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Leptin and adiponectin concentrations in infants with low birth weight: relationship with maternal health and postnatal growth

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Original Article

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Abstract

Health in pregnancy and infancy can affect the risk of chronic non-communicable diseases. We aimed to describe leptin and adiponectin concentrations in low birth weight (LBW) infants and identify possible associations with maternal nutritional status, adequacy for gestational age, nutritional recovery, and current dietary intake. A cross-sectional study with LBW infants (9–12 months) including maternal background and pre-pregnancy nutritional condition was performed. From the Infants: anthropometry at birth and current was expressed as z-score (weight: WAZ, length, head circumference), nutritional recovery, dietary intake, leptin, and adiponectin blood concentrations. The mean age of the 54 infants was 10.0 ± 1.5 months, 32 (59.3%) were female, 36 (66.7%) preterm, 23 (42.6%) small for gestational age (SGA), and 25 pregnancies (46.3%) were twin. Almost all (98%) of the infants intake energy and protein above the recommendation, and 47 (87.6%) consumed ultra-processed foods. At the time of the assessment, 8 (14.8%) were overweight and 4 (7.4%) had short stature. SGA infants showed faster weight recovery (WAZ 1.54; 95% CI 1.17, 1.91; $p = 0.001$), higher leptin's concentration (3.0 ng/ml (1.7, 3.0) versus 1.6 ng/ml (0.9, 2.6); $p = 0.032$)), and leptin/adiponectin ratio (0.13 ± 0.08 versus 0.07 ± 0.07; $p = 0.018$). The pre-gestational BMI was a modifier of the effect of WAZ on leptin levels ($p = 0.027$) in LBW infants. Higher pre-gestational BMI increased the effect of WAZ variation (birth and current) on leptin levels. Concluding, LBW infants showed early changes in leptin and adiponectin concentrations, influenced by maternal (pre-gestational BMI), intrauterine (gestational age adequacy – SGA), and postnatal weight gain. This combination of factors may increase the risk of NCD for this group of children.

Introduction

Low birth weight (LBW, birth weight < 2,500 g) represents 8.5% of live births and is associated with prematurity and/or restricted intrauterine growth.[1] Among maternal LBW-related conditions are nutritional disorders (malnutrition, obesity, and micronutrient deficiency) and diseases (arterial hypertension, diabetes mellitus, and infections).[2,3] A similar aspect of these situations is the change in the supply of nutrients or oxygen via the placenta, influencing growth and body composition at different stages of fetal development.[4]

In the postnatal period, LBW infants can have accelerated weight gain and increased risk of developing diseases such as diabetes mellitus and cardiovascular diseases, especially those born small for gestational age (SGA).[5,6] Recent studies relate this risk to changes in adipose tissue development during the intrauterine and postnatal phase and the secretion of adipokines and inflammatory factors that would be associated with the development of insulin resistance.[7,8] Among more than 100 substances were produced by adipocytes. Leptin and adiponectin are the most studied adipokines with relevance during the first years of life.[9]

Some relevant leptin's actions are appetite and energy expenditure control by hypothalamic action. Leptin concentrations correlate with the amount of body fat and are high at the end of pregnancy. The newborn's levels fall after birth. However, these values increase again as the infant gains weight and accumulates fat mass.[9] There is a possibility to observe an increase in leptin values in situations of visceral fat accumulation and insulin resistance.[8,9] In turn, adiponectin is produced by mature adipose tissue and subcutaneous topography. Adiponectin has anti-atherogenic, anti-diabetic, and anti-inflammatory action.[9] Newborns have higher adiponectin concentrations than children and adults. Also, pregnant women with diabetes mellitus and obesity have lower adiponectin concentrations.[9] Besides this, breast milk is related to decreased obesity in breastfed infants by several mechanisms, including the presence of leptin, lower protein content, favorable microbiota, and flavors diversity.[10,11]

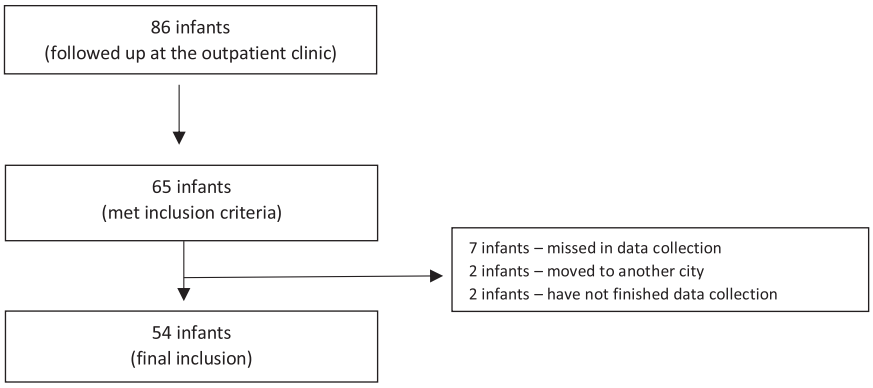

Fig. 1. Flow chart of identification and inclusion of infants in the study.

Therefore, as in the pregnant woman's health and nutritional condition, weight gain and infant feeding interfere in a critical phase and may increase the risk for NCDs.[6,8] We hypothesize that maternal health during pregnancy and infant feeding may influence the levels of adipokines in the first year of life. This study aimed to describe the concentrations of adipokines (leptin and adiponectin) in LBW infants, and the possible associations between leptin and adiponectin with maternal nutritional status, adequacy for gestational age, nutritional recovery, and current dietary intake in this group of infants.

Methods

Study design

This is a cross-sectional study conducted from May 2016 to November 2017, with LBW infants between 9 and 12 months of age, from the universe of children monitored at the Low Birth Weight Clinic (newborns weighing <2500 g and/or gestational age ≥ 34 weeks), after being born at the University Hospital of the Federal University of São Paulo, São Paulo, Brazil. Children with congenital malformations (heart disease, neural tube closure defects, and hydrocephalus), severe dysphagia, using probes or stomas, genetic syndromes, and food restrictions (food allergies, celiac disease) were excluded. The Research Ethics Committee of the Federal University of São Paulo approved the study (N° 0536/2016). All procedures were carried out after the parents/guardians signed the informed consent form.

During the study period, 86 LBW infants attended the outpatient clinic for the first visit. Of these, 65 met the inclusion criteria. Nine children did not participate in the study, and two children did not complete all stages of the assessment. Therefore, the final sample consisted of 54 children (Fig. 1). The non-included patients had characteristics similar to those evaluated in the study regarding gender, gestational age, birth weight, and pregnancy complications.

Data were obtained through information from the electronic medical record of previous visits, structured face-to-face interviews with guardians, anthropometric, dietary assessment, and laboratory tests.

Sociodemographic data and background

In the presential interview with the parents/guardians, data were collected on the socioeconomic status, parental education, obstetric history, health, previous maternal nutritional condition, and the child's birth conditions. The method proposed by the World Health Organization[12] was used for classifying pre-gestational maternal nutritional condition. On this occasion, LBW infant's dietary history information was also obtained, such as time of exclusive and total breastfeeding, use of infant formula and whole cow's milk, time of introduction and composition of complementary feeding, and prophylactic iron and vitamin D supplementation.

Birth anthropometric data measured with <12 h of life were recorded from the child's electronic medical record and used to describe the adequacy of newborns into small (SGA), adequate (AGA), and large for gestational age.[13]

Anthropometry

Anthropometric measurements of weight, length, and head circumference were obtained as recommended by the World Health Organization.[12] Data were entered into the WHO Anthro 3.2.2 program (WHO, 2010), and the anthropometric indicators were presented in the form of z-score for age: Weight (WAZ), Length (LAZ), body mass index (BMIZ), head circumference (HCZ). The cut-off points adopted were those proposed by the WHO, 2006.[14] The variation in the values (Δ) of ΔWAZ, ΔLAZ, and ΔHCZ between birth and the moment of the evaluation was calculated to describe infants' growth and nutritional recovery.

Dietary intake

Those responsible for the children were instructed to inform all the food and beverages consumed in the last 24 h (type of food, brand of processed products, method of preparation, and quantity consumed), based on three reminders for each child, one personally and the other two by telephone, on non-consecutive days, with at most 2 weeks between them, including a weekend day.

Nutritional intake was calculated with the support of the DietWin® program, Plus version, and the values obtained for energy (kcal/d) and proteins (g/kg/d) were compared to the nutritional recommendations proposed by the Dietary Reference Intake, prepared by the Institute of Medicine for the healthy population of Canada and the United States.[15]

Also, a Food Frequency Questionnaire was applied, which identified the frequency (daily, weekly, monthly, sporadic, or not consuming) of consumption of ultra-processed foods in the diet according to the NOVA[16] classification.

Laboratory tests

On the day of the interview and anthropometric measures, 8 ml of blood was collected by peripheral venipuncture in the morning. The samples were aliquoted in dry tubes and centrifuged to separate the serum (4°C, 10 min, 3,500 rpm) to determine adipokine concentrations. The material was stored in Eppendorf® tubes

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and frozen in a −80°C freezer for further analysis. Leptin concentrations were performed by the Milliplex MAP Human Adipokine Magnetic Bead Panel 2-Endocrine Multiplex Assay Kit, developed by Luminex™ xMAP Technology (Millipore, Billerica, MA) with intra-assay <10% CV and inter-assay accuracy <15% CV and standard curve range (assay range) of 0.04 to 600 ng/ml. Adiponectin concentrations were performed by the ELISA method (Human Adiponectin Elisa Kit EZHADP-61K, Sigma Aldrich) with precision for intra-assay <10% CV, inter-assay <15% CV, and standard curve range (assay range) 1.5–100 ng/ml.

Statistical analysis

The data were entered and consolidated in an Excel spreadsheet (Office Microsoft®) and analyzed in the statistical package SPSS 25.0 (IBM®). Categorical variables were presented in absolute and percentage values, compared using the Chi-square test. Continuous variables were assessed for their distribution using the Kolmogorov–Smirnov test, kurtosis values, and distribution using histograms.

The variables with parametric distribution were presented in the form of mean and standard deviation, compared by the Student *t* test for independent and paired variables, in the variation of anthropometric indicators (WAZ, LAZ, and HCZ). Variables with non-parametric distribution (leptin) were presented as medians (interquartile range) and compared using the Mann–Whitney test.

Pearson's (variables with parametric distribution) and Spearman's (variables with non-parametric distribution) correlation coefficients were used to assess the association between leptin, adiponectin values, and leptin/adiponectin ratio with variables related to intake (energy and protein) and anthropometric indicators (WAZ, LAZ, HCZ, and BMIZ). The effect of WAZ variation on leptin levels was assessed on a logarithmic scale using Generalized Linear Models adjusted for pre-gestational BMI, with a 95% confidence interval. The level of significance adopted for all analyses was 5%.

Leptin serum levels described by Savino *et al.*, 2014[17] in healthy infants between 6 and 12 months were 1.8 ± 1.9 ng/ml, and these values were used to calculate the power sample size. Adopting α-bidirectional = 0.05 and β = 0.2, the samples size of 54 infants has the power to detect a difference of 1.1 ng/ml in leptin serum levels.

Results

This study evaluated 54 LBW infants with a mean chronological and adjusted age, for preterm infants, of 10.0 ± 1.5 and 9.1 ± 1.6 months, respectively. We observed that 32 (59.3%) of the children were female, 36 (66.7%) were preterm, and 25 pregnancies (46.3%) were twin. The mean gestational age was 35.9 ± 1.7 weeks, birth weight was 2,222 ± 231 g, and 23 (42.6%) were born SGA (Table 1). None of the infants was conceived by in vitro fertilization.

Among the main maternal characteristics ($n = 42$) were a mean age of 30.1 ± 7.0 years, most women (32, 76.2%) had between 8 and 11 years of schooling, and 28 (66.7%) had a household income of one to three minimum wages. Thirty-four women (81.0%) had complications during pregnancy, mainly urinary tract infection (39.5%), pregnancy-specific hypertensive disease (34.8%), and gestational diabetes (25.5%). Other maternal diseases were reported by 11 mothers (20.3%): chronic renal failure ($n = 2$), congenital heart disease ($n = 2$), cardiac arrhythmia ($n = 1$), systemic lupus erythematosus ($n = 1$), nasal papilloma ($n = 1$), central nervous system tumor ($n = 1$), hypothyroidism ($n = 1$), hepatitis C ($n = 1$), and sickle cell anemia ($n = 1$). Regarding the pre-gestational nutritional condition, 19 women (45.2%) were eutrophic, 8 (19.2%) were malnourished, and 6 (14.3%) and 9 (21.4%) were overweight and obese, respectively.

Table 1. General characteristics of low birth weight infants

Variables		
Birth weight	g	2,222 ± 231
Birth length	cm	43.7 ± 1.7
Birth head circumference	cm	32.2 ± 1.5
Gender	Male	22 (40.7%)
	Female	32 (59.3%)
Twins	Yes	25 (46.3%)
Apgar 5th min	<7	0 (0%)
Prematurity	Yes	36 (66.7%)
Gestational age classification	Small	23 (42.6%)
	Adequate	31 (57.4%)
	Large	0 (0%)

Table 2. Variation of the z-score (Δ) of anthropometric indicators (at birth and at the time of assessment) of low birth weight infants

		Mean (difference)	95% CI	*p*-value
All	ΔWAZ	0.60	0.24, 0.96	0.001
($n = 54$)	ΔHCZ	0.18	−0.13, 0.50	0.255
	ΔLAZ	0.83	0.51, 1.16	<0.001
AGA	ΔWAZ	0.09	−0.52, 0.32	0.634
($n = 31$)	ΔHCZ	0.16	−0.63, 0.31	0.504
	ΔLAZ	0.33	−0.06, 0.72	0.103
SGA	ΔWAZ	1.54	1.17, 1.91	<0.001
($n = 23$)	ΔHCZ	0.66	0.35, 0.97	<0.001
	ΔLAZ	1.52	1.09, 1.96	<0.001

AGA, adequate for gestational age; SGA, small for gestational age; WAZ, weight/age; HCZ, head circumference/age; LAZ, length/age score z.
*Level of significance of the paired *t test*.

At the time of the assessment, all infants received complementary foods. Only four (7.4%) were breastfeeding, 24 (44.4%) received infant formula, and 26 (48.1%) received cow's milk with or without human milk.

Almost all infants (98%) consumed energy above the recommendation, on average, 310.5 ± 92 kcal/d above the estimated need. Protein consumption exceeded the recommendation in all infants, with a mean protein intake of 5.1 ± 1.5 g/kg/d. Also, 87.6% of infants ($n = 47$) consumed ultra-processed foods.

Most of the infants, 44 (81.5%) were eutrophic, eight (14.8%) were overweight, two were undernutrition (3.7%), and four (7.4%) had short stature. The mean variation (Δ) of the z-score of anthropometric indicators (birth and at the time of this assessment) is shown in Table 2, with a statistically significant increase in Δ WAZ (0.60; 95% CI 0.24, 0.96, $p = 0.001$) and LAZ (95% CI 0.83, 0.83, 95% CI 0.51, 1.16, $p < 0.001$).

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Table 3. Maternal, perinatal, sociodemographic characteristics, dietary history, and dietary intake in low birth weight infants stratified by gestational age

Variables		SGA ($n = 23$)	AGA ($n = 31$)	p-value
Overall maternal				
Maternal age	Years	28.9 ± 7.6	30.9 ± 6.4	0.30[1]
Maternal schooling	<11 years	21 (91%)	21 (68%)	0.05[1]
Pre-gestational BMI	kg/m^2	24.0 ± 6.9	25.5 ± 6.6	0.19[1]
Pre-gestational nutritional condition	Malnutrition	7 (30.4%)	1 (3.2%)	0.03[1]
	Eutrophy	7 (30.4%)	18 (58.1%)	
	Obesity	4 (17.4%)	7 (22.6%)	
	Overweight	5 (21.7%)	5 (16.1%)	
Overall infants				
Gender	Male	7 (30%)	15 (48%)	0.26[1]
Gestational age	Preterm	8 (35%)	28 (90%)	<0.01[1]
Twin	Yes	7 (30%)	18 (58%)	0.06[1]
Infant's age	Months	10.1 ± 1.6	10.0 ± 1.4	0.80[1]
Gestational age	Weeks	37.1 ± 1.1	35.0 ± 1.5	<0.01[1]
Birth weight	g	2128 ± 222	2292 ± 215	< 0.01[1]
Dietary history				
Total breastfeeding time	Months	5.0 ± 4.4	4.6 ± 4.1	0.570[2]
Total infant formula time	Months	7.9 ± 3.3	9.5 ± 3.6	0.120[2]
Age onset formula	Months	1.0 ± 0.5	0.3 ± 0.2	0.200[2]
Age onset whole cow's milk	Months	6.5 ± 2.6	6.3 ± 4.0	0.860[2]
Onset complementary foods	Months	6.0 ± 1.0	5.9 ± 0.8	0.830[2]
Daily dietary intake				
Daily energy	kcal/d	979.5 ± 202.4	992.3 ± 147.7	0.330[2]
Daily energy	kcal/kg/d	117.8 ± 31.2	118.6 ± 20.9	0.910[2]
Daily protein	g/kg/d	4.7 ± 1.4	5.4 ± 1.5	0.120[2]
Laboratory variables				
Adiponectin	ng/ml	26.2 ± 7.3	30.1 ± 6.4	0.050[2]
Leptin	ng/ml	3.0 (1.7; 3.0)	1.6 (0.9; 2.6)	0.030[3]
Leptin/adiponectin ratio	ng/ml	0.13 ± 0.08	0.07 ± 0.07	0.018[2]

AGA, adequate for gestational age; SGA, small for gestational age.
[1]Significance level of the Chi-square test.
[2]Significance level of the Student t test.
[3]Significance level of the Mann–Whitney test.

As for adipokines, the median of leptin concentrations, the mean adiponectin levels, and the leptin/adiponectin ratio were 2.0 (1.0; 3.4) ng/ml; 28.4 ± 7.0 ng/ml, and 0.09 ± 0.08, respectively.

Table 3 shows the distribution of the main maternal characteristics and infants stratified by adequacy for gestational age. More important variations were observed in anthropometric indicators of SGA infants than AGA, especially for WAZ (1.54; 95% CI 1.17, 1.91; $p < 0.001$). Also among SGA, we observed a higher percentage of mothers with pre-gestational BMI compatible with undernutrition (7 (30.4%) versus 1 (3.2%); $p = 0.03$), lower frequency of prematurity (8 (35%) versus 28 (90%); $p < 0.01$), and lower birth weight (2,128 ± 222 g versus 2,292 ± 215 g; $p < 0.01$). However, no difference was observed between SGA and AGA concerning the dietary history and current dietary intake (Table 3).

It should also be noted that in SGA infants, leptin concentrations (3.0 (1.7; 3.0) ng/ml versus 1.6 (0.9; 2.6); $p = 0.032$)) and the leptin/adiponectin ratio (0.13 ± 0.08 versus 0.07 ± 0.07; $p = 0.018$) were higher and those of adiponectin (26.2 ± 7.3 µg/ml versus 30.1 ± 6.4 ng/ml; $p = 0.050$) tended to be lower when compared with AGA infants. There was no statistically significant difference in leptin, adiponectin, and leptin/adiponectin concentrations between premature and full-term infants.

Pre-gestational BMI was a modifier of the effect of the variation ΔWAZ on leptin levels ($p = 0.027$) (Fig. 2). The higher the maternal BMI value, the more positive the association between ΔWAZ variation and infants' leptin levels.

None of the variables related to energy, protein intake, duration of breastfeeding, use of infant formulas, or whole cow's milk was associated with leptin, adiponectin, and leptin/adiponectin ratio.

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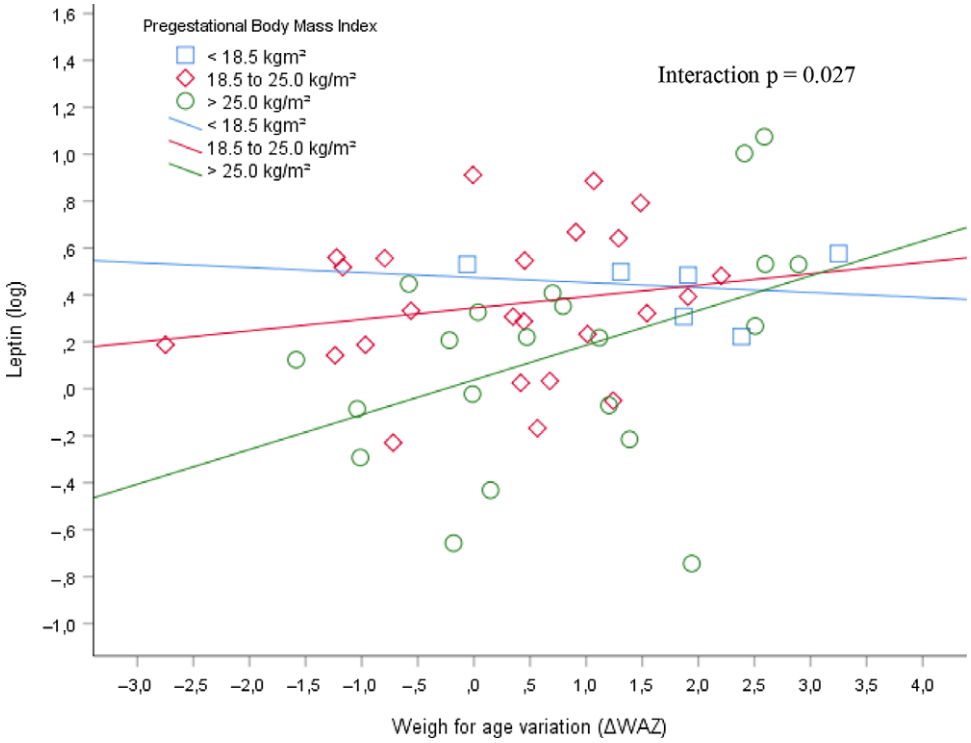

Fig. 2. Association between WAZ variation (ΔWAZ) and leptin levels adjusted for pre-gestational maternal Body Mass Index (BMI).

Discussion

In this study, adipokines were taken at 9–12 months and LBW SGA infants had higher leptin concentrations than AGA infants. Also, leptin concentrations correlated with the WAZ variation, mostly when the mothers were pre-gestational overweight. The feeding of these infants was characterized by excess energy and protein intake, frequent consumption of ultra-processed foods, and low breastfeeding rates. Literature data confirm that the dietary pattern in the first months of life influences weight gain and the risk of obesity in the long term.[18–20] This scenario may justify that almost 15% of these children born with low birth weight are already overweight with <1 year of age.

The maternal nutritional status was relevant in this study in different aspects, such as maternal malnutrition was associated with a higher likelihood of SGA birth, and pre-gestational maternal overweight potentiating the effect of accelerating the infant's postnatal WAZ on the leptin concentrations. These findings suggest that the nutritional condition of women of childbearing age, even before pregnancy, should be considered within the strategies for promoting appropriate intrauterine and postnatal growth.[21–24] In this study, approximately half of the women and 15% of the infants were overweight, which points to the importance of preventing overweight in the pediatric age group from an adequate nutritional condition of women in the pre-gestational stage.

A meta-analysis with 37 cohort studies in developed countries showed that maternal obesity was more critical than excessive weight gain during pregnancy when evaluating overweight and obesity in children up to 18 years of age.[25] Among the various factors that could justify this association, the study authors mention that maternal obesity in the early stages of pregnancy would disrupt the concentrations of adipokines and inflammatory factors during fetal development. These findings are corroborated by another prospective study that evaluated inflammatory markers and adipokines in the three trimesters in healthy pregnant women. The authors observed that overweight/obese women in early pregnancy had higher leptin and insulin levels and lower adiponectin levels.[26]

Among the cited mechanisms involved in adverse outcomes in pregnancy are interactions in placental miRNA expression associated with preeclampsia and restricted intrauterine growth.[27] In a study that assessed the placental miRNA profile in pregnant women with a pre-gestational history of overweight/obesity or excessive gestational weight gain, four among eight placental miRNAs (miR-100, miR-1285, miR-296, and miR-487) that were differentially expressed in maternal obesity were associated with lower birth weight and increased weight gain for children at 1, 4, and 12 months of age.[28] Also, a case-control study with SGA and AGA births showed that the expression of miR-122-5p in childhood was a great predictor of adiponectin levels in young SGA-born adults. Moreover, the presence of miR-122-5p was related to insulin resistance and the risk of developing diabetes.[29]

The amount and distribution of adipose tissue are among the significant determinants of leptin and adiponectin concentrations throughout life. In physiological situations, leptin has an anorexic function and increases energy expenditure at the hypothalamic level. However, situations with accumulated subcutaneous adipose tissue, such as obesity and hyperinsulinemia, can result in hyperleptinemia and the development of central and peripheral resistance to leptin.[8,9] On the other hand, lower adiponectin values are observed in situations of obesity and type 2 diabetes mellitus.[9]

Newborns with low birth weight (preterm and SGA) have less body fat and lower leptin levels than those with adequate birth weight.[8,30] In this study, the median leptin concentration was 2.0 ng/ml. These values are in agreement with a study carried out with 317 healthy infants and younger than 18 months, but who were born AGA; the authors observed a median and 90th percentile

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of leptin levels between 6 and 12 months of age of 1.44 ng/ml and 5.18 ng/ml, respectively.[17]

Although a recent meta-analysis found no difference in leptin concentrations between SGA and AGA[31] newborns, in this study, leptin levels and the leptin/adiponectin ratio in SGA infants was higher than in AGA infants, regardless of gestational age. This finding may suggest that the SGA group showed excessive nutritional recovery with an accumulation of fat, which would result in some level of resistance to leptin's action, which can be considered an unfavorable metabolic profile and risk for NCDs.[8]

Also, our findings are related to recently published experimental studies. In these studies, mice that went through a combination of restricted intrauterine growth and accelerated postnatal growth showed changes in insulin sensibility throughout their lives.[32,33] Their results were enhanced by maternal obesity and an obesogenic postnatal diet,[34] situations we faced during our study.

In another experimental study, the authors showed in rats that the combination of a high-calorie diet (chocolate and soft drinks) in mothers and their offspring could induce permanent changes in leptin signaling. The regulation of appetite was more sensitive to leptin's effect than that of energy expenditure, suggesting different programming of sensitivity to leptin in the hypothalamic arcuate nucleus. Hypothalamic astrocytes contain leptin receptors, and it is postulated that astrogliosis (proliferation of astrocytes) associated with a fat-rich diet would impair leptin's action in the control of energy expenditure in the central nervous system[35,36] in the long term.

This study's strengths are the assessment of dietary intake, gestational history, and maternal nutritional condition. On the other hand, admitted limitations are the absence of body composition measures and the small number of children included.

This study described that LBW infants suffer early changes in leptin and adiponectin concentrations, influenced by maternal (pre-gestational BMI), intrauterine (adequacy for gestational age – SGA), and postnatal factors (excessive weight gain). This combination of factors may increase the risk of NCDs in this group of children.

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Conflicts of interest. None.

Ethical standards. The study received approval from the Research Ethics Committee of Universidade Federal de São Paulo (number: 1.550.249). Children's caregivers (mainly the children's mothers) have signed an informed consent, after an information sheet was explained and delivered to them.

References

1. Silveira MF, Victora CG, Horta BL, *et al.* Low birthweight and preterm birth: trends and inequalities in four population-based birth cohorts in Pelotas, Brazil, 1982–2015. *Int J Epidemiol.* 2019; 48 Suppl 1, i46–i53.
2. Countdown to 2030 Collaboration. Countdown to 2030: tracking progress towards universal coverage for reproductive, maternal, newborn, and child health. *Lancet.* 2018; 391, 1538–1548.
3. Black RE, Taylor CE, Arole S, *et al.* Comprehensive review of the evidence regarding the effectiveness of community-based primary health care in improving maternal, neonatal and child health: 8. summary and recommendations of the Expert Panel. *J Glob Health.* 2017; 7, 010908.
4. Papageorghiou AT, Kennedy SH, Salomon LJ, *et al.* The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care. *Am J Obstet Gynecol.* 2018; 218 Suppl 2, S630–S640.
5. Huang YT, Lin HY, Wang CH, *et al.* Association of preterm birth and small for gestational age with metabolic outcomes in children and adolescents: a population-based cohort study from Taiwan. *Pediatr Neonatol.* 2018; 59, 147–153.
6. Syddall HE, Sayer AA, Simmonds SJ, *et al.* Birth weight, infant weight gain, and cause-specific mortality: the Hertfordshire cohort study. *Am J Epidemiol.* 2005; 161, 1074–1080.
7. Kramer MS, Martin RM, Bogdanovich N, *et al.* Is restricted fetal growth associated with later adiposity? Observational analysis of a randomized trial. *Am J Clin Nutr.* 2014; 100, 176–181.
8. Muhlhausler B, Smith SR. Early-life origins of metabolic dysfunction: role of the adipocyte. *Trends Endocrinol Metab.* 2009; 20, 51–57.
9. Kiess W, Petzold S, Töpfer M, *et al.* Adipocytes and adipose tissue. *Best Pract Res Clin Endocrinol Metab.* 2008; 22, 135–153.
10. Logan CA, Siziba LP, Koenig W, *et al.* Leptin in human milk and child body mass index: results of the ULM birth cohort studies. *Nutrients.* 2019; 11, E1883.
11. Victora CG, Bahl R, Barros AJ, *et al.* Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet.* 2016; 387, 475–490.
12. WHO. *Physical Status: The Use and Interpretation of Anthropometry Physical Status. Report of a WHO Expert Committee. WHO Report Series; 854*, 1995. WHO, Geneva, Switzerland.
13. Villar J, Ismail LC, Victora CG, *et al.* International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. *Lancet.* 2014; 384, 857–868.
14. De Onis M, Onyango A, Borghi E, *et al. WHO Child Growth Standards: Growth Velocity Based on Weight, Length and Head Circumference: Methods and Development*, 2009. World Health Organization, Geneva.
15. Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*, 2006. The National Academies Press, Washington, DC. https://doi.org/10.17226/11537.
16. Monteiro CA, Cannon G, Moubarac JC, *et al.* The UN decade of nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr.* 2018; 21, 5–17.
17. Savino F, Rossi L, Benetti S, *et al.* Serum reference values for leptin in healthy infants. *PLoS One.* 2014; 9, e113024.
18. Rolland-Cachera MF, Michaelsen KF. Protein intake in young children and later health: importance of the time window for programming adiposity. *Am J Clin Nutr.* 2019; 110, 1263–1264.
19. Péneau S, González-Carrascosa R, Gusto G, *et al.* Age at adiposity rebound: determinants and association with nutritional status and the metabolic syndrome at adulthood. *Int J Obes (Lond).* 2016; 40, 1150–1156.
20. Stettler N, Stallings VA, Troxel AB, *et al.* Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation.* 2005; 111, 1897–1903.
21. Van de Beek C, Hoek A, Painter RC, *et al.* Women, their offspring and iMproving lifestyle for better cardiovascular health of both (WOMB project): a protocol of the follow-up of a multicentre randomised controlled trial. *BMJ Open.* 2018; 8, e016579.
22. Stephenson J, Vogel C, Hall J, *et al.* Preconception partnership. Preconception health in England: a proposal for annual reporting with core metrics. *Lancet.* 2019; 393, 2262–2271.
23. Stephenson J, Heslehurst N, Hall J, *et al.* Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet.* 2018; 391, 1830–1841.
24. Brasil. *Pesquisa Nacional de Demografia e Saúde da Criança e da Mulher – PNDS 2006: Dimensões do Processo Reprodutivo e da Saúde da Criança/ Ministério da Saúde, Centro Brasileiro de Análise e Planejamento*, 2009. Ministério da Saúde, Brasília.
25. Voerman E, Santos S, Patro Golab B, *et al.* Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood:

an individual participant data meta-analysis. *PLoS Med.* 2019; 16, e1002744.
26. Perichart-Perera O, Muñoz-Manrique C, Reyes-López A, *et al.* Metabolic markers during pregnancy and their association with maternal and newborn weight status. *PLoS One.* 2017; 12, e0180874.
27. Zhao Z, Moley KH, Gronowski AM. Diagnostic potential for miRNAs as biomarkers for pregnancy-specific diseases. *Clin Biochem.* 2013; 46, 953–960.
28. Carreras-Badosa G, Bonmatí A, Ortega FJ, *et al.* Dysregulation of placental miRNA in maternal obesity is associated with pre- and postnatal growth. *J Clin Endocrinol Metab.* 2017; 102, 2584–2594.
29. Inzaghi E, Kistner A, Germani D, *et al.* A prospective case-control study on miRNA circulating levels in subjects born small for gestational age (SGA) evaluated from childhood into young adulthood. *PLoS One.* 2020; 15, e0228075.
30. Steinbrekera B, Colaizy TT, Vasilakos LK, *et al.* Origins of neonatal leptin deficiency in preterm infants. *Pediatr Res.* 2019; 85, 1016–1023.
31. Goto E. Maternal blood leptin concentration in small for gestational age: a meta-analysis. *Eur J Pediatr.* 2019; 178, 763–770.
32. Fernandez-Twinn DS, Hjort L, Novakovic B, *et al.* Intrauterine programming of obesity and type 2 diabetes. *Diabetologia.* 2019; 62, 1789–1801.
33. Berends LM, Dearden L, Tung YCL, *et al.* Programming of central and peripheral insulin resistance by low birthweight and postnatal catch-up growth in male mice. *Diabetologia.* 2018; 61, 2225–2234.
34. Loche E, Blackmore HL, Carpenter AA, *et al.* Maternal diet-induced obesity programmes cardiac dysfunction in male mice independently of post-weaning diet. *Cardiovasc Res.* 2018; 114, 1372–1384.
35. Kjaergaard M, Nilsson C, Secher A, *et al.* Differential hypothalamic leptin sensitivity in obese rat offspring exposed to maternal and postnatal intake of chocolate and soft drink. *Nutr Diabetes.* 2017; 7, e242.
36. Pan W, Hsuchou H, Xu C, *et al.* Astrocytes modulate distribution and neuronal signaling of leptin in the hypothalamus of obese A vy mice. *J Mol Neurosci.* 2011; 43, 478–484.

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