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Patterns of Infancy Growth and Metabolic Hormonal Profile Are Different in Very-Low-Birth-Weight Preterm Infants Born Small for Gestational Age Compared to Those Born Appropriate for Gestational Age

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Keywords
Preterm infants · Small for gestational age · Very low birth weight · Early growth · Metabolic changes

Abstract
Background/Aims: An increased preterm birth survival rate is associated with long-term neurological and metabolic risks; thus, our aim was to evaluate whether early patterns of infancy anthropometry and metabolic hormonal profile differ in preterm infants born small for gestational age (SGA) or appropriate for gestational age (AGA) from birth to 36 months of corrected age (CA). ***Methods:*** We recruited 110 very-low-birth-weight (VLBW) preterm infants (AGA = 60 and SGA = 50) with a mean birth weight of –2.39 ± 0.77 versus 0.57 ± 0.54 standard deviation scores (SDS) ($p < 0.01$) and birth length of –2.1 ± 1.05 versus –0.44 ± 0.82 SDS ($p < 0.01$), respectively. Anthropometry and blood sampling for insulin, insulin-like growth factor (IGF)-II, IGF-I, and leptin were performed for up to 3 years. ***Results:*** All neonates increased their weight, length, and head circumference SDS during the early inpatient period. Up to 90% reached a normal length within this period. The IGF-II, insulin, and glycemia concentrations changed in parallel with weight. In the first year of CA, only SGA infants gained weight and height SDS. The homoeostatic model assessment had a trend toward higher values in SGA infants at 24 and 36 months ($p = 0.06$ and $p = 0.07$). ***Conclusion:*** Being SGA is the strongest predictor of early recovery of height in VLBW preterm infants. Follow-up will allow us to determine whether the differences in the growth patterns of VLBW preterm infants by birth weight SDS persist.

Introduction

Preterm births, together with an increased survival rate, have led to an increase in the number of prematurely born subjects. In the USA, the incidence of preterm

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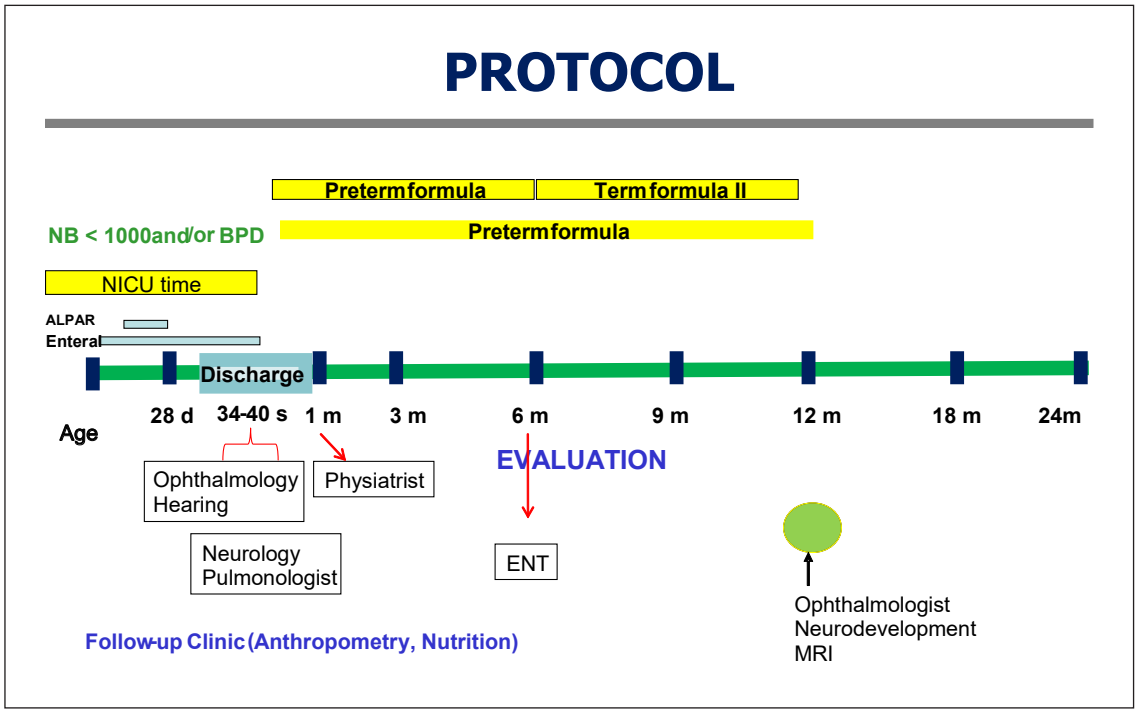

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Fig. 1. Diagram of the routine follow-up of the national program for very-low-birth-weight premature infants.

births is 12–13%, similar to that of other developed countries. In Chile, the incidence is ≈5–12%, depending on the expertise of the reproductive and maternity unit, but the great majority (>85%) are born moderately preterm or near term (gestational age <37 and >32 weeks), and are usually termed low birth weight (weight below 2,500 g) [1]. Among premature newborns, those with very low birth weight (VLBW) (weight below 1,500 g and/or gestational age below 32 weeks) present an additional challenge due to their increased risk of sequelae and long-term disabilities, which have been inversely associated with early postnatal growth and circulating growth factors [2].

Nevertheless, over the last decade, alterations in body composition and increased metabolic risks have been added to the list of associated morbidities in these children. These changes have been recognized early during infancy [3]. In VLBW-born children, similar to term small-for-gestational-age (SGA) children, the most important event associated with a future reduction in insulin sensitivity and increased adiposity is early catch-up growth (CUG) [4, 5].

In infants born with VLBW, the incidence of intrauterine growth retardation (IUGR) is higher than in term- and moderately preterm-born infants. This growth impairment is exacerbated during the first weeks of postnatal life in a considerable number of VLBW preterm children. This is due to difficulties in meeting protein and energy requirements, which leads to a larger proportion of preterm infants that must perform a later catch-up (CU) in growth, during a different period compared to those term-born SGA children [6].

Insulin-like growth factors (IGFs) are key regulators of postnatal growth, and serum levels reflect short-term growth in VLBW infants [7]. In the early months of postnatal life, the circulating levels of IGF-I are dependent primarily on nutritional intake and less on circulating growth hormone [8]. Little information about early patterns of infancy anthropometry and metabolic/growth hormone profiles in VLBW infants exists, so we designed a prospective study of VLBW infants who were followed from birth to 36 months of corrected age (CA) to study whether VLBW preterm infants born either SGA or appropriate for gestational age (AGA) differ in these aspects.

Subjects and Methods

Study Population

Subjects were recruited consecutively at birth from the neonatal unit at the Hospital San Borja Arriaran from May 2008 to July 2011,

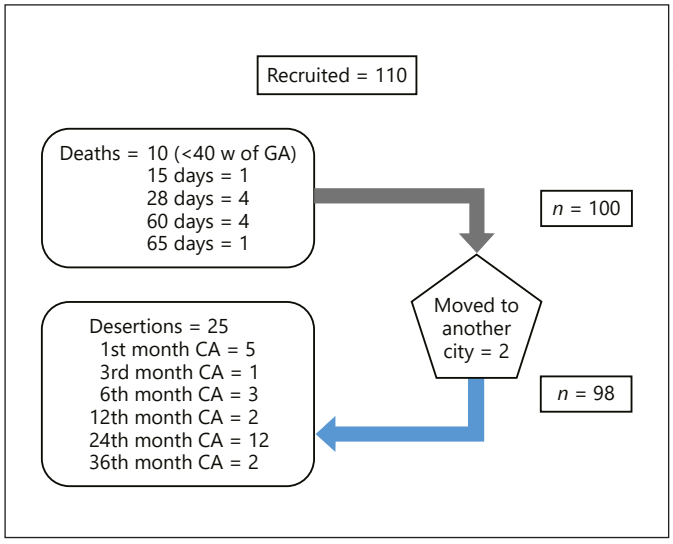

Fig. 2. A total of 110 very-low-birth-weight preterm newborns were recruited and the flowchart shows the reasons for dropout.

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Table 1. Clinical characterization at birth of all very-low-birth-weight study subjects

Total (n = 110)	SGA (n = 50)	AGA (n = 60)	SGA vs. AGA p
Gestational age	30.50±2.50	28.7±1.8	<0.001
Girls/boys	23/27	27/33	ns
Weight, g	1,102±241	1,124±248	ns
Weight, SD	–2.39±0.77	–0.57±0.54	<0.01
Length, cm	36.9±3.19	37.7±2.7	ns
Length, SD	–2.1±1.05	–0.44±0.82	<0.01
HC, cm	26.7±1.9	26.7±2.1	ns
HC, SD	–1.87±0.98	–0.75±1.08	<0.05

SGA, small for gestational age; AGA, appropriate for gestational age; HC, head circumference.

and they were subsequently followed up to 3 years of age at the premature follow-up clinic and at the Institute of Maternal and Child Research, University of Chile. All infants were delivered preterm, and those who fulfilled the VLBW classification criteria underwent a clinical evaluation during their second day of life. Those with significant medical, neurological, or genetic conditions were excluded from further participation. Feeding practices for all VLBW infants during the first weeks of life and until 1 year of CA have been described elsewhere [9]. Total caloric and macronutrient intake (lipids, protein, and carbohydrates), either parenteral or oral, were registered weekly by a neonatal dietician and after discharge at regular visits at neonatal intensive care unit (NICU) follow-up clinics. Relevant biodemographics, clinical, nutritional and anthropometric data obtained during hospitalization (until they reached approx. 8 weeks or weighed 2 kg) and after discharge were collected in a prospective fashion at the NICU follow-up clinics. All infants participating in this prospective trial were part of the routine follow-up of the National Program for VLBW and extremely low-birth-weight (birth weight below 1,000 g) premature infants [10] (Fig. 1).

The study was approved by the institutional review board at the participating institutions. All parents or guardians gave their written informed consent.

Measurements

All children had their weight, length, and head circumference measured at birth, weekly while at the NICU until discharge (at approx. 2 kg) and then at 0 (40 weeks), 1, 3, 6, 12, 24, and 36 months of CA. Skin folds were measured weekly until discharge and then at CA 0, 6, 12, 24, and 36 months by one trained dietitian (P.J.). All measurements at the NICU were performed by one trained dietitian (P.J.) and then at discharge by one pediatric endocrinologist (M.I.H.). An infant stadiometer was used to measure the supine length, and weight was measured using a manual scale with a 10-g gradation (Seca, Hamburg, Germany). Head circumference was measured with inextensible metallic metric tape. Birth and inpatient measurements were transformed into standard deviation scores (SDS) at birth using national references validated for premature growth [11], and after 40 weeks of CA using the WHO growth standards [12]. Newborn size for gestational age was classified as small (SGA) if weight at birth was less than the 10th percentile, appropriate (AGA) if weight was greater than or equal to the 10th percentile and less than or equal to the 90th percentile, and large when weight was greater than the 90th percentile, for gestational age.

All children gave a pre-fed venous blood sample for serum IGF-I, IGF-II, leptin, glycemia and insulin concentrations obtained at 72 h and at 14, 28, and 60 days (in-hospital) and after discharge at 40 weeks of gestational age, and 1, 3, 6, 12, 24, and 36 months of CA. The serum was frozen at –20 °C until assay. Insulin sensitivity was assessed by calculating the homoeostatic model assessment (HOMA-IR), which has been validated as a measure of insulin resistance in nondiabetic children, at the same time points.

Assays

The fasting duration after discharge was at least 4 h. The serum IGF-I levels were determined using a locally developed radioimmunoassay (RIA) [13], which required sample extraction as a first step. The sensitivity of this assay is 5 ng/mL. The IGF-II concentration was measured by RIA with a sensitivity of 10 ng/mL. Serum leptin was measured by RIA. The intra-assay coefficients of variation (CVs) were 8.6% for IGF-I, 4.8% for IGF-II, and 4.6% for leptin. The interassay CVs were 10.2% for IGF-I, 7.9% for IGF-II, and 6.2% for leptin. Serum insulin was measured using a commercial immunoradiometric (IRMA) with intra- and interassay CVs of 3.8 and 4.7%, respectively. No cross-reactivity with pro-insulin in our insulin RIA was declared by the manufacturer. IRMA and RIA kits were obtained from Diasource Immnunoassays SA (Nivelles, Belgium). Glucose was measured using the glucose oxidase method from Roche Diagnostics (Mannheim, Germany).

Calculations and Statistical Analysis

The results are expressed as the mean ± SD or the median and interquartile range. Data were normalized by log transformation to achieve a normal distribution, allowing the use of parametric

Table 2. Anthropometric changes during the inpatient period

	SGA	AGA	*p*
Weight, SDS/week	0.66±0.24*	0.75±0.03*	<0.01
Length, SDS/week	0.40±0.02*	0.41±0.02*	ns
HC, SDS/week	0.58±0.02*	0.56±0.02*	ns
ΔSDS-weight (NB-8 weeks)	2.68±1.43	2.32±0.96	ns
ΔSDS-height (NB-8 weeks)	1.92±1.11	2.03±1.42	ns
ΔSDS-HC (NB-8 weeks)	4.56± 0.38	4.8±1.31	ns
Abdominal circumference, cm/week	1.20±0.1*	1.16±0.7*	ns
Biceps skin fold thickness, mm/week	0.39±0.05*	0.47±0.04*	ns
Triceps skin fold thickness, mm/week	0.3±0.04*	0.25±0.05*	ns

SGA, small for gestational age; AGA, appropriate for gestational age; HC, head circumference; NB, newborn. * $p < 0.001$ within the same group.

statistics. The data normal distribution was calculated using the Shapiro-Wilkson test. Differences between groups were assessed by the Student *t* test or a nonparametric test (Mann-Whitney U), depending on the normality of the data. At follow-up evaluation, comparisons were made for each subject group according to birth weight and SDS (SGA and AGA) using the Student *t* test.

Significant CU was defined as a change in weight or length between 0 and 12 months greater than 0.67 SDS, which represents the width of each percentile band in standard growth charts [4]. Height and weight SDS (*z* score) were dichotomized to distinguish those children who were below –2 SD and above –2 SD (allowing to distinguish between those with very low weight or length growth velocity, compared to the remaining children). Thereafter, the same calculations were performed using a –1 SD cutoff criteria. These outcomes were associated with covariables by logistic regression analysis and expressed as odds ratios. The evolution of the height SDS was associated with the metabolic parameters using a regression analysis with repeated measures, as estimated through mixed models. The results are presented with 95% confidence intervals and 5% significance. The data were analyzed with statistical package STATA v. 12.0.

Table 3. Number (*n*) and proportion (%) of total infants, and according to birth weight SDS, who had either weight or length <–2 SDS during the study period

Weight below –2 SDS	VLBWPT		AGA		SGA		*p*
	n	%	*n*	%	*n*	%	
Weeks							
1	45	42.9	5	8.8	40	83.3	<0.001
2	30	29.4	1	1.8	29	63.0	<0.001
4	5	5.0	0	0.0	5	11.4	<0.001
8	0	0.0	0	0.0	0	0.0	ns
Months							
0	5	4.9	1	2.2	4	8.3	0.025
1	10	12.2	0	0.0	10	25.6	0.0004
3	15	16.3	1	2.0	14	32.6	0.0001
6	11	12.6	0	0.0	11	26.8	0.0002
12	4	5.0	0	0.0	4	10.8	0.024
24	1	1.9	0	0.0	1	4.3	0.2651
36	1	2.9	0	0.0	1	7.7	0.1791
Height below –2 SDS	**VLBWPT**		**AGA**		**SGA**		***p***
	n	%	*n*	%	*n*	%	
Weeks							
1	21	21.6	2	3.9	19	41.3	0.0001
2	16	16.5	0	0.0	16	34.8	0.0001
4	8	7.9	0	0.0	8	18.2	0.0008
8	0	0.0	0	0.0	0	0.0	ns
Months							
0	20	23.5	2	4.4	18	47.2	0.0001
1	25	28.9	2	4.3	23	55.8	0.0001
3	25	27.2	1	2.0	24	55.8	0.0001
6	13	14.9	1	2.2	12	29.3	0.0004
12	6	10.0	0	0.0	6	21.6	0.0050
24	3	5.8	0	0.0	3	13.0	0.00489
36	1	2.9	0	0.0	1	7.7	0.1791

Weeks: after birth; months: after corrected age 0 or 40 weeks of gestational age. VLBWPT, very-low-birth-weight preterm infant; AGA, appropriate for gestational age; SGA, small for gestational age.

Results

A total of 110 VLBW preterm newborns (AGA [*n* = 60, 54%, 24–31] vs. SGA [*n* = 50, 46%, 25–36] weeks of gestation) were recruited. The number of patients with complete anthropometry and blood samples during follow-up was 73 (41 AGA/32 SGA) in the first year, 52 (28 AGA/24 SGA) in the second year, and 48 (27 AGA/21 SGA) in the third year. Figure 2 shows a flowchart of the reasons for dropout.

Anthropometric Characteristic

The clinical characteristics of these subjects at birth are presented in Table 1.

Inpatient Period (<8 Weeks of Life or <2 kg of Weight)

Changes in the anthropometry during the inpatient (NICU) period are shown in Figure 3. Both SGA and AGA neonates increased their weight, length, and head circumference SDS during the early inpatient period.

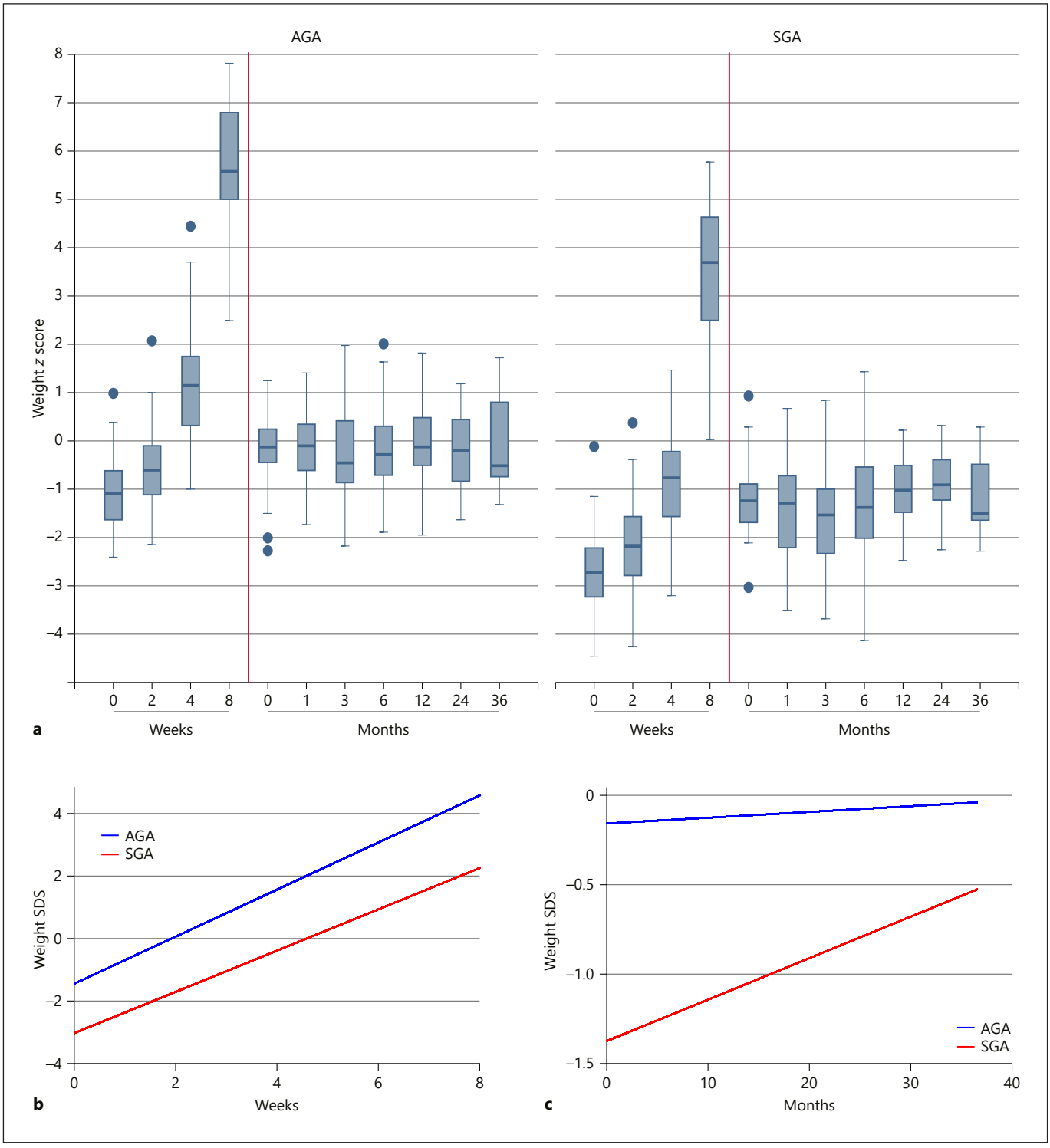
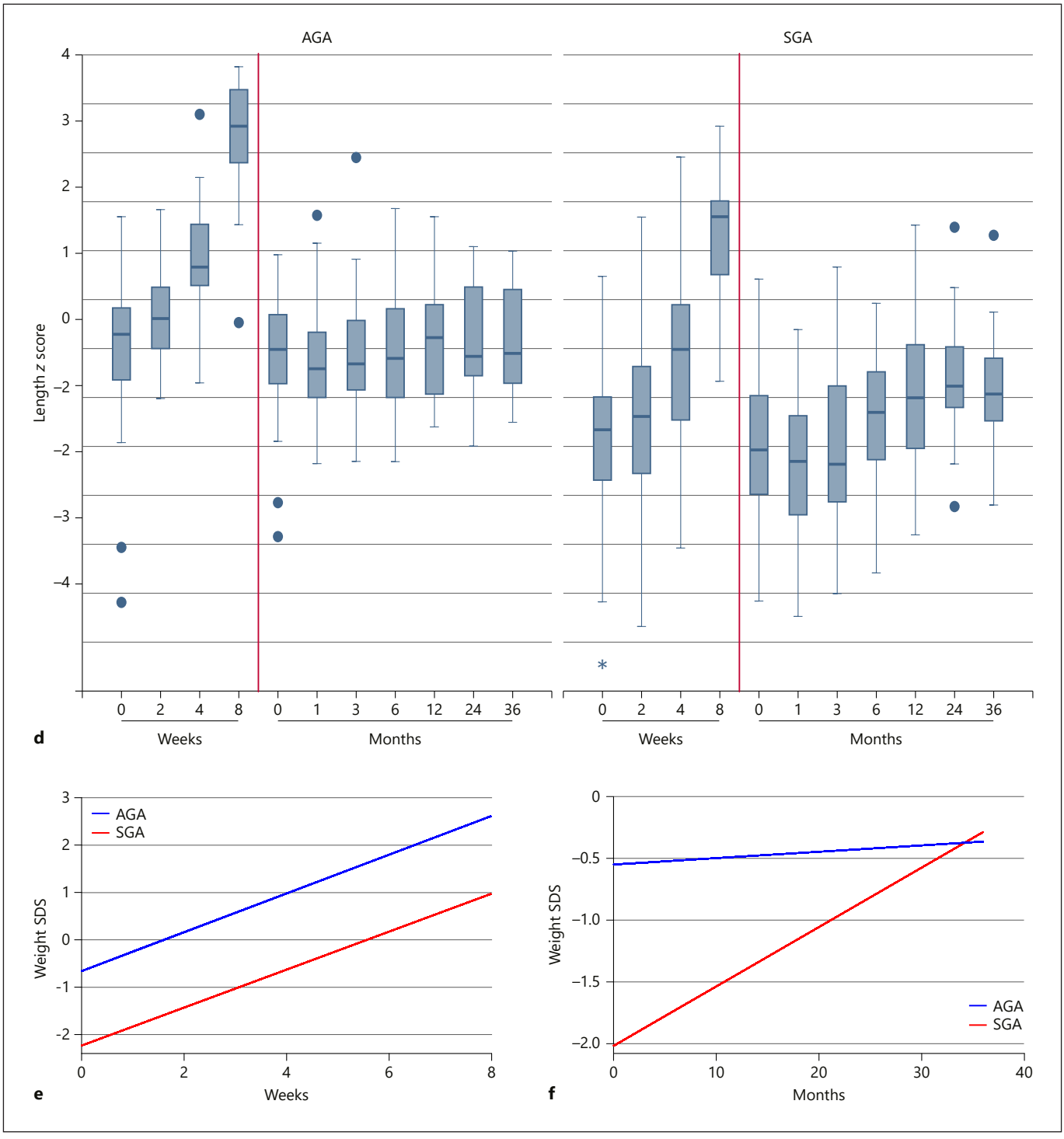


Fig. 3. First, second, and third years of growth shown as median and interquartile range is depicted. **a** Weight SDS. **b** Smoothed curves for inpatient weight SDS. **c** Smoothed curves for outpatient weight SDS. **d** Length SDS. **e** Smoothed curves for inpatient period length SDS. **f** Smoothed curves for the outpatient period length SDS. **g** Head circumference SDS.

(Figure continued on next pages.)



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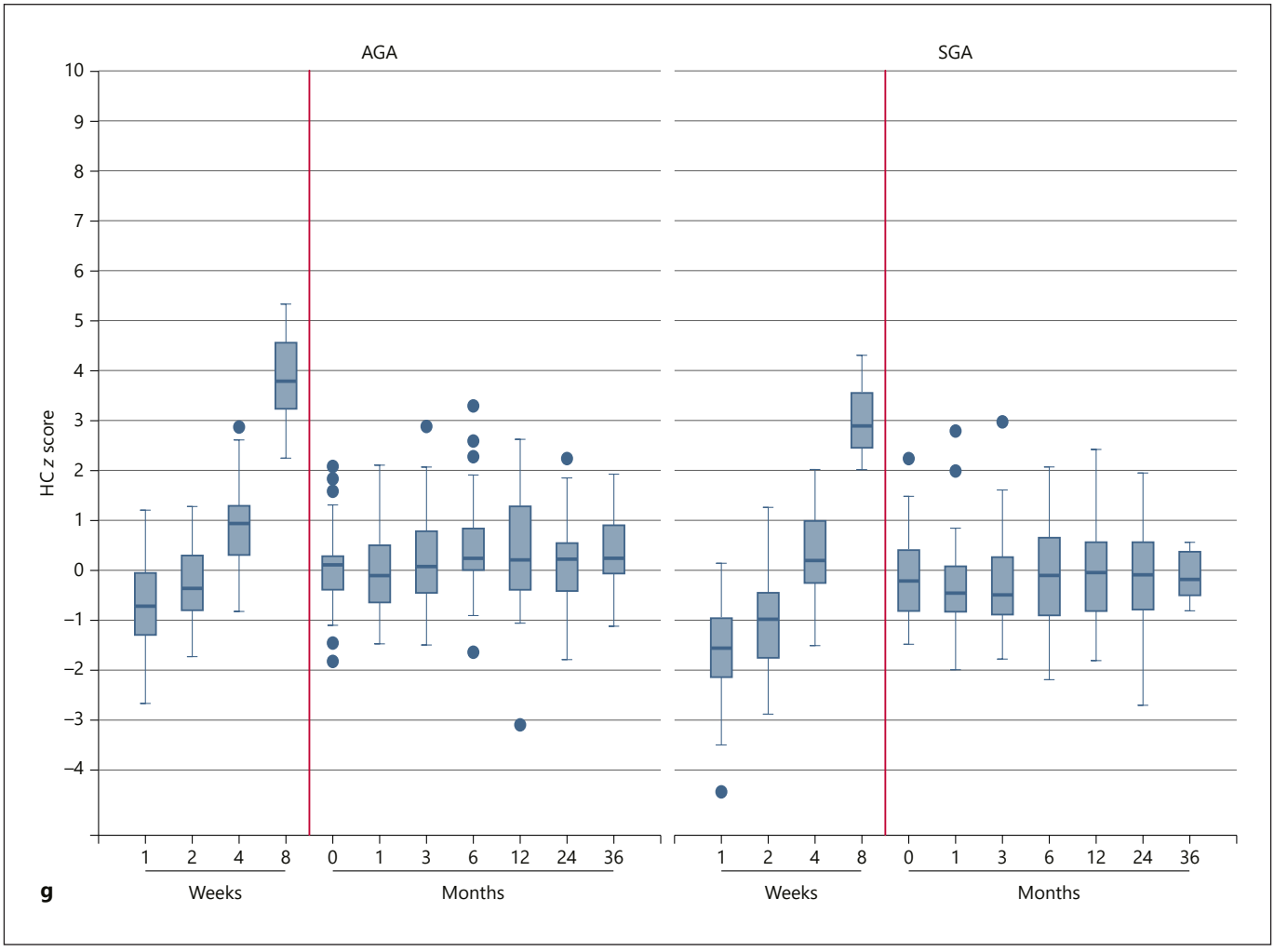
Weight gain started earlier in SGA than in those born AGA (0.66 ± 0.24 SDS/week since day 15 in SGA vs. 0.75 ± 0.03 SDS/week since day 21 in AGA, $p < 0.01$). The smoothed curves show that whereas the SGA infants remained lighter than those born AGA, there was a parallel gain in both groups. Similarly, length and head circumference (SDS/week) increased during this period, with no differences in birth weight SDS (Table 2).



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At term age (40 weeks of CA), 1 VLBW preterm infant born AGA and 4 infants born SGA remained below –2 SD in weight ($p < 0.05$). In length, 2 VLBW AGA infants (4.4%) versus 18 SGA infants were short (47.2%; below –2 SDS, $p < 0.0001$) (Table 3).

Outpatient Period: After Discharge (Term CA) up to Three Years

Changes in the anthropometric parameters are depicted in Figure 3. During the first year, only SGA infants slightly gained weight and height SDS, but these gains were significantly greater than those of their AGA counterparts (achieving an increase in weight of 0.02 vs. 0.003 SDS/month and in length of 0.05 vs. 0.005 SDS/month, respectively, $p < 0.01$). A detailed analysis of the first, second, and third years of growth after term is shown in Figure 3. At 1 year of age, none of the infants born AGA compared to 4 infants born SGA were underweight (weight below –2 SD) ($p < 0.05$), and this difference was even greater for length: none (0%) of the infants born AGA versus 8 (21.6%) of those born SGA ($p < 0.01$) remained short (length below –2 SD). VLBW preterm infants born SGA achieved 3.3 times more CU in height compared to their counterparts born AGA ($p = 0.027$).

Skin Folds and Abdominal Circumference

No differences in the abdominal circumference or skin folds (absolute values or increase/week) were found between groups in the inpatient or outpatient periods (data not shown).

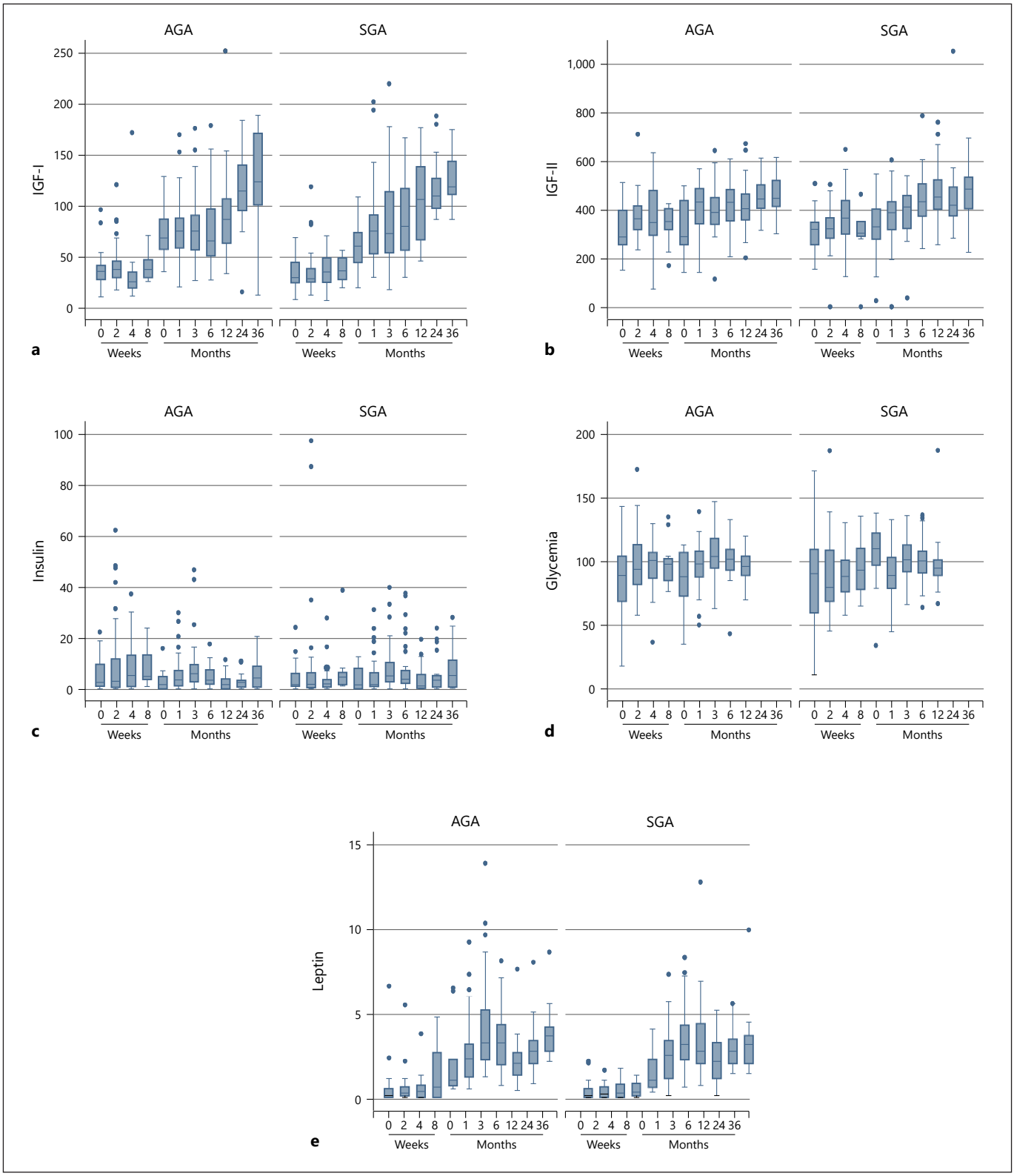

Fig. 4. Median and interquartile range of IGF-I (ng/mL), IGF-II (ng/mL), insulin (μUI/mL), glycemia (mg/dL), and leptin (ng/mL) concentrations during the inpatient period (< 8 weeks of life or <2 kg of weight) and outpatient period (CA 0 [40 weeks], 1, 3, 6, 12, 24, and 36 months of CA).

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Table 4. Odds ratios of significant associations between the anthropometric measures and hormone concentrations during the first year which contributed to weight catch-up (weight change >0.67 SDS during the first year), length below –1 SDS at 1 year, and short stature (length below –2 SDS) at 1 year

	OR	*p*
A		
Weight SDS 0 months	0.5	<0.05
Weight/length SDS 0 months	0.4	<0.05
Length 3 months SDS	1.4	<0.01
Weight 6 months SDS	1.6	<0.05
B		
Below <–1 SDS		
Glycemia inpatient	0.97	<0.05
Leptin outpatient	0.6	<0.03
Birth length SDS	0.35	<0.01
Birth weight SDS	1.6	<0.01
SGA	3.1	<0.05
C		
Below –2 SDS		
Birth length SDS	0.12	<0.01
SGA	1.00	<0.001

SGA, small for gestational age; AGA, appropriate for gestational age. A: Weight catch-up during the first year (+0.67 SDS) was observed in AGA 36.11% vs. SGA 32.14%. B: Length below –1 SDS at 1 year in the total group was 41% (SGA 55% vs. AGA 28%). C: Length below –2 SDS at 1 year in the total group was 8% (SGA 100% vs. AGA 17%).

Hormonal Assessment

Inpatient Period

IGF-I did not change in the entire group during the first 8 weeks after birth compared to the newborn sampling ($p = 0.44$). Stratified by birth weight and SDS, IGF-I decreased slightly only at 28 days, to approx. 7.7 ng/mL in AGA ($p < 0.05$), compared to the newborn sample (Fig. 4a). IGF-II and insulin increased similarly by 14 and 28 days in both groups (Fig. 4b). The leptin concentrations were always lower in SGA than in their AGA counterparts during this period, but they were only significantly increased in those born SGA compared to the newborn period by 0.29 ± 0.12 ng/mL at week 8 of life ($p < 0.05$) (Fig. 4f). The mean glucose levels increased in weeks 2, 4, and 8 in all infants, regardless of their birth weight SDS, compared to the newborn concentration, but the increase was only significant in those born AGA in these same weeks. In parallel, HOMA-IR increased in both groups compared with baseline, but only after 15 days of life, and this difference reached significance with regard to baseline (SGA $p < 0.05$, AGA $p < 0.005$). Insulin and glycemia concentrations changed in parallel to weight and length increase during this period (Fig. 4). Interestingly, IGF-II was slightly but significantly associated with weight gain and head circumference SDS (β of –0.001 for weight and β of –0.0009 for head circumference).

After Discharge up to Three Years of CA

The IGF-I concentration during all sampling times after term increased (compared to term age sampling at ≈40 weeks) slightly but significantly ($p < 0.001$) in both groups (Fig. 4a), and only during the first month was this increase higher in those born SGA compared to those born AGA ($p < 0.05$). IGF-II increased in a similar fashion, although this increase occurred only in those born AGA at month 1; thereafter, this increase was verified in both groups of infants and was greater in infants born SGA than in AGA-born infants at 12 months ($p < 0.01$) (Fig. 4b). Insulin and HOMA increased in all participants at 3, 24, and 36 months compared to term age ($p < 0.01$). HOMA-IR had a trend of higher values in SGA infants at 24 and 36 months compared to their counterparts ($p = 0.06$ and $p = 0.07$, respectively). Compared to age at term, insulin increased in all infants at month 3 and at month 36. Similarly, leptin increased at all time points compared to age at term only in those infants born SGA and only for months 3, 6, and 36 in those born AGA ($p < 0.01$) (Fig. 4).

Next, we used this information to calculate predictors of significant weight and length gain (CU growth). As shown in Table 4, most of the predictors were anthropometric measurements. In addition, those infants who underwent CUG in weight had slightly higher but not statistically significantly different insulin levels at month 24 ($p = 0.06$). Conversely, those who underwent CUG in length had higher glycemia levels at month 12 and insulin concentrations at month 24 ($p < 0.05$), and a tendency to have higher IGF-I concentrations at month 12.

The mean weekly caloric intake and protein, lipid or carbohydrate intake during the inpatient and outpatient periods did not differ in SGA and AGA VLBW infants and did not correlate with any of the anthropometric parameters evaluated.

Discussion

In this prospective study, we show that independent of their birth weight and SDS, all preterm infants born with VLBW start gaining weight and length during the early inpatient period.

In spite of an earlier weight increase in VLBW infants born SGA, they remained lighter than their counterparts born AGA at the CA at term. Furthermore, postnatal growth restraint was present only in 4.4% of those VLBW infants born AGA. This number is considerably lower than previously reported [14]; however, these data were based on the estimated fetal weight growth charts published in 1996, included a rather high percent of extremely low-birth-weight infants (<29 weeks of gestation) and in contrast to our study did not exclude sick infants. Instead, our observation is in agreement with the current reference data developed using Swedish infants who were born preterm [15].

Postnatal growth assessment in VLBW preterm infants is controversial, depending on which growth chart is used. Some of these charts are 4 decades old and may not be suitable for the current population. Thus, it has been proposed that after a CA of 40 weeks, the WHO growth charts should be used to monitor postnatal growth [16].

The postnatal growth pattern of our VLBW preterm cohort is consistent with that of previous reports, in which an initial weight loss is observed, with the lowest postnatal weight between the fourth and seventh days and a recovery period between days 8 and 24, followed by an increase in the growth rate starting in the second week [17, 18]. In earlier reports, VLBW infants usually weighed less than the 10th percentile by 36 weeks' postmenstrual age, and they remained thinner and leaner than term newborns by 40 weeks after the last menstrual period, and this pattern was exacerbated in those who were born SGA [19].

Instead, in our more contemporary cohort, during the inpatient period, all of the VLBW infants gained weight and length during the first 8 weeks such that by 40 weeks after the last menstrual period, only 4.9% of VLBW preterm infants remained below –2 SDS (AGA 2.2 vs. 8.3% SGA) in weight. Thus, a significant number of SGA VLBW infants changed their SGA condition with regard to weight SDS when they reached term CA.

Regarding height, 23.5% remained below –2 SDS (AGA 4.4 vs. SGA 47.2%). In spite of this significant length improvement, many remained short compared with their AGA counterparts, confirming earlier reports that length at birth is a better predictor of persistent short height. The apparent discrepancy between the percent below –2 SDS in the inpatient and outpatient data can be derived using our local reference preterm growth charts, and thereafter, we moved to the recommended WHO standards.

The data on the concentrations of IGF-II, insulin, and glucose paralleled the increase in weight and length observed in this early period of life.

These findings suggest the importance of the role of IGF-II in the regulation of growth in childhood. Both IGF-I and IGF-II are detected in the fetal circulation during early gestation, but their specific actions vary by fetal tissue and gestational age, and their effects are regulated by the nutrient supply [8, 20]. To date, the role of IGF-II has been described as the primary growth factor supporting prenatal growth, but its role has not been explored in postnatal longitudinal growth. During fetal life, the IGF-II gene is imprinted and expressed only from the paternal allele in several tissues and the fetal placenta, excluding the brain. However, after birth, IGF-II expression becomes biallelic in tissues such as the liver, in different species including humans, but not mice [21, 22]. It is well known that in mice, disruption of the paternal IGF-II allele causes severe prenatal growth disruption. Recently, Begemann el al. [23] reported paternally inherited IGF-II mutations in severe intrauterine growth restriction and Silver-Russell syndrome cases.

It would thus be important to determine the factors that regulate its concentration during this period of life. It is known that glucocorticoids decrease the expression of the IGF-II gene. Striking differences in their levels occur after the critical period for these premature infants up to the first weeks of life, when these infants are very labile and perhaps have very different levels of endogenous cortisol [24]. In our population, only during the inpatient period were IGF-II concentrations slightly inversely correlated with weight and head circumference increases. We do not have a plausible explanation for this association yet.

There are few studies reporting early concentrations of these growth and metabolic factors and their association with early growth patterns. In a report by Lo et al. [25], the change in total IGF-I (week 0 to week 3 after birth) was positive. We did not replicate this finding, and serum protein concentrations could have contributed; however, we did not have this information. After the CA at term, the IGF-I concentrations increased independent of birth weight SDS. Higher IGF-I concentrations in early life have been found to be associated with later risks of noncommunicable diseases [26] but are positively associated with brain volume and maturation patterns [2]. In fact, higher IGF-I levels in preterm infants during the first weeks after delivery have shown to be protective against the development of retinal and bronchopulmonary dysplasia with an increase of 5 ng/mL in the mean IGF-I during postmenstrual ages 30–33 weeks, decreasing the risk of proliferative retinopathy of prematurity by 45% [27]. In our cohort, the levels of the IGF-I started to increase

after 4 weeks of life and were significantly higher than at birth by 8 weeks, reaching concentrations over 33 ng/mL, independent of birth weight SDS.

In contrast, nutrition is a key determinant of IGF-I concentrations [25, 28, 29] and early higher protein intake is associated with higher IGF-I serum levels. Interestingly, in our cohort, infants started their weight and length gain at a time when the IGF-I concentrations did not change compared to the newborn period, which was perhaps associated with lower protein serum concentrations. This finding is in contrast to the outcomes in term SGA children, in whom IGF-I is associated with early length and weight CU [30].

Higher IGF-I levels are associated with early obesity, early maturational tempo and higher cancer risks [31, 32]. Similar to the early postnatal period, VLBW children, regardless of their birth weight SDS, have been reported to have low plasma IGF-I and IGFBP-3 levels in mid-childhood, which suggests partial growth hormone resistance [33] and/or insulin resistance [34].

These differences in the early IGF-I concentrations in term SGA compared to the pattern in premature children may be translated into differences in body weight later in life, as premature children tend to be leaner.

After reaching term age, infants born VLBW SGA grew significantly faster in weight and length than did those born VLBW AGA, thus allowing a high percent (92.7%) of VLBW SGA to reach normalcy at age 1. Similar to the inpatient period, when these children reached a weight greater or equal to 2 kg, their IGF-I concentrations were not associated with weight or length gain. Thus, the early determinants of IGF-I concentrations in this population of VLBW infants appear to be independent of these anthropometric measurements. Recent studies have suggested that the concentrations are tightly regulated by fasting and refeeding and are even more directly regulated by the formula amino acid composition [7, 25, 36].

Differences in growth patterns described in VLBW research may be due to differences in the nutrition protocols. In a short-term (12-week) trial, O'Connor et al. [35] demonstrated that adding a multinutrient fortifier to human milk containing extra nutrients for 12 weeks after discharge led to increased weight, length, and head circumference at 12 weeks and found that infants in the intervention arm remained longer and had greater whole-body bone mineral content ($p = 0.02$) until 12 months. In contrast, in a longer follow-up of VLBW infants using an enriched formula compared to term formula (higher protein, calcium, phosphorus, and micronutrients and 10% more energy/100 mL), Koo and Hockman [37] showed reduced weight, length, and body fat at 1 year. In a large prospective study in Chile, premature infants receiving preterm formula for longer periods (6 months or more) displayed lower total fat mass by the 2nd year and lower trunk fat mass within their first year compared to those who received these solely formula during the NICU. The body composition changes were accompanied by a decrease in fasting insulin by the first and second years. This result suggests that preterm infants fed formulas enriched with docosahexaenoic may potentially have a healthier metabolic profile, as demonstrated in older SGA subjects [9, 38].

In premature infants, the relationship between the macro- and micronutrient content of their nutrition and growth is even more important than in term infants, given their vulnerability. Difficulties in nutritional recovery are in turn linked to longitudinal growth. Regan et al. [39] reported that higher carbohydrate intake during the first month of life was associated with increased weight gain and future insulin resistance. Our children were similarly fed (by protocol) and no associations between longitudinal growth or changes in weight or length and the amount or quality of nutrients were found in our study.

During the first months of life, similar to term SGA infants, most of our preterm VLBW infants performed active CUG, achieving normal growth within the first 2 years of life. Up to 90% reached a normal length within this period. Although low birth weight and immature gestational age play the most significant roles in the incidence of growth restriction, there are other important factors that could influence growth, such as gender, the need for respiratory support, necrotizing enterocolitis and exposure to postnatal steroids. By protocol, we excluded newborns with serious medical conditions and also neurological and genetic diseases. Furthermore, the participants received the recommended nutrients and were assessed by a dietician to ensure their intake.

Little is known about which factors determine CUG in preterm infants or among SGA-born infants. Finken et al. [40] reported an association between the R23K polymorphism in the glucocorticoid receptor gene and CUG in preterm infants, and Schreiner et al. [41] reported an association with the d3-isoform polymorphism of the growth hormone receptor gene.

In our study, weight in SDS at birth was the only predictor of premature recovery of length in VLBW preterms born SGA.

The strength of this study is the enrollment and follow-up of a significant number of "healthy" VLBW preterm infants, stratified by their birth weight SDS, who belonged

to a similar socioeconomic level and had a strictly homogeneous feeding protocol. In addition, due to the national program for premature follow-up, most of the recruited patients were followed, with a retention rate of >80%.

Our study had some limitations as well. We did not have information about smoking during pregnancy or conditions that are known to be related to the risk of IUGR, so we cannot establish whether the SGA infants are constitutionally small or are IUGR.

In summary, we found that during the first year of life, there are clear differences in the growth pattern and hormonal profile in VLBW preterm infants born SGA versus those born AGA. The birth weight in SDS is the only predictor of premature recovery of height in VLBW preterm infants born SGA. Further follow-up will allow us to determine whether the differences in the growth pattern of VLBW preterm infants by birth weight SDS persist.

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Statement of Ethics

The study was approved by the institutional review board at the participating institutions. All parents or guardians gave their written informed consent The work described has been carried out in accordance with the code of ethics of the world Medical association (declaration of Helsinki).

Disclosure Statement

The authors have nothing to disclose.

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