Sustained Neonatal Inflammation Is Associated with Poor Growth in Infants Born Very Preterm during the First Year of Life

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Objective To determine whether a sustained neonatal systemic inflammatory response was associated with poor postnatal growth among infants born very preterm during the first year of life.

Study design We studied prospectively 192 infants born preterm (birth weight ≤1.5 kg and gestational age ≤31 weeks). Weight, length, and head circumference were measured at birth, term, 4, and 12 months of corrected age. Serial C-reactive protein and procalcitonin were measured at 1, 3, 7, 14, and 28 days of age and averaged for each infant. A sustained neonatal systemic inflammatory response was defined as an average C-reactive protein level greater than the median for the group. Analysis was undertaken with linear mixed models.

Results Decreases in mean z scores for weight, length, and head circumference were associated with the presence of a sustained neonatal systemic inflammatory response from birth to 12 months of corrected age (β [95% CI] = –0.282 [–0.306 to –0.258]; –1.899 [–2.028,–1.769]; –0.806 [–0.910, to –0.701], $P < .001$, respectively) in main effect models. This association remained significant after including interaction terms for bronchopulmonary dysplasia, neonatal sepsis, and necrotizing enterocolitis (β [95% CI] = –0.393 [–0.520 to –0.265]; –2.128 [–2.754, –1.503]; –1.102 [–1.604, –0.600]; $P < .001$; respectively) in interaction models.

Conclusions A sustained neonatal systemic inflammatory response was associated with poor postnatal growth, particularly poor linear growth. Serial C-reactive protein and procalcitonin may be useful markers for identifying infants at risk for postnatal growth failure. *(J Pediatr 2019;205:91-7).*

Poor postnatal growth is an important complication of preterm birth. Infants born very preterm are lighter and shorter with a greater fat mass relative to lean mass than their counterparts born at term at hospital discharge.[1-7] Abnormal early growth in infants born very preterm has been related to an increased risk of neurodevelopmental disabilities and cardiovascular diseases.[8-13] Weight, linear growth, and head circumference gains are not always closely linked. Growth in length and head circumference predominantly represent lean body mass and protein accretion and indicate organ growth and differentiation, and weight gain represents total body mass, including fat mass, and indicates the balance between energy intake and expenditure.[14]

Although the significance of poor weight gain has been studied extensively, the importance of linear growth failure in infants born very preterm has only emerged recently. Several recent studies showed that standardized length was more stunted and remained lower longer than standardized weight and head circumference.[8,10] This pattern differs from the classic pattern of child malnutrition wherein weight is compromised but length and head circumference are spared and suggests that non-nutritional factors may play a role in this suppression.[15,16] The non-nutritional factors underlying suboptimal linear growth in infants born very preterm are poorly understood, although there is some evidence that inflammation, related to neonatal illness (sepsis, necrotizing enterocolitis [NEC], and bronchopulmonary dysplasia [BPD]), is associated with reduced length at 24 months of corrected age.[17] An independent association between neonatal inflammatory markers such as C-reactive protein (CRP) and procalcitonin with postnatal growth has not been reported previously.

In this study, we sought to determine whether neonatal sustained systemic inflammatory response (SIR) was associated with poor postnatal growth among infants born very preterm. We hypothesized that infants born very preterm persistently exposed to low or moderate inflammatory stress with even modest increases in CRP and procalcitonin levels during hospitalization would demonstrate poor postnatal growth.

Methods

This study was an observational analysis of data from a cohort of infants born from 2006 to 2016 at Hospital Privado Universitario de Córdoba (Argentina),

BMI	Body mass index
BPD	Bronchopulmonary dysplasia
CRP	C-reactive protein
NEC	Necrotizing enterocolitis
SIR	Systemic inflammatory response

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admitted to the neonatal intensive care unit, and followed at term, 4, and 12 months of corrected age. Eligible patients had birth weights <1500 g that were appropriate for gestational age (between the 3rd and 97th percentile[18]) and gestational ages ≤31 weeks. Infants with major birth malformations and death before 12 months of corrected age were excluded. The study was approved by the institutional review board at Hospital Privado Universitario de Cordoba, and the infants' caregivers gave informed consent.

Prospectively recorded maternal and infant clinical information included factors that could affect growth, such as prenatal steroids, chorioamnionitis, birth weight, gestational age, sepsis, NEC, and BPD.[10] Prenatal steroid treatment was defined as ≥1 doses of betamethasone or dexamethasone before delivery. Chorioamnionitis was defined as placental inflammatory infiltrates (reviewed by the hospital's pathologist). Gestational age was determined by the last menstrual period and ultrasound examination before 20 weeks of gestation. Sepsis was defined as a clinical suspicion of infection confirmed by a positive blood culture. NEC was defined as stage II or greater by the Bell classification. BPD was defined as oxygen >21% requirement at corrected age 36 of weeks.[19-21]

We obtained blood samples from peripheral veins for CRP and procalcitonin on days 1, 3, 7, 14, and 28 (±1 day) of life when routine blood examination tests were performed. We calculated the average of the 5 consecutive samples of CRP and procalcitonin for each infant and using these averages, we obtained the median for all participants (**Table I**). An infant was categorized as having an SIR if the average of the 5 CRP and procalcitonin values were above the median of all participants (**Table I**).[22] High-sensitivity CRP concentrations were measured on a Roche/Hitachi modular P analyzer (Roche Diagnostics, Indianapolis, Indiana) with a particle-enhanced immunoturbidimetric method using latex particles coated with monoclonal antibodies anti-CRP (CRPL3), following the manufacturer's instructions. Serum procalcitonin was determined by a quantitative measurement method using the Elecsys BRAHMS procalcitonin automated electrochemiluminescence assay (BRAHMS AG, Henningsdorf, Germany) in the Roche Cobas e system (Roche Diagnostics, Basel, Switzerland), following the manufacturer's instructions. The results below the level of detection were recorded with the value of the lower limit of determination (0.06 mg/L for CRP and 0.02 ng/mL for procalcitonin).

Infants were weighed and measured by trained study staff at birth and at term, 4, and 12 months of corrected age. Weight was measured to nearest 5 g on a calibrated electronic scale. Length was measured to the nearest 0.1 cm using a recumbent length board. Head circumference was measured to the nearest 1 mm as the largest occipitofrontal circumference using a nonstretchable tape measure. All measurements were converted to z scores using international standards for growth at birth INTERGROWTH-21st for infants born very preterm and for term, 4, and 12 months of corrected ages using World Health Organization standards.[18,23] Growth velocity for all measurements was calculated as the z-score change from birth to each time point using the following subtractions: (1) term-corrected age – birth, (2) 4 months of corrected age – birth, and (3) 12 months of corrected age – birth.[24]

Fluids were started at 80 mL/kg/d and increased to 150-180 mL/kg/d over 7 days. On the first postnatal day, infants received 10% amino acid solution at 1.5 g/kg/d with 5.6 mg/kg/min of glucose. Amino acids were increased by 0.5 g/kg/d to a goal of 4 g/kg/d, the glucose infusion was increased by

Table I. Perinatal characteristics

Characteristics	All participants n = 192	Sustained systemic inflammatory response		*P*
		Absent n = 96	Present n = 96	
CRP, mg/dL, median (IQR)	1.00 (0.28 to 2.83)	0.28 (0.18 to 0.52)	2.83 (1.58 to 6.12)	<.001
Procalcitonin, ng/mL, median (IQR)	0.37 (0.06 to 2.53)	0.25 (0.08 to 1.71)	1.67 (0.10 to 3.52)	<.001
Gestational age, wk, median (IQR)	30 (27.5 to 32)	29.5 (27 to 32)	30 (29 to 31.5)	.143
Birth weight, g, median (IQR)	1225 (915 to 1445)	1210 (795 to 1445)	1235 (1010 to 1445)	.118
Birth length, cm, median (IQR)	39 (36 to 41)	39 (35.5 to 42)	39 (37.5 to 41)	.794
Birth head circumference, cm, median (IQR)	27 (25 to 28.5)	27 (25 to 28)	27.3 (26 to 29)	.145
Male sex, n (%)	76 (39.6)	36 (37.5)	40 (41.7)	.555
Cumulative caloric deficit at 28 d of life, Kcal/kg, mean (SD)	−1426 (181)	−1450 (178)	−1433 (184)	.516
Cumulative protein deficit at 28 d of life, g/kg, mean (SD)	−27.9 (4)	−28.3 (3)	−29.0 (4)	.172
Neonatal sepsis, n (%)	58 (30.7)	21 (21.9)	37 (38.5)	.018
BPD, n (%)	16 (4.2)	2 (2.1)	14(14.6)	.004
NEC, n (%)	16 (8.3)	4 (4.2)	12 (12.5)	.037
Postnatal ibuprofen, n (%)	26 (13.5)	14 (14.6)	12 (12.5)	.673
Maternal age, mean (SD)	28.6 (5.5)	28.7 (5.5)	28.5 (5.6)	.861
Tertiary education, n (%)	104 (54.2)	51 (53.1)	53 (55.2)	.885
Smoking during pregnancy, n (%)	11 (5.7)	5 (5.2)	6 (6.2)	1.000
Parity ≥1, n (%)	116 (60.4)	54 (56.2)	62 (64.6)	.302
Cesarean delivery, n (%)	134 (69.8)	70 (72.9)	64 (66.7)	.432
Prenatal corticosteroids, n (%)	176 (91.7)	90 (93.7)	86 (89.6)	.296
Chorioamnionitis, n (%)	56 (29.2)	30 (31.2)	26 (27.1)	.525
Gestational diabetes, n (%)	20 (10.4)	8 (8.3)	12 (12.5)	.478
Pre-eclampsia or eclampsia, n (%)	76 (39.6)	40 (41.7)	36 (37.5)	.555

1 mg/kg/min every 24 hours to a maximum of 13 mg/kg/min, and 20% lipid solution was initiated at 0.5 g/kg/d and increased 0.5 g/kg/d to a goal of 3.5 g/kg/d. Parenteral nutrition was maintained until enteral feeding reached 100 kcal/kg/d.

Enteral feeding was started on the first postnatal day with fortified expressed breast milk or preterm formula (24 kcal/oz) at 10 mL/kg/d and increased by 10 mL/kg/d for 7 days, and by 15-20 mL/kg/d thereafter until reaching 180 mL/kg/d. If human milk fortifier was not available, infants fed breast milk were given 50% and 66% preterm formula when they reached 100 and 150 mL/kg/d respectively. Cumulative energy and protein deficits were defined as the difference between actual and recommended energy and protein intakes.[25]

Statistical Analyses

Of the 192 subjects, 96 had no sustained SIR and 96 had sustained SIR. We estimated that this sample had 0.80 power to detect a difference of 0.20 in mean z-score change between the 2 groups ($\alpha = 0.05$) and 0.80 power to detect a 10% difference between both groups for categorical variables.

Data are reported in absolute (n) and relative (%) frequencies, mean ± SD, or medians with IQR, and the differences between groups were examined by the Fisher exact test, *t* test, or Mann–Whitney *U* test as applicable. Longitudinal analysis of the association between growth velocity expressed as mean z-score change and all relevant clinical covariates were conducted using linear mixed effects models. Variables with $P < .10$ in bivariate analysis were considered for inclusion in mixed models. Main effects models were used to evaluate z-score change with full adjustment (controlling for all significant covariates). The magnitude of difference in growth gain from the reference group (without sustained SIR) was expressed as the β coefficient with 95% CIs. We performed interaction models to evaluate the effect modification according to neonatal inflammatory complications (BPD, sepsis, and NEC). The final models were chosen to have the best fit statistics defined by the lowest restricted maximum likelihood and the lowest Akaike information criterion.[26] Statistical significance was set at $P < .01$. All analyses were performed by using IBM SPSS statistical software, version 24 (IBM Corp, Armonk, New York).

Results

During the study period, 240 infants born very preterm were admitted to the neonatal intensive care unit. In total, 48 (20%) infants were excluded, 22 (9.2%) because they died before 12 months of corrected age, 3 (1.2%) had major malformations, 21 (8.7%) were small for gestational age, and 2 (0.8%) did not complete the follow-up, leaving 192 infants for analysis. Of these, 96 were categorized as having sustained SIR based on an average CRP > median for all participants. Infants with sustained SIR were similar to those without SIR in measurements at birth, gestational age, sex, cumulative caloric and protein deficits at 28 day of life, prenatal, maternal, and postnatal characteristics (**Table I**). Infants with SIR had significantly greater CRP and procalcitonin values and greater rates of neonatal inflammatory complications (BPD, sepsis, and NEC) than infants without SIR.

Association between Sustained SIR and Weight, Length, and Head Circumference from Birth to 12 Months of Corrected Age

The associations between SIR and z-score changes for weight, length, and head circumference from birth to 12 months of corrected age with adjustment for all significant covariates are shown in **Table II**. The difference in z-score changes for weight, length, and head circumference from birth to 12 months of corrected age is expressed as the β coefficient with 95% CI using the group without SIR as the reference. For weight, for example, the group with neonatal sustained SIR had a β coefficient of –0.282 (95% CI –0.306 to –0.258), interpreted as –0.282 decreased z-score mean for weight from birth to 12 months of corrected age, compared with the reference group without neonatal sustained SIR, which was statistically significant ($P < .001$). Similarly, decreased length and head circumference measures from birth to 12 months of corrected age were significantly associated with neonatal SIR (**Table II**, main effect models).

To study the potential mediating effect of neonatal sepsis, BPD, and NEC on the SIR, we included these inflammatory complications as interaction terms to determine whether growth trajectories varied. In the interaction models controlled for sepsis, BPD, and NEC, the association between SIR and decreased growth persisted with statistical significance for weight, length, and head circumference from birth to 12 months of corrected age (**Table II**, interaction models).

Effects of SIR on Catch-Up Growth at Term, 4, and 12 Months of Corrected Age

Figure 1 shows z scores for measurements at birth, term, 4, and 12 months of corrected age for infants with and without SIR. A z score of 0 represents the mean for the reference population. From birth to term corrected age, mean z scores for weight, length, and head circumference decreased in both groups, with and without SIR, but decreased more in the group with SIR than in the group without SIR (–1.20 ± 0.04 vs –0.96 ± 0.03, –3.42 ± 0.06 vs –1.62 ± 0.02, –1.43 ± 0.05 vs –0.88 ± 0.03, respectively; all *P* values < .01).

From term to 4 months of corrected age, weight z scores were lower in the group with SIR than in the group without SIR (–1.41 ± 0.10 vs –0.98 ± 0.02, respectively) $P < .01$. For length, there was a significant difference between both groups at 4 months of corrected age (SIR: –3.60 ± 0.10; no SIR: –1.60 ± 0.03, $P < .01$). Length z scores were stable to increased in the group without SIR, whereas z scores decreased significantly from term to 4 months of corrected age in the group with SIR. For head circumference, the z score at 4 months of corrected age was increased from the birth z score in the group without SIR, suggesting that infants had, on average, caught up in head circumference by 4 months of corrected age. The head circumference z score in the group with SIR increased from term-corrected age but was significantly lower than the group without SIR (–0.92 ± 0.07 vs 0.06 ± 0.02, $P < .01$) at 4 months of corrected age.

Table II. Associations between neonatal sustained SIR and mean z-score change for weight, length, and head circumference from birth to 12 months of corrected age (linear mixed models)

Models	Anthropometric measurement	Variables	β	95% CI	Mean z-score change from birth to 12 mo of corrected age	95% CI	*P* value
Main effect model	Weight	Without SIR	Reference		−1.244	−1.287 to −1.201	
		With SIR	−0.282	−0.306 to −0.258	−1.527	−1.564 to −1.489	<.001
		BPD	−0.002	−0.067 to 0.063			.949
		Neonatal sepsis	−0.004	−0.030 to 0.022			.743
		NEC	−0.034	−0.078 to 0.009			.128
Interaction model		Without SIR	Reference		−1.202	−1.251 to −1.152	
		With SIR	−0.393	−0.520 to −0.265	−1.531	−1.570 to −1.492	<.001
		BPD × SIR	−0.008	−0.074 to 0.058			.818
		Sepsis × SIR	−0.016	−0.056 to 0.024			.435
		NEC × SIR	−0.039	−0.093 to 0.014			.145
Main effect model	Length	Without SIR	Reference		−1.296	−1.515 to −1.077	
		With SIR	−1.899	−2.028 to −1.769	−3.195	−3.383 to −3.007	<.001
		BPD	−0.090	−0.413 to 0.232			.582
		Neonatal sepsis	−0.102	−0.037 to 0.242			.151
		NEC	−0.101	−0.337 to 0.133			.396
Interaction model		Without SIR	Reference		−1.203	−1.433 to −0.972	
		With SIR	−2.128	−2.754 to −1.503	−3.209	−3.410 to −3.009	
		BPD × SIR	−0.096	−0.425 to 0.233			.568
		Sepsis × SIR	−0.099	−0.323 to 0.123			.378
		NEC × SIR	−0.138	−0.443 to 0.167			.375
Main effect model	Head circumference	Without SIR	Reference		−0.222	−0.400 to −0.045	
		With SIR	−0.806	−0.910 to −0.701	−1.028	−1.180 to −0.876	<.001
		BPD	−0.177	−0.438 to 0.084			.184
		Neonatal sepsis	−0.072	−0.185 to 0.041			.211
		NEC	−0.014	−0.205 to 0.176			.882
Interaction model		Without SIR	Reference		−0.092	−0.277 to −0.092	
		With SIR	−1.102	−1.604 to −0.600	−1.019	−1.180 to −0.858	<.001
		BPD × SIR	−0.135	−0.399 to 0.129			.316
		Sepsis × SIR	−0.011	−0.166 to 0.143			.884
		NEC × SIR	−0.044	−0.289 to 0.201			.726

From 4 to 12 months of corrected age, the weight z score was increased from the birth z score in the group without SIR, suggesting that infants had on average caught up in weight by 12 months of corrected age. Although the weight z score in the group with SIR increased from 4 months of corrected age, it was still significantly lower than the group without SIR at 12 months (−0.68 ± 0.12 vs −0.18 ± 0.01, $P < .01$). The length z score was increased from birth in the group without SIR,

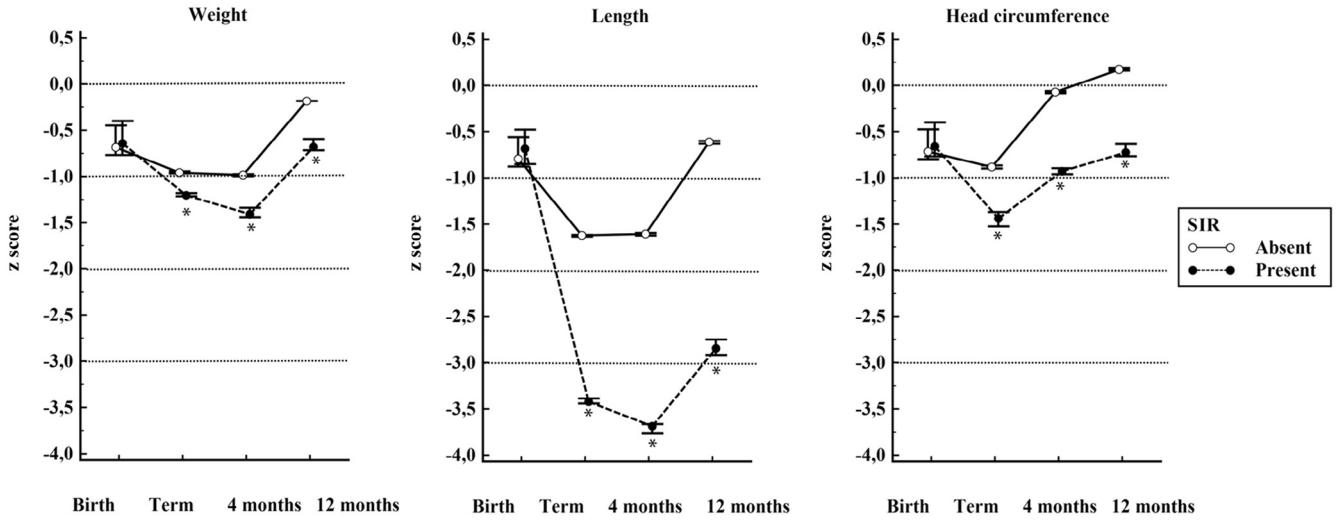

Figure 1. Infant size z scores at birth, term, 4, and 12 months of corrected age for weight, length, and head circumference. All differences marked with an *asterisk* were significant at $P < .01$. *P* values refer to statistical significance of the difference between the z score at each time point and the z score at birth between the groups with and without SIR.

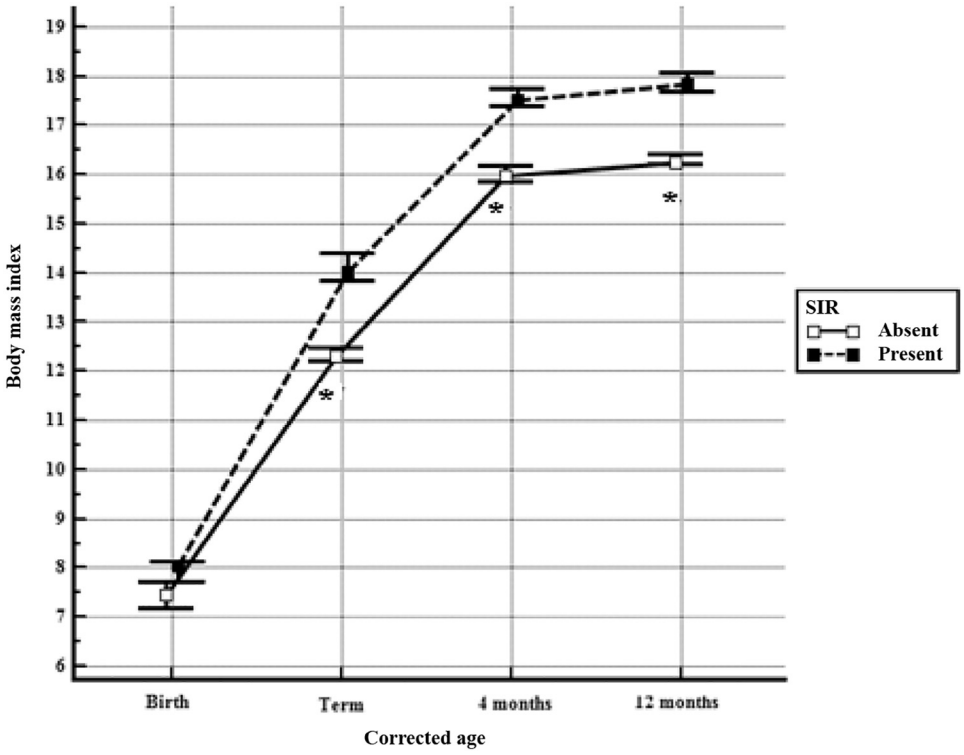

Figure 2. Infant BMI at birth, term, 4, and 12 months of corrected age. BMI in infants with SIR was significantly greater than BMI in infants without SIR at term, 4, and 12 months of corrected age. All differences marked with an *asterisk* were significant at $P < .01$.

suggesting that infants without SIR had, on average, caught up in length by 12 months of corrected age. The length z score in the group with SIR increased from 4 months of corrected age but was still significantly lower than the group without SIR (-2.84 ± 0.16 vs -0.61 ± 0.02, $P < .01$). The head circumference z score in the group without SIR increased from birth and 4 months of corrected age to 12 months of corrected age. In the group with SIR, the head circumference z score increased from 4 months of corrected age but was significantly lower than the group without SIR (-0.72 ± 0.13 vs 0.17 ± 0.02, $P < .01$).

The length z scores in the group with SIR were more severely depressed and remained lower longer than z scores of weight and head circumference at all corrected ages. Infants with SIR had an average body mass index (BMI) that was statistically significantly greater than infants without SIR at all corrected ages after birth, as shown in **Figure 2**. The BMI differences between the groups with and without SIR were 14.0 ± 0.6 vs 12.3 ± 0.2 at term-corrected age, $P < .01$; 17.5 ± 0.3 vs 15.9 ± 0.3 at 4 months of corrected age, $P < .01$; and 17.8 ± 0.3 vs 16.3 ± 0.1 at 12 months of corrected age, $P < .01$.

Discussion

Sustained neonatal SIR was associated with decreased weight, length, and head circumference gains among 192 infants born very preterm who were followed from birth to 12 months of corrected age. This association remained significant after including interaction terms for neonatal inflammatory complications (sepsis, BPD, and NEC). In a previous study, Mestan et al have documented poorer postnatal weight gain in infants born very preterm associated with placental inflammatory response (defined by the presence of placental inflammatory infiltrates). In 2012, Ramel et al reported slower postnatal linear growth velocity in infants born very preterm with neonatal inflammatory illness (sepsis, BPD, and NEC defined by clinical measures).[10,27] Our study extended these findings by linking SIR, defined as sustained elevations of CRP and procalcitonin during the neonatal period, with poor postnatal growth, particularly linear growth. The importance of postnatal linear stunting needs emphasis because linear growth reflects protein accretion and lean body mass, which in turn is related to organ growth and development.[14]

In our cohort, the prevalence rate of BPD, sepsis, and NEC was greater among infants with sustained neonatal SIR, in concordance with the findings of Mestan et al and Ramel et al.[10,27] Prenatal factors, such as the administration of maternal steroids and chorioamnionitis, have seemed to be important modifiers of inflammatory response and poor growth association. We did not find significant differences in chorioamnionitis and prenatal steroid exposure between infants with and without SIR. This finding is consistent with the data reported by Mestan et al, that placental inflammatory response did not correlate with growth failure at 36 weeks of corrected age, and it

suggests that the association between neonatal sustained SIR and poor postnatal growth may be independent of intrauterine exposures.[24,28] Because intrauterine growth restriction of the placental dysfunction type, according to McElrath's preterm birth typology, is a known factor associated with poor postnatal growth, we excluded infants with birth weights below the third percentile.[29]

The infants studied in our cohort demonstrated linear growth suppression to a much greater degree than weight and head circumference. Length z scores were more severely depressed and remained lower longer than z scores of weight and head circumference. Furthermore, the BMI was greater in infants exposed to SIR. Similar results have been reported by Ramel et al in infants with neonatal inflammatory complications. The authors suggest that these findings are unlike the classic wasting undernutrition, whereby weight is compromised but length and head circumference are spared and suggest that non-nutritional factors play an important role in this suppression.[10] Among non-nutritional factors, inflammation seems to play an important role in decreased linear growth, as suggested by a study of children with stunted growth wherein SIR was defined as 1 CPR increase above the 95th percentile for age. Although that study correlated elevated CRP with decreased linear growth, the association has not been examined in infants born very preterm until our present study.[30]

The proposed mechanism to explain the association of sustained SIR and poor postnatal linear growth is the inhibitory effect of cytokines on the growth hormone axis at systemic and local levels, preventing the release of insulin-like growth factor 1 in the liver. This has been observed in children with chronic inflammatory diseases, but this finding has not yet been confirmed in infants born very preterm.[10] At a local level, the insulin-like growth factor 1 signal pathway also may be altered in chronic inflammatory conditions. Some studies have shown that tumor necrosis factor-α, interleukin-6, and interleukin-1β dysregulate insulin-like growth factor 1 intracellular mediators and extracellular signal–regulated kinases, and phosphoinositide 3-kinase in chondrocytes. Inflammation is sustained by the activation of several immune cell types, which secrete soluble cytokines, as chemokines, interferons, and interleukins, activating bone resorption and inhibiting bone growth formation processes at a local level.[31]

Although this study was limited to a single center, serial growth measurements obtained from a single center are likely to be more reliable than comparisons of growth outcomes across multiple centers. The generalizability of our findings may be limited somewhat by the relatively high socioeconomic status of our participant mothers. Nevertheless, we performed an analysis adjusted for maternal education and many other important confounders related to neonatal complications and neonatal intensive care unit treatments. In fact, the major strength of this study was the capacity to monitor postnatal growth gain closely in a well-controlled setting from birth to 12 months of corrected age. Additional follow-up monitoring is needed to determine whether the association found in this study persists into early childhood and beyond and may help predict future long-term disorders, such as failure to thrive, neurodevelopmental disabilities, metabolic syndrome, and cardiovascular diseases.

This study supports the growing evidence that neonatal sustained SIR, even mild or moderate, may have lasting effects on preterm linear growth during infancy. Because linear growth represents lean body mass and protein accretion and also indexes organ growth and development, including the brain, our findings have important preventive implications. Serial CRP measurements may be a useful marker for identifying infants at risk of postnatal growth failure and for guiding neonatal management to minimize inflammatory stress considering alternatives to shorten invasive mechanical ventilation, parenteral nutrition, and avoiding unnecessary blood transfusions, among others.[32] ■

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