Poor postnatal weight growth is a late finding after sepsis in very preterm infants

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ABSTRACT

Objective To characterise the association between sepsis and postnatal weight growth when accounting for the degree of growth restriction present at birth.

Design Retrospective matched cohort study using data from the Postnatal Growth and Retinopathy of Prematurity study. Participants were born with birth weights of <1500 g or gestational ages of <32 weeks between 2006 and 2011 at 29 neonatal centres in the USA and Canada. Sepsis was defined as a culture-confirmed bacterial or fungal infection of the blood or cerebrospinal fluid before 36 weeks' postmenstrual age (PMA). Growth was assessed as the change in weight z-score between birth and 36 weeks' PMA.

Results Of 4785 eligible infants, 813 (17%) developed sepsis and 693 (85%) were matched 1:1 to controls. Sepsis was associated with a greater decline in weight z-score (mean difference −0.09, 95% CI −0.14 to −0.03). Postnatal weight growth failure (decline in weight z-score>1) was present in 237 (34%) infants with sepsis and 179 (26%) controls (adjusted OR 1.49, 95% CI 1.12 to 1.97). Longitudinal growth trajectories showed similar initial changes in weight z-scores between infants with and without sepsis. By 3 weeks after sepsis onset, there was a greater decline in weight z-scores relative to birth values in those with sepsis than without sepsis (delta z-score −0.89 vs −0.77; mean difference −0.12, 95% CI −0.18 to −0.05). This significant difference persisted until 36 weeks or discharge.

Conclusion Infants with sepsis had similar early weight growth trajectories as infants without sepsis but developed significant deficits in weight that were not apparent until several weeks after the onset of sepsis.

What is already known on this topic?

- Sepsis predisposes preterm infants to significant morbidities, including poor growth and development.
- The temporal relationship between sepsis and postnatal growth, however, is not well established, and prior studies infrequently accounted for growth status at birth.

What this study adds?

- Sepsis was associated with an increased risk of poor postnatal weight growth in very preterm infants.
- Infants with sepsis had similar early weight growth trajectories as those without but developed significant deficits in growth that were not apparent until several weeks after the onset of sepsis.

INTRODUCTION

Very preterm infants are at high risk for multiple neonatal morbidities including sepsis and postnatal growth failure.[1–3] Sepsis is a leading cause of mortality among this population.[4] Postnatal growth failure is associated with increased risk of later adverse outcomes, including neurodevelopmental impairment in childhood[5–8] and cardiovascular disease, diabetes and obesity in adulthood.[9 10]

Prior studies demonstrate an association between sepsis and postnatal growth failure among preterm infants.[5 11] It is unclear whether this apparent relationship will persist after accounting for the degree of growth restriction present at birth. The temporal association between sepsis and growth is also poorly described. For instance, it is uncertain whether poor prenatal or early postnatal growth are antecedent events that predispose infants to develop sepsis or whether subsequent postsepsis growth failure occurs. Improved understanding of the determinants of postnatal growth is important to identify infants at high risk of poor growth and to develop strategies and interventions that prevent and treat growth failure.[12 13] Better characterisation of growth trajectories among infants with and without sepsis, after accounting for intrauterine growth, may inform the nature and timing of such interventions.[14]

The objectives of this study were to examine the association between sepsis and postnatal weight growth failure in very preterm infants using definitions that account for growth status at birth and to compare growth trajectory patterns over time between infants with and without sepsis during the birth hospitalisation. We hypothesised that infants who develop sepsis will demonstrate worse postinfection weight growth when compared with similar infants without sepsis.

PATIENTS AND METHODS

Data source and study population

We performed a secondary matched analysis using data from the multicentre Postnatal Growth and Retinopathy of Prematurity (G-ROP) study.[15 16]

G-ROP enrolled infants at 29 neonatal centres in the USA and Canada who underwent eye examinations and had a known outcome for retinopathy. Clinical data including frequent weight measurements were collected at regular intervals from birth.

We analysed infants born between January 2006 and December 2011, with birth weights of <1500 g or gestational ages of <32 weeks, who survived to 36 weeks' postmenstrual age (PMA) or were discharged between 34 and 36 weeks' PMA. All evaluated infants had at least one non-birthweight weight entry within 14 days after birth, at least 20 total weights and a final weight at ≥34 weeks' PMA. Infants with known chromosomal abnormalities, syndromic diagnoses or surgical necrotising enterocolitis were excluded.

Study exposure and outcome definitions

Sepsis was defined as a culture-confirmed blood or cerebrospinal fluid infection from a bacterial or fungal organism before 36 weeks' PMA. Suspected contaminants and 'culture-negative sepsis' episodes were not considered sepsis events.

We analysed the outcome of postnatal weight growth relative to growth status at birth in multiple ways.[2] First, we assessed change in weight z-score from birth to 36 weeks' PMA or discharge, if it occurred between 34 and 36 weeks' PMA, as a continuous variable. Second, we characterised poor postnatal weight growth as a dichotomous outcome using three previously reported cut-offs for growth failure: decrease in weight z-score greater than 1 (ie, a change in z-score values of <−1), 1.5 and 2 from birth to 36 weeks' PMA or discharge.[17] Third, we performed a longitudinal comparison of delta z-score values before and after sepsis onset. Weight z-scores were calculated using sex-specific median and SD values using Olsen growth curves: (observed weight−expected weight)/SD.[18] The expected weight at each PMA was defined as the median birth weight at the corresponding gestational age.[18] For example, if a baby was discharged at 34 weeks' PMA, the discharge weight was compared with the median BW at 34 weeks' GA.[18] Delta z-scores were calculated by subtracting the weight z-score at birth from the z-score at 36 weeks' PMA or discharge (if between 34 and 36 weeks' PMA), consistent with previous reports.[17]

We assessed for differences in rates of enteral feeding in the week before and after sepsis onset between the two groups. Caloric and volume intake data were not available.

Statistical analysis

To minimise confounding, infants with sepsis were matched 1:1 to infants without sepsis by sex, completed gestation weeks, birth weight (within 100 g), delivery mode and race/ethnicity. Descriptive statistics and standardised mean differences were calculated to compare characteristics of infants with sepsis and their matched controls.

Univariable and multivariable logistic and linear mixed effects models were used to evaluate the association between sepsis and postnatal growth outcomes. Models included random intercepts for both centre-level clustering and case–control matching to

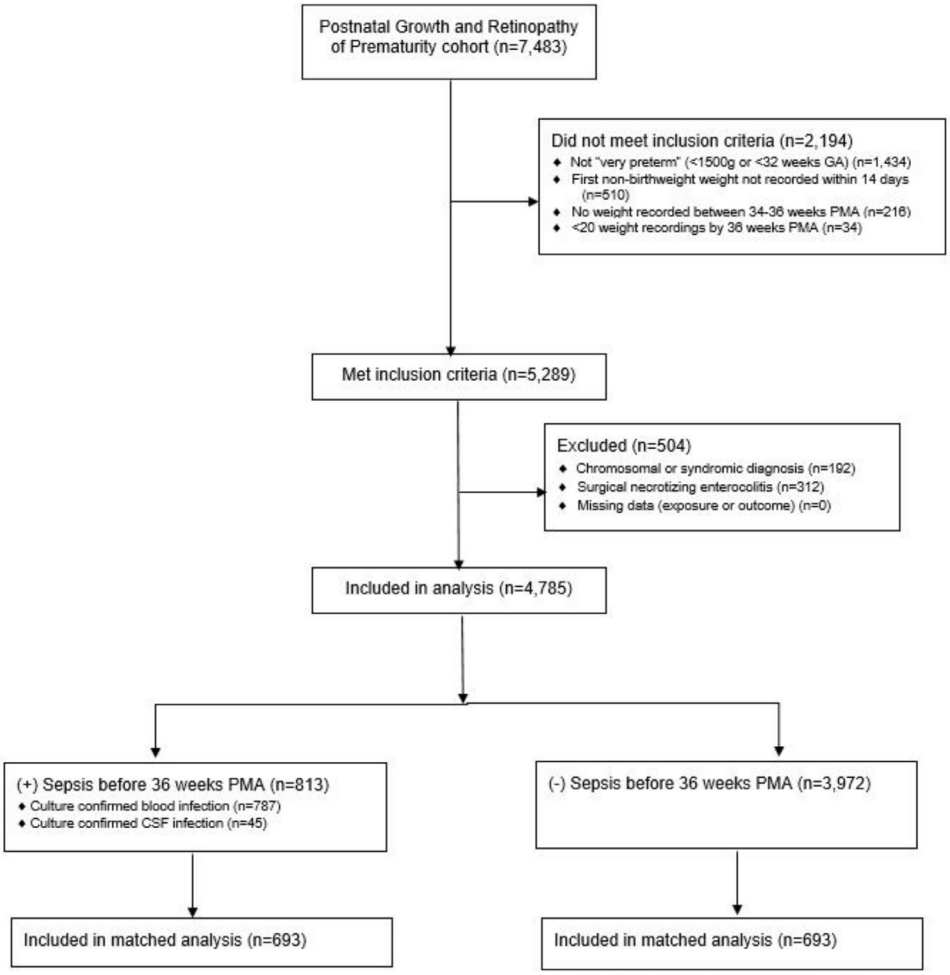

Figure 1 Flow diagram demonstrating patients included in the analysis. CSF, cerebrospinal fluid; GA, gestational age; PMA, postmenstrual age.

Table 1 Comparison of original and matched samples

Characteristics	Original sample					Matched sample*				
	With sepsis (N=813)		Without sepsis (N=3972)		SMD	With sepsis (N=693)		Without sepsis (N=693)		SMD
BW (g), mean (SD)	847.9	(250.5)	1028.0	(263.1)	0.70	859.8	(244.9)	861.9	(245.8)	0.01
BW z-score, mean (SD)	−0.5	(1.0)	−0.5	(0.9)	0.00	−0.5	(0.9)	−0.5	(0.9)	0.00
Birth length (cm), mean(SD)	33.6	(3.5)	36.0	(3.5)	0.67	33.8	(3.5)	34.0	(3.4)	0.06
Birth HC (cm), mean(SD)	23.6	(2.4)	25.2	(2.3)	0.68	23.7	(2.4)	23.7	(2.2)	0.03
GA (weeks), mean(SD)	26.4	(2.0)	28.1	(2.1)	0.80	26.5	(2.0)	26.5	(2.0)	0.01
1 min APGAR score, mean(SD)	4.2	(2.4)	5.0	(2.5)	0.32	4.3	(2.4)	4.3	(2.5)	0.01
5 min Apgar score, mean(SD)	6.5	(2.1)	7.1	(1.9)	0.28	6.6	(2.0)	6.5	(2.1)	0.02
Female sex (%)	400	(49)	1963	(49)	0.00	333	(48)	333	(48)	0.00
Maternal ethnicity, Hispanic or Latino (%)	75	(9)	278	(7)	0.10	41	(6)	41	(6)	0.00
Maternal race					0.19					0.00
White/Caucasian (%)	358	(44)	1949	(49)		326	(47)	326	(47)	
Black/African–American (%)	304	(37)	1277	(32)		276	(40)	276	(40)	
Others (%)	151	(19)	746	(19)		91	(13)	91	(13)	
Vaginal delivery (%)	302	(37)	1268	(32)	0.11	244	(35)	244	(35)	0.00
Multiple gestation (%)	196	(24)	1090	(27)	0.08	175	(25)	168	(24)	0.02
Gestational diabetes (%)	44	(5)	295	(7)	0.08	31	(4)	41	(6)	0.11
Chorioamnionitis (%)	120	(15)	516	(13)	0.07	103	(15)	129	(19)	0.12
Prenatal steroids (%)	615	(76)	3162	(80)	0.10	525	(76)	550	(79)	0.08

SMDs are expressed as absolute values.
*Among the 1386 infants in the matched cohort, 1196 (86%) had a final weight determination at 36 weeks' PMA and 190 (14%) had a final weight measured between 34 and 36 weeks' PMA. A similar proportion of infants were discharged between 34 and 36 weeks' PMA in both groups (13% of infants with sepsis and 15% of infants without sepsis; difference of 2%, 95% CI −1% to 6%).
BW, birth weight; GA, gestational age; HC, head circumference; PMA, postmenstrual age; SMD, standardised mean difference.

adjust for their correlations. Multivariable models were adjusted for birth weight and gestational age as continuous variables because these are known risk factors for growth failure, and exact matching was not performed for these covariates. An interaction term between sepsis status and the timing of sepsis onset (first 3 days vs after 3 days) in the infected infant of the matched pair was added to assess for effect modification by the occurrence of 'early' versus 'late' onset sepsis. A post hoc analysis compared the risk for decrease in weight z-score of >1 between infants with one episode of sepsis to those with two or more episodes. All analyses that considered the time of sepsis onset used data from the first sepsis episode.

We assessed longitudinal differences in weight growth before and after sepsis onset between the matched groups using locally estimated scatterplot smoothing. The day of sepsis diagnosis in the infected infant defined the time point of sepsis onset for each matched pair. As these plots demonstrated non-linear temporal changes in delta z-score values, we compared delta z-scores between the groups at weekly intervals using mean differences and corresponding 95% CIs. We only included days with at least 100 weight data points for each group to enable reasonably unbiased estimates of the mean delta z-scores.

All statistical analyses were performed using SAS V.9.4.

RESULTS

Study cohort

The G-ROP study evaluated 7483 infants with a known outcome for retinopathy.[16] Among the original cohort, 4785 infants were eligible for inclusion in this analysis, including 813 (17%) infants who developed sepsis and 3972 (83%) who did not (figure 1). Of these, 693 (85%) with a history of sepsis were successfully matched to 693 without sepsis. Significant differences in the measured baseline characteristics between the groups were resolved by matching (table 1). Among the 693 matched infants with sepsis, 51 had early-onset sepsis and 642 had late-onset sepsis. On average, the first sepsis episode occurred 20.3 (SD 15.3) days after birth, with a range of 0–89 days. A total of 124 (18%) infants had more than one sepsis episode.

Sepsis was associated with a greater decline in weight z-score between birth and 36 weeks' PMA or discharge when considering the outcome as continuous variable, (mean difference −0.09, 95% CI −0.14 to −0.03) (table 2). In total, 237 (34%) infants with sepsis vs 179 (26%) without sepsis demonstrated a decline in weight z-score of >1 from birth to 36 weeks' PMA. In the adjusted analysis, sepsis was associated with a 49% increase in the odds of growth failure defined by this threshold (adjusted OR (aOR) 1.49, 95% CI 1.12, 1.97). The direction and magnitude of the association between sepsis and poor weight growth was similar when growth failure was defined using a decline in z-score of >1.5 and >2, although the CIs for the adjusted ORs for the >1.5 cut-off narrowly included the point of equivalence (table 2).

A post hoc analysis suggested greater risk of growth failure, defined as a decline in weight z-score of >1, among infants with two or more sepsis episodes (aOR 1.77, 95% CI 1.07 to 2.91) than one sepsis episode (aOR 1.43, 95% CI 1.06 to 1.92). There was no evidence of a significant subgroup effect when stratifying the cohort by the timing of sepsis (early onset vs late onset) for any of the study outcomes.

Figure 2 graphs the longitudinal weight growth trajectories before and after the time point of sepsis onset in the two study groups. While both groups demonstrated declines in weight z-scores over time, a more severe decrease in weight gain emerged after sepsis onset in those with sepsis. Comparisons of the delta z-scores at weekly intervals show similar growth patterns between the groups until 3 weeks after the diagnosis of

Table 2 Univariable and multivariable analyses for association between sepsis and postnatal weight growth

Outcome	With sepsis (n=693)	Without sepsis (n=693)	P value*	With sepsis compared with without sepsis: Unadjusted mean difference (95% CI)†	With sepsis compared with without sepsis: Adjusted mean difference (95% CI)†‡
Delta z-score,§ mean (SE)	−0.73 (0.05)	−0.65 (0.05)		−0.09 (−0.14 to −0.03)	−0.09 (−0.14 to −0.03)
Postnatal growth failure				Unadjusted OR (95% CI)¶	Adjusted OR (95% CI)‡¶
Decrease in z-score >1	237 (34%)	179 (26%)	<0.001	1.40 (1.09 to 1.79)	1.49 (1.12 to 1.97)
Decrease in z-score >1.5	92 (13%)	69 (10%)	0.02	1.37 (0.98 to 1.93)	1.41 (0.95 to 2.10)
Decrease in z-score >2	40 (5%)	24 (4%)	0.04	1.64 (0.97 to 2.76)	1.94 (1.06 to 3.57)

*P value calculated using McNemar test.
†Linear mixed effects model with clinic and matched pairs modelled as random intercepts.
‡Adjusted for birth weight and gestational age.
§Calculated as z-score at 36 weeks' postmenstrual age or discharge minus the z-score at birth.
¶Logistic regression model with clinic and matched pairs modelled as random intercepts.

sepsis, at which point the delta z-score values were significantly lower in the infected group through 9 weeks after sepsis onset (table 3).

Although the G-ROP dataset includes limited information on nutritional intake, review of the available data suggests potentially relevant differences in the rates of enteral feeding before and after sepsis onset in the two study groups. In the week before the diagnosis of sepsis, a similar number of infants were receiving at least some form of enteral nutrition (456 [66%] who developed sepsis vs 481 [69%] without sepsis; 4% difference, 95% CI −1.3 to 8.5). One week after sepsis onset, 455 (66%) infants with sepsis received enteral feedings compared with 587 (85%) without sepsis (19% difference, 95% CI 14.6 to 23.5).

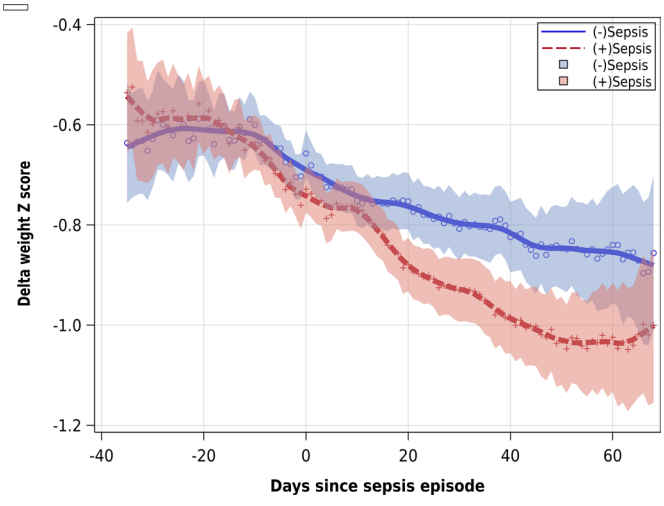

Figure 2 Delta weight z-score comparison between infants with and without sepsis. Legend: Comparison of delta weight z-score before, at and after sepsis episode time point between matched subjects with and without sepsis. The day of the sepsis onset was assigned for each matched pair according to the day of sepsis diagnosis in the infected infant. Only days with at least 100 wt data points for each group are shown, and not all data points include matched pairs, as some pairs only had weight data in one group at certain time points. The daily values for the two groups (shown as o and +) represent means of the actual measurements, and the lines for the two groups represent the estimates determined from the locally estimated scatterplot smoothing analysis.

DISCUSSION

Prior studies demonstrating an association between sepsis and postnatal weight growth failure infrequently accounted for the presence and severity of growth restriction at birth, which may bias the estimated association between these two postnatal morbidities.[5 11] Moreover, the temporal relationship between sepsis and growth failure is not well established. To address these knowledge gaps, we conducted a matched cohort study that examined the association between sepsis and postnatal weight growth trajectories in very preterm infants. We assessed for changes in weight z-scores relative to birth indices to account for each infant's growth status at the time of delivery. Our results suggest there is a significant negative relationship between sepsis and postnatal weight growth. Furthermore, a post hoc analysis indicates a dose–response relationship may exist, whereby additional episodes of sepsis predispose infants to a higher risk of growth failure. Notably, our examination of longitudinal weight growth patterns between matched infants with and without sepsis showed similar growth in the weeks immediately prior to the time of sepsis diagnosis. However, significant differences in weight growth were apparent by approximately 3 weeks following the onset of sepsis and persisted for at least 2 months after the diagnosis of sepsis.

In a cohort of over 6000 preterm infants, Stoll *et al*[5] found that infection occurring in the newborn period was associated with impaired growth at 36 weeks' PMA and during early childhood. This prior study defined small for gestational age and growth failure using growth cutoffs of less than the 10th percentile and adjusted the analyses for birth weight and gestational age.[5] This approach provided important information about the potential association between sepsis and poor weight gain, but it may not fully account for the relationship between intrauterine and extrauterine growth. It is also unclear from these data whether sepsis increases the risk of growth failure and/or whether infants destined to have poor growth are at increased risk of sepsis.[2 13] We observed similar early weight growth patterns among infants who developed sepsis and matched controls who did not, but divergent patterns with significantly worse growth in the infected infants after the diagnosis of sepsis. This suggests that sepsis is likely an antecedent event that predisposes to poor subsequent growth.

Understanding growth trajectories in preterm infants is important for setting standards for optimal growth and weight gain, identifying infants at risk of impaired growth due to high-risk morbidities, and monitoring the effects of therapeutic

Table 3 Comparison of delta z-score at weekly intervals between infants with sepsis and matched infants without sepsis

Days since sepsis episode time point	Paired subjects with delta z-score (N)		Mean (SD) for delta z-score		
	With sepsis (N=693)	Without sepsis (N=693)	With sepsis	Without sepsis	Mean difference (95% CI)
−35	94	94	−0.53 (0.61)	−0.64 (0.62)	0.11 (−0.02 to 0.24)
−28	154	154	−0.57 (0.66)	−0.60 (0.61)	0.03 (−0.07 to 0.13)
−21	234	234	−0.56 (0.61)	−0.58 (0.59)	0.02 (−0.05 to 0.10)
−14	352	352	−0.60 (0.60)	−0.64 (0.57)	0.03 (−0.03 to 0.10)
−7	516	516	−0.68 (0.60)	−0.65 (0.57)	−0.03 (−0.08 to 0.02)
0	614	614	−0.73 (0.59)	−0.67 (0.60)	−0.06 (−0.11 to −0.01)
7	594	594	−0.76 (0.63)	−0.73 (0.60)	−0.03 (−0.09 to 0.03)
14	569	569	−0.81 (0.64)	−0.76 (0.64)	−0.05 (−0.11 to 0.005)
21	550	550	−0.89 (0.68)	−0.77 (0.71)	−0.12 (−0.18 to −0.05)
28	492	492	−0.93 (0.68)	−0.79 (0.73)	−0.14 (−0.21 to −0.07)
35	426	426	−0.94 (0.74)	−0.81 (0.72)	−0.13 (−0.21 to −0.05)
42	371	371	−0.99 (0.77)	−0.81 (0.74)	−0.18 (−0.26 to −0.10)
49	286	286	−1.02 (0.79)	−0.84 (0.72)	−0.17 (−0.27 to −0.07)
56	206	206	−1.02 (0.77)	−0.85 (0.81)	−0.18 (−0.30 to −0.06)
63	138	138	−1.06 (0.73)	−0.89 (0.85)	−0.17 (−0.33 to −0.01)

Only matched infants who both had weight data at the time point were included. Paired t-test was used to calculate the 95% CI of the mean difference.

interventions. Longitudinal growth curves of very preterm infants reported by Ehrenkranz *et al*[11] showed that infants with major morbidities gained weight more slowly than infants without. Our results are congruent, and offer further insight into the association between sepsis and postnatal weight growth.

Our findings also have important clinical implications. Clinicians should be aware that very preterm infants who develop sepsis are at greater risk of poor postnatal weight gain and that, in some infants, this growth failure may be severe. It is biologically plausible that sepsis interferes with optimal growth. Infections trigger inflammation, increase metabolic demand and may lead clinicians to reduce patients' enteral feedings and nutrient intake.[19] Strategies to optimise growth among high-risk infants, particularly following sepsis onset, require continued study.[20]

Our analyses also advance understanding of the complex relationship between sepsis and postnatal weight growth. Visual display of longitudinal growth patterns reveals several key findings. Extrauterine weight gain, when gauged according to intrauterine growth curves, decreased over time among infants who developed sepsis and matched controls who did not. Moreover, weight gain was generally similar between the groups in the weeks immediately prior to and after the time of sepsis diagnosis. However, we do observe a slight but not statistically significant worsening of the growth trajectory 1–2 weeks before sepsis onset followed by a modest uptick in growth 1–2 weeks after the sepsis diagnosis among the infected infants. These subtle changes in growth patterns may represent early signs of emerging physiological instability followed by a 'pseudo-improvement' in growth related to fluid resuscitation and third spacing of intravascular volume. On average, it was not until 3 weeks after the diagnosis of sepsis that clear separation in growth between the groups was observed. Collectively, these findings raise concern that initial weight gain after sepsis onset may provide false reassurance and lead to delayed initiation of nutritional interventions until the full extent of the prolonged growth disparity becomes apparent in later weeks. As such, prophylactic administration of additional calories in the days or weeks after sepsis onset may be a fruitful area for future study. Lastly, it appears there may be early signs of catch-up weight gain at the end of the study period in the sepsis group. While these findings are reassuring, prior data suggest that growth failure associated with sepsis may persist into early childhood.[5]

The strengths of this study include the large and heterogeneous population of very preterm infants. More than 98% of infants had >20 wt measurements, which enabled a robust analysis of weight trajectories that accounted for growth status at birth. Our study does have limitations. All weights were assessed in reference to Olsen curves which define intrauterine, not extrauterine, growth standards.[21] Longitudinal length and head circumference data were not available nor was detailed information on nutritional or caloric intake. Future studies that collect robust nutrition data will enable an important mechanistic analysis to identify potential causes of our novel findings. We were unable to assess for growth outcomes after the study end point at 36 weeks' PMA, and our study data do not inform how deficits in growth after sepsis may affect long-term growth and development. Lastly, as evolution of care over time may affect infant morbidity rates and growth patterns, replication of our findings using more contemporary data may have utility.

CONCLUSIONS

We found that sepsis was associated with an increased risk of poor postnatal weight growth in very preterm infants. Notably, infants with sepsis had similar early growth trajectories as infants without sepsis but developed significant deficits in growth that were not apparent until several weeks after the onset of sepsis. Strategies and interventions to optimise growth among preterm infants with sepsis should be an area of future study.

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REFERENCES

1 Horbar JD, Ehrenkranz RA, Badger GJ, *et al*. Weight growth velocity and postnatal growth failure in infants 501 to 1500 Grams: 2000-2013. *Pediatrics* 2015;136:e84–92.
2 Dusick AM, Poindexter BB, Ehrenkranz RA, *et al*. Growth failure in the preterm infant: can we catch up? *Semin Perinatol* 2003;27:302–10.
3 Hack M, Breslau N, Fanaroff AA. Differential effects of intrauterine and postnatal brain growth failure in infants of very low birth weight. *Am J Dis Child* 1989;143:63.
4 Stoll BJ, Hansen N. Infections in VLBW infants: studies from the NICHD neonatal research network. *Semin Perinatol* 2003;27:293–301.
5 Stoll BJ, Hansen NI, Adams-Chapman I, *et al*. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357.
6 Meyers JM, Bann CM, Stoll BJ, *et al*. Neurodevelopmental outcomes in postnatal growth-restricted preterm infants with postnatal head-sparing. *J Perinatol* 2016;36:1116–21.
7 Franz AR, Pohlandt F, Bode H, *et al*. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. *Pediatrics* 2009;123:e101–9.
8 Hay WW, Lucas A, Heird WC, *et al*. Workshop summary: nutrition of the extremely low birth weight infant. *Pediatrics* 1999;104:1360–8.
9 Hack M, Schluchter M, Cartar L, *et al*. Growth of very low birth weight infants to age 20 years. *Pediatrics* 2003;112:e30–8.
10 Hack M, Breslau N, Weissman B, *et al*. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med* 1991;325:231–7.
11 Ehrenkranz RA, Younes N, Lemons JA, *et al*. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics* 1999;104:280–9.
12 Fanaro S. Which is the ideal target for preterm growth? *Minerva Pediatr* 2010;62:77–82.
13 Marks K-A, Reichman B, Lusky A, *et al*. Fetal growth and postnatal growth failure in very-low-birthweight infants. *Acta Paediatr* 2006;95:236–42.

14 De Curtis M, Rigo J. Extrauterine growth restriction in very-low-birthweight infants. *Acta Paediatr* 2004;93:1563–8.
15 Binenbaum G, Tomlinson LA. Postnatal growth and retinopathy of prematurity study: rationale, design, and subject characteristics. *Ophthalmic Epidemiol* 2017;24:36–47.
16 Binenbaum G, Bell EF, Donohue P, *et al*. Development of modified screening criteria for retinopathy of prematurity: primary results from the postnatal growth and retinopathy of prematurity study. *JAMA Ophthalmol* 2018;136:1034–40.
17 Goldberg DL, Becker PJ, Brigham K, *et al*. Identifying malnutrition in preterm and neonatal populations: recommended indicators. *J Acad Nutr Diet* 2018;118:1571–82.
18 Olsen IE, Groveman SA, Lawson ML, *et al*. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125:e214–24.
19 Hibbert JE, Currie A, Strunk T. Sepsis-Induced immunosuppression in neonates. *Front Pediatr* 2018;6:357.
20 Stefanescu BM, Gillam-Krakauer M, Stefanescu AR, *et al*. Very low birth weight infant care: adherence to a new nutrition protocol improves growth outcomes and reduces infectious risk. *Early Hum Dev* 2016;94:25–30.
21 Rochow N, Landau-Crangle E, So HY, *et al*. Z-score differences based on cross-sectional growth charts do not reflect the growth rate of very low birth weight infants. *PLoS One* 2019;14:e0216048.