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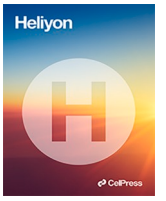

Breast milk leptin concentrations and infant anthropometric indicators in SGA versus non-SGA breastfed infants born at term

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ABSTRACT

Leptin concentrations in breast milk can influence metabolic programming during the first months of life. Small for gestational age (SGA) newborns show a peculiar growth pattern after birth, which can lead to adulthood diseases. This study aims to assess an association between leptin concentration in mature breast milk and the infant anthropometric indicators of the SGA and the non-SGA groups, in addition, to comparing the hormone level between these groups. A longitudinal study was performed with mother-infant pairs. The maternal sociodemographic information was collected in the first 48 h postpartum. Breast milk was collected at one month postpartum and leptin concentrations were obtained by immunoassays. The infant anthropometric measurements were collected at three and six months postpartum and included weight, height (to body mass index-BMI calculated), triceps skinfold (TSF), and subscapular skinfold (SSF). The BMI for age (BMI/A), TSF, and SSF were calculated by Z-score indicators. Data from 67 mother-infant pairs ($n = 16$ SGA and $n = 51$ non-SGA) were analyzed. In univariate analyses, the breast milk of the SGA group had lower leptin concentrations than the non-SGA group ($p = 0.006$), however, after adjustment, there was no difference between groups ($p = 0.181$). In the SGA group, there was a significant association between leptin concentrations and lower SSF at six months in infants, after adjustment ($p = 0.003$). In the non-SGA group, the breast milk leptin was associated with lower BMI/A at three and six months in infants, after adjustment ($p = 0.002$ and $p = 0.010$, respectively). The association between breast milk leptin concentrations with SSF in the SGA group and BMI/A in the non-SGA group suggests that leptin may be a modulating factor in infant growth in the first months of life.

1. Introduction

In the first months of life, breast milk is one of the most nutritionally important foods for the child's growth and development [1]. Although previous research on the impact of metabolic hormones on health outcomes in children shows conflicting results, it is

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possible that infant growth and body composition can be influenced by the metabolic hormones (i.e., insulin, leptin, adiponectin, ghrelin) present in breast milk [2]).

In particular, the peptide hormone leptin regulates food intake, body mass, and reproductive function and plays a role in fetal growth, proinflammatory immune responses, angiogenesis, and lipolysis [3]. Also leptin was identified as playing a crucial role in the postnatal programming of a healthy phenotype, establishing the concept of long-term regulation of body fat stores [4]. A recent systematic review showed an inverse relationship between leptin in human milk and infant weight and five researchers reported the effect on satiety and self-regulation of infant intake [5]. Even though numerous factors are involved in the development of obesity in adulthood, there is evidence that leptin resistance promotes reduced satiety over-consumption of nutrients, and increased body mass index (BMI) [3].

Moreover, clinical conditions during gestation, such as intrauterine growth restriction (IUGR), and neonate growth, like infants born small for gestational age (SGA), may influence the patterns of growth and development of infants [6], leading to a high risk of overweight and metabolic diseases in adulthood [7]. A longitudinal study of our research group observed that leptin concentrations in mature milk were negatively correlated to weight gain at one month postpartum and that there was a significant decrease in leptin concentrations from mature milk in mothers of SGA infants, proposing the existence of post-neonatal modulation of this hormone in the breast milk [8].

The influence of leptin concentrations in breast milk on infants exposed to adverse intrauterine environments, like SGA infants, remains unexplored. Thus, the objective of this study was to investigate the association between leptin concentrations in mature breast milk and the infant anthropometric indicators in the SGA group, compared to the non-SGA group, at three and six months of age.

2. Methods

2.1. Study sample

This longitudinal study is part of research entitled: “Impact of Perinatal Different Intrauterine Environments on Child Growth and Development in the First Six Months of Life - IVAPSA study”. Details about the convenience sample size and protocols used in this study have been published elsewhere [9], as well as some baseline results [10].

The postpartum recruitment and interviews occurred between 2011 and 2016. The study included 400 pairs of mother-infant who had their delivery assistance in three public hospitals in Porto Alegre, the capital of Rio Grande do Sul, a state in southern Brazil. The mother-child pairs were distributed into five study interest groups according to the following maternal gestational conditions: hypertension, diabetes mellitus, smoking, IUGR with the birth of SGA newborns, and a control group. Exclusion criteria were HIV-positive newborns, twins or higher-order multiples, preterm (gestational age under 37 weeks), those with congenital malformations, or those requiring hospitalization.

To avoid the influence of other maternal metabolic factors during pregnancy, mother-child pairs from hypertension, *diabetes mellitus*, and smoking groups were not used. Thus, according to the objectives of this manuscript, two groups were used: 1) SGA group: newborns at term with IUGR who had a birth weight below the 5th percentile for fetal growth [11]; 2) non-SGA group: newborns at term without IUGR. In both groups, there were no mothers with any of the gestational conditions investigated by the IVAPSA research (hypertensive disorders, *diabetes mellitus,* and smoking during pregnancy).

2.2. Data collection

According to the research protocol, after the initial interview in the first 48 h postpartum, the interviews and evaluations were scheduled for the 7th and 15th days and for the 1st, 3rd, and 6th months, to monitor the child’s health periodically. For this manuscript, were used the information obtained in the postpartum period and at the 1st, 3rd, and 6th months of pairs of mother-infant.

The covariables were obtained through standardized questionnaires applied by trained researchers: level of maternal education (years of schooling), maternal age (years), and pregnancy marital status (with or without a partner). For socioeconomic evaluation, an instrument used by the government to classify the Brazilian population into categories A, B, C, D, and E was applied. Among them, category A was the richest socioeconomic class and category E was the poorest. This instrument considers the level of education, consumer goods, and specific rooms in the house. Maternal skin color was self-reported and then defined by the interviewer as white or non-white.

2.3. Prenatal and perinatal data

Prenatal (parity, gestational age, and weight gain during pregnancy) and perinatal (type of delivery, sex, weight, length, and Apgar score of the newborn) information was obtained from hospital medical records.

2.4. Anthropometric data

Anthropometric measurements of each pair of mother-infant were collected in all interviews. The weight (g) of the child was obtained by weighing the mother and child together and subtracting the mother’s weight, using a digital scale, properly tared (Marte®, Scientific, São Paulo, Brazil), that was accurate to within 50 g. The infants were completely naked, without diapers, while they were weighed. The infants’ length (cm) was measured in the supine position on a flat, stable surface with a portable stadiometer

(Alturexata®, Belo Horizonte, Brazil). Triceps skinfold (TSF, in mm) was measured at the midpoint between the acromion and the olecranon, while subscapular skinfold (SSF, in mm) was measured diagonally below the inferior angle of the scapula at three and six months postpartum using a skinfold caliper (Lange®, Ann Arbor, Michigan, USA).

Anthropometric measurements were performed in duplicate and the mean value was used. The researchers were trained periodically and used standardized techniques with calibrated equipment. Also, a training manual was used to ensure standardization of instructions and consistency of training standards for project workers throughout the life of the research [12].

The maternal anthropometric measurements were collected at all interviews and consisted of weight (kg), height (m), TSF (mm), and SSF (mm). BMI was calculated as weight in kilogram divided by the height in meter square i.e. kg/m^2. The maternal BMI at the first prenatal visit in the first month was obtained from the records in the pregnant woman's booklet, a mandatory document to be filled out during the pregnant woman's prenatal follow-up. Maternal BMI at one month was calculated by measuring weight (kg) and measured height (m) with the same formula. BMI was categorized as underweight ($<18.5\ kg/m^2$), healthy weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese ($\geq 30.0\ kg/m^2$) [13].

The infants' anthropometric data were classified in Anthro version 3.2.2® about BMI for age (BMI/A) indicator, TSF, and SSF measurements Z-scores at three and six months, using World Health Organization parameters [14].

2.5. Breast milk data

Breast milk, hindmilk or foremilk, was collected (1–5 mL) one month after postpartum, at which time all infants were breastfed. Previous studies have found that variation does not exist for leptin concentrations in breast milk, justifying the random sampling [15, 16].

The collection procedure was carried out by the mothers under appropriate supervision by a researcher. The milk was manually expressed into sterile flasks, and the samples were immediately aliquoted into labeled 1.5-mL tubes and stored at −80 °C.

For the leptin assay, the milk samples were thawed and centrifuged at 15,000 rpm at 4 °C for 30 min to isolate the fat, which could interfere with the measurements. The isolated fat, to which no protease inhibitor had been added, was discarded without having been measured. Leptin was quantified in skim milk using an ELISA kit (Millipore®). All samples were assayed in duplicate in a single assay with a detection limit of 0.2 ng/mL and an intra-assay variation of 4.9%.

2.6. Breastfeeding practices

Breastfeeding practices were analyzed during the interviews from birth to six months by structured questionnaires, developed by the researchers. In our analysis, only children who were breastfed for at least one month were included.

2.7. Statistical analyses

The categorical variables were represented by an absolute number (n) and relative frequency (%). The variable maternal age and maternal schooling were represented by mean ± standard deviation (SD) and the pre-gestational BMI and maternal BMI at one month's variables were represented by the median and interquartile range (IR) (median [p25, p75]), respecting the results of the Shapiro-Wilk normality test.

The proportions of the studied variables were compared between the groups by the chi-square test. To compare the mean of the variables maternal age and schooling between the groups, the t-test for independent samples was performed. For the non-parametric variable, we compared the BMI distribution between the groups by the Mann-Whitney test.

The logarithmic transformation was performed in the variable leptin (base-10 logarithm-leptin) since it was significant in the normality test. The new variable was compared between the groups by the ANCOVA test being adjusted for maternal age, skin color, and maternal BMI values at one month. To represent the results of the log-leptin variable the exponential calculation was applied to return the original metric of the variable. This result was expressed in a geometric mean and 95% confidence interval.

A multiple linear regression analysis was performed to examine the association between log-leptin and anthropometric data in newborns with the SGA and the non-SGA groups, before and after controlling for the covariate. The model was adjusted for maternal BMI values at one month.

The significance level was set at 5% ($p < 0.05$). The variables were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0.

2.8. Ethical aspects

Ethical approval to conduct this study was granted by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (number 11–0097) and the Ethics Committee of the Grupo Hospitalar Conceição (number 11–027). Postpartum women, who met the eligibility criteria were invited to participate in the study and, after signing the informed consent form, were included.

3. Results

Data from 67 mother-infant pairs were analyzed with 23.9% ($n = 16$) in the SGA group and 76.1% ($n = 51$) in the non-SGA group. The maternal and familial characteristics of each group are presented in Table 1. The authors found that the proportion of mothers

with non-white skin color was significantly higher in the SGA group when compared to the non-SGA group ($p = 0.037$). There was no socioeconomic status A among participants and there were no differences in socioeconomic status between groups ($p = 0.125$). The median of pre-pregnancy BMI and maternal BMI at one month postpartum in the SGA group is lower than the distribution of the non-SGA group ($p = 0.007$; $p = 0.005$, respectively). Also, there were differences between groups and BMI in the one-month postpartum category (overweight x no overweight) ($p = 0.027$). However, there were no significant differences between groups ($p = 0.117$), when was created the category with just obesity. The median [IR] leptin concentration in mature milk ($n = 67$) was 0.40 ng/mL [0.25; 0.80]. Maternal pre-pregnancy BMI and maternal BMI at one month postpartum were positively correlated with leptin concentrations in the overall sample ($p < 0.001$; $r = 0.653$) and in each group ($p < 0.05$).

In univariate analyses, the breast milk of the SGA group had significantly lower leptin concentrations than the non-SGA group ($p = 0.006$). Although the results are in the same direction, when we adjusted by maternal BMI at one month postpartum, there was no difference between groups ($p = 0.181$) (Table 2).

Table 3 shows the results of breast milk leptin at one month and the infants' anthropometric measures at three and six months for the SGA and the non-SGA groups. There was a significant association between breast milk leptin concentrations and lower SSF Z-scores at six months of the infants, after adjustment ($p = 0.003$). In addition, in the non-SGA group, there was an association between breast milk leptin concentrations and lower BMI/A at three and six months of the infants, after adjustment ($p = 0.002$ and $p = 0.010$, respectively).

4. Discussion

In this study, the findings indicated some significant association between leptin concentrations in breast milk and infant growth and anthropometric indicators at three months or six months, with variations before and after adjustment. Moreover, mature breast milk leptin concentrations were lower in the SGA group in unadjusted models, but there was no significant difference between groups after covariate adjustment. Furthermore, genetic and other hormonal factors of the mother and child need to be considered.

Fetal growth patterns are the result of several components from maternal, fetal, placental, and genetic factors, acting in a complex way [17,18]. Mothers' health conditions are one of the key variables as risk factors for IUGR fetuses, such as maternal age, inter-pregnancy interval, ethnicity or race, maternal pre-pregnancy weight, and maternal diet [19]. Particularly, in the present study, the results found that the SGA group has mothers with a higher proportion of non-white skin color and lower BMI values, compared to the non-SGA group. Thus, despite this group not presenting evidence of clinical a during pregnancy, its social and biological background can infer a higher risk for SGA newborns.

In this study, breast milk leptin concentrations were correlated with the maternal BMI (pre-pregnancy and at one month) in each group. These findings were corroborated by several previous studies, which found a positive correlation between breast milk leptin concentrations and maternal BMI values [16,20–28], leptin and maternal skinfolds [26], and maternal body fat [25]. Breast milk leptin concentrations have also been proportionally related to maternal BMI values and adiposity [2]. However, some authors have not found these same correlations in their studies [29–31].

An interesting study with 430 breastfed infants examined the variation of three breast milk hormones according to maternal

Table 1
Maternal and familial characteristics for SGA and non-SGA group.

Variables	Overall ($n = 67$; 100%)	SGA ($n = 16$; 23.9%)	Non-SGA ($n = 51$; 76.1%)	*p-value*
Maternal				
Age (years)[a]	25.6 (7.3)	22.8 (5.5)	26.5 (7.6)	0.072
Reported skin color[c]				
White	40 (59.7)	5 (31.3)	35 (68.6)	**0.037**
Non-white	27 (40.3)	11 (68.7)	16 (31.4)	
Education (years)[a]	9.6 (2.6)	9.9 (1.8)	9.5 (2.8)	0.605
Marital status[c]				
Married or living with a partner	58 (86.6)	14 (87.5)	44 (86.3)	>0.999
Single, without a partner, separated or divorced	9 (13.4)	2 (12.5)	7 (13.7)	
Pre-pregnancy BMI (Kg/m^2) ($n = 63$)[b]	22.9 [20.2; 28.0]	20.3 [19.6; 22.3]	24.0 [20.7; 29.1]	**0.007**
BMI at one month postpartum (Kg/m^2) ($n = 66$)[b]	24.8 [22.5; 30.4]	23.0 [20.8; 24.6]	27.3 [23.7; 32.2]	**0.005**
BMI at one month postpartum	32 (48.5)	3 (20.0)	29 (56.9)	**0.027**
Overweight	34 (51.5)	12 (80.0)	22 (43.1)	
No overweight ($n = 66$)[b]				
Familial				
Socioeconomic class[c d]				
B	26 (38.8)	4 (25.0)	22 (43.1)	0.125
C	38 (56.7)	10 (62.5)	28 (54.9)	
D and E	3 (4.5)	2 (12.5)	1 (2.0)	

SGA: small for gestational age; BMI: body mass index.
[a] mean (SD), Student's t-test.
[b] median [IR], Kruskal-Wallis test.
[c] *n* (%), Pearson chi-square test, or Fisher's exact test.
[d] Socioeconomic class is determined using the ABEP (Brazilian Association of Survey Companies) questionnaire.

Table 2
Breast milk leptin concentration at one month for SGA and non-SGA group.

Statistical models	SGA Mean [CI 95%]	Non-SGA Mean [CI 95%]	*p-value*	Effect size	Observed power
Leptin concentrations, [a]Model 1 ($n = 67$)	0.213 [0.129; 0.350]	0.483 [0.366; 0.639]	**0.006**	0.113	0.808
Leptin concentrations, [b]Model 2 ($n = 66$)	0.311 [0.202; 0.481]	0.437 [0.347; 0.549]	0.181	0.028	0.265

SGA: small for gestational age; CI: confidence interval.
Effect size: Partial Eta Squared.
[a] Model 1: (*t*-test) without adjustment.
[b] Model 2: (ANCOVA) adjusted by: mean maternal BMI at one month postpartum.

Table 3
Breast milk leptin at one month and the infants' anthropometric measures at three and six months for SGA and non-SGA group.

Variables	SGA		Non-SGA	
	β (*p*) [*n*]		β (*p*) [*n*]	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Infant anthropometric measures 3 months				
BMI/A Z-score	−0.365 (0.451) [14]	−0.665 (0.275) [13]	−0.694 (0.065) [47]	−1.432 (**0.002**) [47]
TSF Z-score	−0.780 (**0.040**) [13]	−0.946 (0.052) [12]	−0.352 (0.468) [48]	0.177 (0.780) [48]
SSF Z-score	−0.451 (0.517) [13]	−0.784 (0.378) [12]	−0.189 (0.746) [46]	−0.229 (0.767) [46]
Infant anthropometric measures 6 months				
BMI/A Z-score	−0.997 **(0.012)** [12]	−0.764 (0.112) [12]	−0.729 (0.102) [43]	−1.437 (**0.010**) [43]
TSF Z-score	−1.160 **(0.017)** [12]	−0.685 (0.222) [12]	−0.383 (0.437) [47]	0.367 (0.551) [47]
SSF Z-score	−1.217 **(0.007)** [12]	−1.572 **(0.003)** [12]	−1.345 **(0.019)** [45]	−1.257 (0.096) [45]

SGA: small for gestational age; BMI/A: body mass index for age; TSF: triceps skinfold; SSF: subscapular skinfold.
Adjusted by maternal BMI at one month postpartum.
Linear regression.

characteristics and determined their association with infant body composition at four months and one year. The authors found that independent of maternal factors; higher breast milk leptin was associated with lower infant weight-for-length Z-scores at four months and one year [32].

Several studies investigating the influence of leptin on infant anthropometric measures have obtained different results, including inverse correlations between leptin and weight, BMI, weight gain, or length in investigations up to two years of age [21,23,25,27,29,31,33,34]. Other studies have found no relation between leptin and these variables [15,30].

Regarding the effects of breast milk leptin concentrations on infant body composition, a study using skinfold measurement found a significant negative correlation between leptin and lean mass at six months of age [21]. The authors [24] found a significant negative relationship between breast milk leptin levels at one month and infant length, fat percentage, total fat mass, and trunk fat mass at six months of age. However, other studies have not confirmed a significant correlation between leptin and body composition, although they employed different methodologies. Also, the authors [23] used a full-body dual-energy X-ray absorptiometry (DXA) scan to measure body composition and considered one-month postpartum breast milk leptin concentrations.

This study suggests the existence of a possible association between leptin and anthropometric variables at six months, which signals that leptin ingested through breast milk may play an important role in the nutritional status of breastfed children. The leptin concentration of mature breast milk in the SGA group was lower when compared to the non-SGA group and was observed only before the model fitted to the mean maternal BMI at one month postpartum. The ingestion of leptin through breast milk could promote rapid weight gain during the first months of life, providing a relation between maternal body composition and growth, development, and the regulation of energy balance in infants and adulthood [2,4].

Leptin binds to hypothalamic receptors in adults, resulting in the inhibition of orexigenic neuropeptides and the stimulation of anorectic neuropeptides [35]. In addition, it acts to inhibit lipogenesis, stimulating lipolysis and fatty acid oxidation in adipocytes. Through these actions, leptin could modulate appetite and satiety in breastfed infants, whereas a lack of such modulation could result in an accumulation of energy stores. Leptin may also be related to the long-term control of body weight through the development, during certain critical periods, of neural circuits that control food intake and fat throughout life [36]. In an experimental study with Wistar rats, supplementation with physiological doses of leptin during lactation was associated with lower food intake, resulting in significantly lower body weight and proportionally lower fat mass in adulthood, preventing obesity and other related diseases [37].

The authors found that breast milk from the SGA mothers' group had significantly lower leptin concentrations than the non-SGA group and did not persist after being adjusted by maternal BMI at one month, although the results point in the same direction. We thought that greater statistical power, such as the number of participants in each group, would be important to evaluate further

analysis. However, the rigorous methodology for inclusion in the sample groups restricted the sample size [9].

An epidemiological literature review about the relationship between the appetite-regulating hormone leptin in human milk with growth and infant weight gain found that there was evidence to establish their direct effect association on the growth and development of infant weight [5]. However, the mechanism by which leptin is related to infant weight gain is still unclear, as the results are conflicting, because a variety of maternal confounding factors, such as BMI, diet, and lifestyle, among other variables, are often neglected [5].

Among the limitations of the study may be cited is the small sample size. Despite the existence of more accurate methodologies for the measurement of body composition, skinfolds have been recommended for this age group [38,39]. To avoid the variation of agreement between evaluators, standardized techniques of evaluation, team training, and monitoring were included. The strengths of this study include its originality in identifying early aspects of growth and the possibility of analyzing longitudinal maternal and child data at important moments of development, including breastfed analyses. Also, the implications of the study results may be that leptin present in human milk plays an important role in the nutritional status of breastfed infants in the 6th month and can be integrated as one more variable to investigate child metabolic growth, especially among SGA children.

5. Conclusion

The concentrations of leptin in the mature milk of the group of mothers with SGA newborns associated with lower SSF Z-scores of these infants in the 6th month could influence by the gestational clinical conditions (IUGR). In addition, there was a lower value of BMI/A at three and six months for infants in the non-SGA group. The results suggest that the leptin concentrations in mature breast milk could facilitate catch-up weight gain, particularly in the modulation of fat mass during the first months of life. Future studies with larger populations are needed to understand the long-term consequences of leptin metabolism comprehensively.

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Author contribution statement

Sara Brunetto; Juliana Rombaldi Bernardi: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Isabel Cristina Ribas Werlang: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Marina Nunes: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Ciliana Rechenmacher; Thiago Beltram Marcelino: Performed the experiments; Analyzed and interpreted the data.

Clécio Homrich da Silva; Marcelo Zubaran Goldani: Conceived and designed the experiments; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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