 0.34$ ;  $P < 0.03$ ) and was absent in small infants (term-SGA and preterm-AGA groups). These differences were probably due to differences in body fat. Leptin levels have been shown to correlate closely with adiposity (6,14). Increased adiposity is characteristic of term-LGA infants, while decreased adiposity is the rule in preterm and term-SGA infants (15,16).

In adults, the close correlation between adiposity and circulating leptin levels supports the generally held concept that leptin is a signal from the body fat mass to the brain, where it affects satiety. It would, however, be difficult to apply this concept to the fetal situation. There, the mother is in complete control of the energy supply to the fetus, who has no need for feelings of hunger and satiety. On the other hand, "adult" plasma leptin levels, as found in this study, are entirely compatible with a role for leptin in fetal hematopoiesis, as was recently suggested (10,11). Indeed, it is possible that one main reason for the abundant presence of fat in bone marrow may be to release leptin and to stimulate adjacent hematopoietic stem cells.

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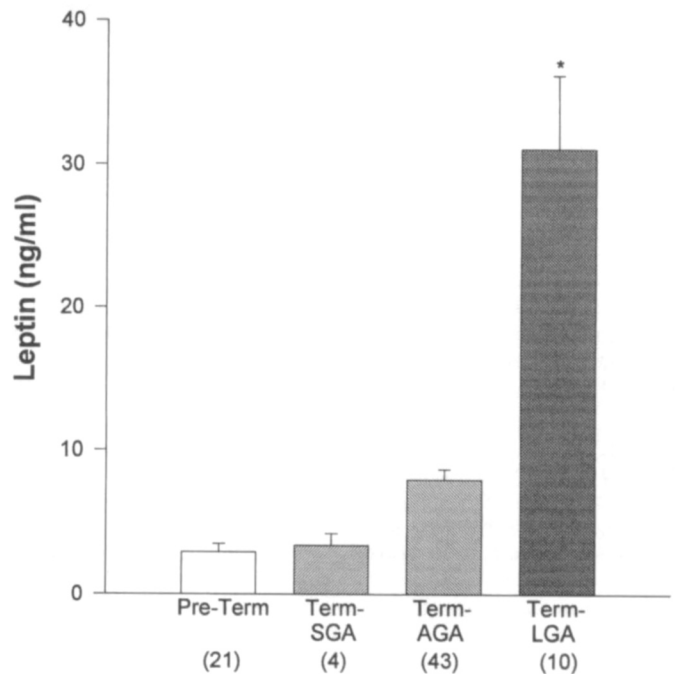


FIG. 1. Plasma leptin concentrations in the cord blood of 21 preterm-AGA, 4 term-SGA, 43 term-AGA, and 10 term-LGA infants. \* $P < 0.05$ , compared with the term-AGA infants.

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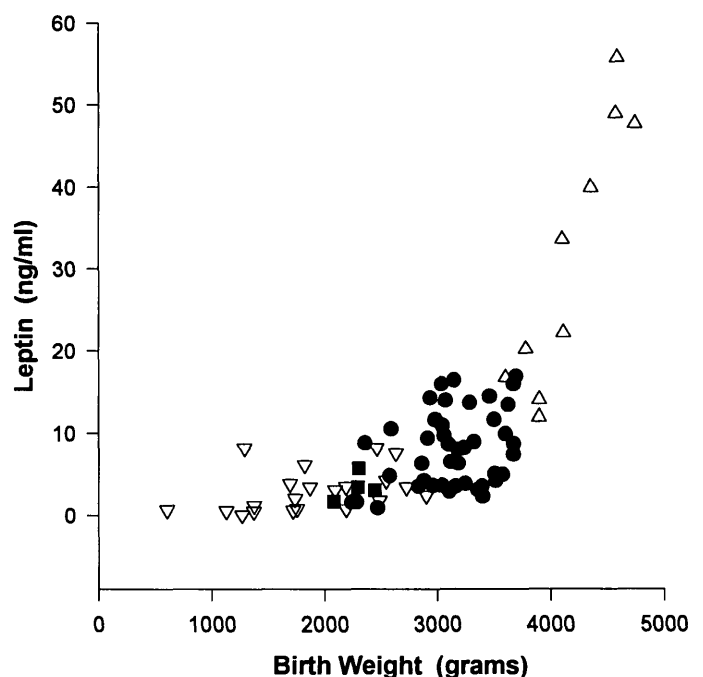


FIG. 2. Correlation of plasma leptin concentrations and birth weight in term-AGA (●), term-LGA (△), term-SGA (■), and preterm-AGA (▽) infants ( $r = 0.74$ ,  $P < 0.001$ ).

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