

# Association between umbilical cord leptin and weight gain according to feeding type in the early postnatal period, a brief report

Consuelo Treviño-Garza,\* Leonardo Mancillas-Adame,† Jesús Z. Villarreal-Pérez,†  
Manuel E. De la O-Cavazos,\* Cynthia M. Estrada-Zúñiga,\* Francisco J. Bosques-Padilla,‡ Jesús Argente§

\*Departamento de Pediatría, †División de Endocrinología,

‡División de Gastroenterología, Hospital Universitario Dr. José E. González, Universidad Autónoma de Nuevo León.

§Departamento de Pediatría y de Endocrinología Pediátrica, Hospital Infantil Universitario Niño Jesús, Departamento de Pediatría, Universidad Autónoma de Madrid. CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto Carlos III. Madrid, España.

**Asociación entre la leptina en cordón umbilical y aumento de peso de acuerdo con el tipo de alimentación en el periodo posnatal temprano, un breve informe**

## RESUMEN

**Antecedentes.** La ganancia de peso en la infancia depende del estado nutricional in utero y el crecimiento posnatal, así como de las prácticas de alimentación, cultura, accesibilidad a los alimentos y el nivel educativo de los padres. **Objetivo.** Evaluar la relación de los niveles de leptina del cordón umbilical y la influencia del tipo de alimentación (seno materno vs. fórmula) en la ganancia de peso a los tres meses de vida en recién nacidos sanos. **Material y métodos.** Noventa y nueve recién nacidos a término (masculinos,  $n = 48$ ; femenino,  $n = 51$ ) fueron incluidos en dos grupos de acuerdo con el tipo de alimentación: alimentados al seno materno ( $n = 49$ ) y alimentados con fórmula ( $n = 50$ ). La leptina fue medida de la sangre obtenida de la vena del cordón umbilical. **Resultados.** Las concentraciones de leptina del cordón umbilical y la ganancia de peso a los tres meses tuvieron una correlación inversa en lactantes alimentados con fórmula ( $r = -0.294$ ,  $P = 0.038$ ), estos hallazgos no fueron reflejados en lactantes alimentados al seno materno ( $r = -0.212$ ,  $P = 0.144$ ). **Conclusiones.** En esta cohorte mexicana de alimentación al seno materno, los niveles de leptina en el cordón umbilical fueron un predictor significativo de la ganancia de peso en infantes alimentados con fórmula.

**Palabras clave.** Leptina. Alimentación al seno materno. Alimentación con fórmula. Ganancia de peso. Periodo posnatal.

## ABSTRACT

**Background.** Weight gain in infancy depends on in utero nutritional status, with postnatal growth also dependent on feeding practices, culture, food accessibility and parents' education. **Objective.** To evaluate the relationship between umbilical cord blood leptin levels and feeding mode (breast-fed vs. formula) on weight gain at three months of life. **Material and methods.** Ninety-nine full-term newborns (male,  $n = 48$ ; female,  $n = 51$ ) were included in two groups according to feeding type: breast-fed ( $n = 49$ ) and formula-fed ( $n = 50$ ). Leptin was measured in blood obtained from the umbilical cord vein. **Results.** Umbilical cord leptin levels and weight gain at three months had a significant inverse correlation in formula-fed infants ( $r = -0.294$ ,  $P = 0.038$ ). This finding was not reflected in breast-fed infants ( $r = -0.212$ ,  $P = 0.144$ ). **Conclusions.** In our Mexican breastfeeding cohort, umbilical cord leptin levels were a significant predictor of weight gain in formula-fed infants.

**Key words.** Leptin. Breast-fed. Formula-fed. Weight gain. Early postnatal period.

## INTRODUCTION

Weight gain in infancy depends on *in utero* nutritional status, with postnatal growth indexes also depending on feeding practices, culture, accessibility to food, and parents' education.<sup>1-3</sup> Body weight and adipose mass are directly associated with leptin and inversely with adiponectin levels in infants, with early levels being predictive of future weight gain.<sup>4-7</sup> Moreover, some reports found that low cord blood leptin might be a predictor of postnatal weight gain.<sup>7</sup>

Leptin, a hormone involved in energy intake regulation, is present in breast milk, but not in formula.<sup>8</sup> Although its biological effect in human neonates is unknown, studies in animal models have shown that leptin is assimilated and reaches blood concentrations that are high enough to have a potential biological effect.<sup>9-10</sup> Whether breast-feeding affects leptin levels in the neonate has not been properly studied. Furthermore, whether there is an interaction between cord blood leptin levels and the response to the type of postnatal feeding is unknown.

The aim of this study was to provide additional information to the previous Breastfeeding cohort findings<sup>11</sup> regarding the relationship between umbilical cord blood leptin levels and feeding mode (breast-fed *vs.* formula) on weight gain at three months of life in healthy term newborns.

## MATERIAL AND METHODS

We carried out a prospective study from January 2006 to December 2007 at the Universidad Autónoma de Nuevo León Medical School and the Dr. Jose E. Gonzalez University Hospital in Monterrey, Mexico. The study was approved by the Ethics and Research Committee of the University Hospital. Parents provided written informed consent before data collection and blood sampling.

A cohort of 99 healthy term newborns (> 37 weeks gestation; 48 males and 51 females) were included. Newborns of mothers with gestational diabetes or pregestational diabetes mellitus were excluded. Elimination criteria included any disease that required inpatient management, gastrointestinal disease, food intolerance, surgery or any acute or chronic condition that could modify food intake. The cohort was divided into two groups according to feeding type: breast-fed (n = 49) and formula-fed (n = 50). The sex distribution in breast-fed newborns was 26 male and 23 female subjects and in the formula-fed

group, there were 22 males and 28 females. Newborns were classified by Z-score according to gender, birth weight, and weight for age at 3 months.<sup>12</sup>

The database on Child Growth and Malnutrition uses a Z-score cut-off point of less than -2 SD to classify low weight for-age and a cut-off point of more than +2 SD as high weight-for-age, with > +2 to -2 SD as normal weight. Feeding mode was freely chosen by the parents after participating in a prenatal education program on the benefits of breast milk. Breast-feeding was defined according to World Health Organization operational definitions raised at a consensus held in 2007.<sup>13</sup> Weight gain was calculated in absolute values by subtracting birth weight from the weight at the three-month old follow-up visit.

One blood sample was taken from the umbilical cord vein from each child immediately after birth and centrifuged at 3,000 rpm. Aliquots of serum were separated, frozen, and stored at -20°C for later analysis of leptin. Weight registries were documented prospectively by a single observer with a Torrey scale (Torrey, S.A. de C.V., Monterrey, Mexico) at birth and at 3 months  $\pm$  3 days of age.

## Hormone assay

Leptin was measured by radioimmunoassay (RIA) using a commercial kit (Linco Research, Saint Charles, Missouri, USA) according to the manufacturer's instructions. The sensitivity was 0.5 ng/mL and the intra- and inter-assay coefficients were 3.4% and 6.4%, respectively.

## Statistical analysis

Data from the population participating in the original study were used. Data analysis was carried out with SPSS v. 13 for Windows. Continuous variables are expressed as means and standard deviations; categorical data are expressed as frequencies and percentages. Non-normal distribution was transformed to natural logarithm (ln) for analysis.

The correlation of ln leptin values with weight gain measures and feeding type was carried-out by using linear regression analysis. A *P*-value of < 0.05 was considered statistically significant.

## RESULTS

The total cohort population was included for analysis. None of the cohort participants developed

**Table 1.** Demographic characteristics of breast-fed and formula-fed newborns and weight gain at three months of age.

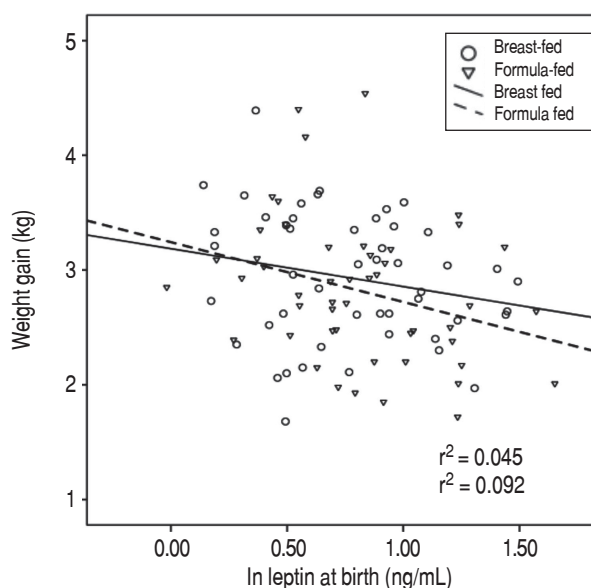
Characteristic	Feeding type		P
	Breast-fed (n = 49)	Formula-fed (n = 50)	
Maternal age (years)	23.4 ± 5.4	23.5 ± 5.8	0.894
Mother with stable partner, n (%)	43 (88)	43 (86)	0.796
Education	-	-	0.773
Basic, n (%)	5 (10.2)	7 (14)	-
High school, n (%)	41 (83.7)	39 (78)	-
Higher, n (%)	3 (6.1)	4 (8)	-
Occupation	-	-	0.630
Housewife, n (%)	46 (93.9)	48 (96)	-
Other, n (%)	3 (6.1)	2 (4)	-
Prenatal care ≥ 5 visits, n (%)	45 (91.8)	46 (92)	0.976
Socioeconomic level	-	-	0.371
Low, n (%)	44 (89.8)	40 (80)	-
Middle, n (%)	3 (6.1)	7 (14)	-
High, n (%)	2 (4.1)	3 (6)	-
Birth weight (kg)	3.33 ± 0.47	3.34 ± 0.37	0.949
Length (cm)	49.95 ± 2.01	49.80 ± 1.72	0.673
Male/Female	26/23	22/28	0.424
Ln leptin (ng/ml) in umbilical cord	0.769 ± 0.365	0.808 ± 0.360	0.590
Weight gain at three months (kg)	2.93 ± 0.56	2.83 ± 0.62	0.400

Data are presented as means ± SD.

any serious diseases that required inpatient management or produced food intolerance during the three-month follow up.

As previously reported,<sup>11</sup> no differences were found between breast and formula-fed groups regarding maternal age, marital status, education or socioeconomic level. Likewise, no differences were found between the two groups for anthropometric, biochemical, or social variables, which were reported in a previous publication.<sup>11</sup> In brief, we did not find differences in birth weight, birth length, or known factors that affect weight gain among breast-fed or formula-fed subjects at birth (Table 1).

Umbilical cord ln leptin levels (ng/mL) in breast-fed infants were 0.769 ± 0.365, while in formula-fed infants they were 0.808 ± 0.360, with no significant differences in ln leptin levels between the two groups ( $P = 0.59$ ) (Table 1). There were no differences in net weight gain between groups. There was a negative correlation between umbilical cord ln leptin levels and weight gain at three months in formula-fed infants ( $r = -0.294$ ,  $P = 0.038$ ), which was not seen in breast-fed infants ( $r = -0.212$ ,  $P = 0.144$ ) (Figure 1). No gender influence was noted on weight gain prediction. Variance in weight gain explained by ln leptin at birth was 4.5% in breast-fed infants and 9.2% in those who were formula-fed.



**Figure 1.** Correlation between cord blood leptin concentration (ng/mL) and weight gain (kilograms) in breast-fed and formula-fed groups at three months of age.

## DISCUSSION

Our study was designed to provide additional information to the Breastfeeding cohort findings<sup>11</sup> regarding the interaction between postnatal feeding

mode (breast-milk versus formula) and the usefulness of cord blood leptin levels as predictors of weight gain in healthy term newborns.

Maternal nutritional status has been shown to influence not only the birth weight of the offspring, but also the propensity towards obesity in adult life. As maternal diet is reported to influence cord blood leptin levels at birth,<sup>14</sup> these levels could possibly predict the future weight gain of these individuals. Indeed, cord blood leptin levels have been reported to be inversely associated with weight gain at 6 months of age and with body mass index (BMI) at 3 years of age after multivariate analysis.<sup>6</sup> We found a significant negative correlation between umbilical cord leptin levels and weight gain at 3 months of age, but only in the formula-fed group. This differential response between the formula and breast fed groups cannot be explained by differences in umbilical cord ln leptin levels. Thus, it is possible that the predictive value of prenatal leptin levels is modified by and/or interacts with postnatal circulating leptin levels, the interaction of endogenous leptin levels at birth as a predictor of neonatal weight gain according to feeding type has not been described.

Leptin has been shown to be present in human milk, and in animal models it has been shown to enter the bloodstream from the gastrointestinal tract.<sup>15,16</sup> Together these observations support the hypothesis that leptin in human milk can affect circulating leptin levels in infants. The basic principle of this hypothesis has been demonstrated by the transfer of other bioactive substances of human milk to newborns. Infant formulas do not contain leptin.<sup>9,17</sup> As we can assure that there was strict compliance with the type of feeding, according to the WHO definition, as a result of a close surveillance of the cohort, the difference in oral leptin intake during this 3-month period is different. The influence of leptin on neonatal weight gain in breast-fed infants is known in animal models and humans.<sup>4-7</sup> These findings reinforce the hypothesis of a response of fat tissue to leptin during lactation.<sup>10,18</sup>

Children are capable of regulating their energy intake based on their physiological needs, which includes responses to the internal stimuli of hunger and satiety. An important finding in our cohort is a negative relationship between ln leptin at birth and weight gain during the first three months of life in formula-fed children, but not in breast-fed children. A potential explanation includes the fact that in the neuroendocrine system regulating appetite, high levels of circulating leptin may cause a decrease in neuropeptide Y in the hypothalamus, which leads to

a subsequent decrease in caloric intake.<sup>19</sup> In addition, a low concentration of leptin is interpreted as a decrease in energy reserves, which influences the ventro-medial nucleus of the hypothalamus to reduce energy expenditure.<sup>20,21</sup> On the other hand, Hediger, *et al.*<sup>22</sup> proposed that the protective effect of breast feeding on weight regulation in early childhood is caused by the greater caloric density of baby formula and not only by any properties that are inherent to breast milk. These authors also suggest that the higher protein/nitrogen content in formula *vs.* breast milk could explain this metabolic response. Although there is no consensus, our findings support the fact that leptin levels during intrauterine and early neonatal periods and their interaction with environmental conditions, such as diet, can be important mechanisms that link early nutrition with obesity at later stages of life. However, further studies are warranted to determine if and how the early intrauterine and postnatal nutritional environments influence the synthesis, secretion, and action of leptin in later life.

## CONCLUSION

In the group of formula-fed term newborns, umbilical cord leptin levels predicts weight gain, in a negative correlation that explains 9.2% of variance, while in breast-fed infants ln umbilical cord leptin does not predict weight gain.

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*Correspondence and reprint request:*

**Consuelo Treviño-Garza, M.D.**  
 Departamento de Pediatría  
 Universidad Autónoma de Nuevo León  
 Hospital Universitario Dr. José E. González  
 Av. Madero Pte. y Ave. Gonzalitos s/n  
 Col. Mitras Centro  
 64460, Monterrey, N. L.  
 Tel.: (81) 8348-5421, (81) 8346-9959  
 Fax: (81) 8348-9865  
 E-mail: cotrevin@hotmail.com

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