Growth Failure Prevalence in Neonates with Gastroschisis : A Statewide Cohort Study

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Objectives To perform a multicenter study to assess growth failure in hospitalized infants with gastroschisis.
Study design This study included neonates with gastroschisis within sites in the University of California Fetal Consortium. The study's primary outcome was growth failure at hospital discharge, defined as a weight or length z score decrease >0.8 from birth. Regression analysis was performed to assess changes in z scores over time.
Results Among 125 infants with gastroschisis, the median gestational age was 37 weeks (IQR 35-37). Length of stay was 32 days (23-60); 55% developed weight or length growth failure at discharge (28% had weight growth failure, 42% had length growth failure, and 15% had both weight and length growth failure). Weight and length z scores at 14 days, 30 days, and discharge were less than birth ($P < .01$ for all). Weight and length z scores declined from birth to 30 days (−0.10 and −0.11 z score units/week, respectively, $P < .001$). Length growth failure at discharge was associated with weight and length z score changes over time ($P < .05$ for both). Lower gestational age was associated with weight growth failure (OR 0.70 for each gestational age week, 95% CI 0.55-0.89, $P = .004$).
Conclusions Growth failure, in particular linear growth failure, is common in infants with gastroschisis. These data suggest the need to improve nutritional management in these infants. *(J Pediatr 2021;233:112-8)*.

In adults and children, malnutrition is underdiagnosed and associated with increased sepsis and mortality rates and prolonged hospital stays.[1-3] In neonates, growth failure is associated with poor neurodevelopment, and catch-up growth appears to be protective.[4-7] Infants with gastroschisis are at high risk for growth failure. Up to 80% of these infants are born prematurely, with an average gestational age of 36 weeks[8]; 15% of infants with gastroschisis have intrauterine growth restriction (IUGR).[9] These infants are often exposed in utero to tobacco and illicit drugs.[10,11] All infants with gastroschisis are at risk for intestinal strictures, necrotizing enterocolitis, sepsis, and prolonged feeding intolerance. Approximately 20% of infants with short bowel syndrome have gastroschisis.[12] Infants with short bowel syndrome require prolonged parenteral nutrition, which is associated with growth stunting and intestinal failure associated liver disease.[12]

Most growth studies in infants with gastroschisis are retrospective, single site, have small sample sizes, and involve infants with other gastrointestinal anomalies.[13-21] Understanding the extent of growth failure is also complicated because studies characterize growth failure differently. Z scores are considered the gold standard for defining growth failure and reflect the SD of the population. Our objective was to determine the incidence and degree of growth failure and describe changes in weight, length, and head circumference (HC) z scores over time in a large contemporary cohort of infants with gastroschisis.

We hypothesized that >40% of infants with gastroschisis would have growth failure, defined as a decline in the z score for weight or length >0.8 at hospital discharge, that weight and length z scores would be lower at hospital discharge than birth, but HC would be unchanged, that prematurity, small for gestational age (SGA), sepsis,

HC	Head circumference
IUGR	Intrauterine growth restriction
NICU	Neonatal intensive care unit
SGA	Small for gestational age
UCFC	University of California Fetal Consortium

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and necrotizing enterocolitis would negatively correlate with growth failure, and that age at first feed and full feeds would positively correlate with growth failure.

Methods

Infants with gastroschisis were eligible for this retrospective cohort study if they were cared for at one of the sites in the University of California Fetal Consortium (UCFC) and born between February 2015 and July 2019. Patients who died prior to discharge from the neonatal intensive care unit (NICU) were excluded. In 2015, the UCFC implemented a surgical, obstetrical, and neonatal pathway to standardize care for infants with gastroschisis. This pathway prioritizes vaginal delivery, prompt closure of the intestinal defect, minimizing the use of paralytics, antibiotics, and opioids. The pathway recommends initiating 20 cc/kg/day of human milk after 48 hours of nonbilious Repogle output and advancing feeds by 20 cc/kg/day (**Table I**; available at www.jpeds.com). This pathway does not provide any recommendations for parenteral nutrition or fortification of enteral nutrition. The UCFC published a moderate to high adherence (60%-96%) to individual components of this pathway.[22] Implementation of this pathway was associated with a decrease in median ventilator and antibiotic days, and earlier initiation of feeds.[22]

Our primary outcome was weight or length growth failure at hospital discharge. Growth failure was classified as mild, moderate, or severe.[23] Mild growth failure was defined as a z score change from birth greater than or equal to 0.8, but less than 1.2. Moderate growth failure was defined as a z score change from birth >1.2, but <2. Severe growth failure was defined as a z score change from birth >2.

This study was a retrospective analysis of a quality improvement project. Growth data was collected prospectively. Chart review of the maternal record included: illicit drug/alcohol/tobacco use, IUGR, and maternal age. IUGR was defined as weight <10th percentile on ultrasound for a given gestational age.[24] Chart review of the neonatal record included: gestational age, mode of delivery, duration of parenteral nutrition, days to reach full enteral feeds, and complications such as sepsis and necrotizing enterocolitis. Full feed was defined as 100 cc/kg/day of enteral nutrition or ad libitum feeding, whichever occurred first. Late onset sepsis was defined as a positive blood culture after 72 hours of age. Necrotizing enterocolitis was defined by Bell stage 2 or greater.[25] Gastroschisis diagnosis was differentiated as simple vs complex. Complex gastroschisis was defined as gastroschisis with intestinal atresia, intestinal stricture, ischemic bowel prior to closure, or severe pulmonary hypoplasia.[22]

Weight, length, and HC and their respective z scores were measured by clinical staff at birth, and approximately 14 and 30 days of age, and at discharge. Length was measured using rigid length boards for all sites except one. Means and SDs to calculate z scores were obtained from Fenton et al for preterm infants (<37 weeks gestational age) and the World Health Organization for term infants.[26,27] Growth velocity was calculated using a 2-point model with birth weight as a starting point and accounted for birth weight (g/kg/day).[28] Length and HC velocity was expressed as cm/week. SGA was defined as <10th percentile for birth weight using the appropriate growth chart.

Statistical Analyses

To achieve at least 80% power with a 1-sided binomial test at a 5% significance level, a sample size of 120 would detect an incidence of 41% in the primary outcome (weight or length growth failure), when the population incidence was assumed to be 30%. Quantitative variables were summarized using quartiles (median and IQRs), and differences were examined using the paired *t* test, mean differences, and 95% CI. Qualitative variables are summarized using frequencies and percentages, and were compared using the Fisher exact test. Generalized linear mixed models for repeated measures were used to estimate the rate of change in weight, length, and HC z scores over time. The growth velocity (weight, length, and HC) between infants with and without growth failure were compared using the Wilcoxon test.

The association between gestational age, birth weight z score, IUGR, SGA, length of stay, complicated gastroschisis, days until first feed, site, surgical method, late onset sepsis, and days until abdominal closure, discharge weight growth failure, and discharge length growth failure were examined using a series of univariable logistic regression models. The results are summarized using ORs and their 95% CI. All tests were 2 sided and *P* values of less than .05 were considered statistically significant. The analyses were performed using SAS 2016 (SAS Institute Inc).

Results

Infants with gastroschisis (n = 132) were eligible for this study, and 125 infants were included. No infants died or were transferred to another hospital. Seven infants were excluded due to missing birth growth measures. Of those included, 120 infants had growth data at 14 days, 90 infants at 30 days, and 125 infants at NICU discharge. Patients were treated at one of the UCFC sites: University of California San Francisco (28), University of California Davis (27), University of California Los Angeles (32), University of California Irvine (20), University of California San Diego (14), and Rady Children's Hospital (6).

Demographic and hospital course data are summarized in **Table II**: 14% (17 infants) had complex gastroschisis, 4% (5 infants) developed necrotizing enterocolitis, 2 of whom required surgery and 1 infant developed abdominal compartment syndrome requiring surgical intervention. When feeds were initiated, 90% (105 infants) received either maternal breastmilk or donor milk. At discharge, 42% (48 infants) received human milk, 31% (37 infants) received human milk and formula, 25% (29 infants) received formula only, and 2% (2 infants) received parenteral nutrition.

The mean day for growth data collected at 14 days of age was 13.7 days (CI 13.1, 14.4) for weight, 15.9 days (CI 8.6,

Table II. Characteristics of infants with gastroschisis

Subject characteristics	Percent (n) or median (IQR)	n
Sex, female	46 (54)	117
Gestational age	37 (35,37)	125
Birth weight (g)	2458 (2165,2802)	124
Birth length (cm)	46 (43,48)	123
Birth HC (cm)	32 (30.5,33)	124
Birth weight z score	−0.9 (−1.5, −0.1)	122
Birth length z score	−0.9 (−1.7, 0.1)	121
Birth HC z score	−1.1 (−1.7, −0.2)	122
SGA	43 (54)	122
IUGR	32 (40)	124
Maternal tobacco use	11 (14)	124
Maternal alcohol use	3 (4)	125
Maternal illicit drug use	18 (21)	120
Complicated gastroschisis	14 (17)	122
Length of stay (d)	33 (23,60)	120
Necrotizing enterocolitis	4 (5)	119
Late onset sepsis	9 (11)	120
Age of first feed (d)	12 (9,18)	115
Age at full feeds (d)	24 (18,43)	123
Days to closure	2 (0,4)	123
Abdominal compartment syndrome	1 (1)	125
Silo utilized	72 (90)	125

n, number of observations.
SGA is a birth weight less than the 10th percentile. IUGR is a fetal weight estimated to be less than the 10th percentile on ultrasound. Complicated gastroschisis is defined as pulmonary hypoplasia, intestinal atresia or stricture, or ischemic bowel prior to closure. Necrotizing enterocolitis is defined as Bell stage 2 or greater. Late onset sepsis is a positive blood culture after 72 hours of age.

23.1) for length, and 15.6 days (CI 8.5, 22.1) for HC. The mean day for growth data collected at 30 days was 31.5 days (CI 24.2, 38.7) for weight, 30.9 days (CI 22, 39.8) for length, and 30.3 days (CI 22.7, 38) for HC. Mean day for growth data collected at NICU discharge was 50.3 days (CI 40.1, 60.5) for weight, 48.1 days (CI 38, 58.2) for length, and 47.9 days (CI 38.6, and 57.2) for HC.

Overall, 55% of infants in this study had the primary outcome. **Table III** provides data on the incidence of growth failure; 28% (35 infants) had weight growth failure at discharge, 42% (53 infants) had length growth failure, and 15% (19 infants) had both weight and length growth failure at discharge. The mean (CI) z scores at birth, 14 and 30 days of age, and discharge are displayed in **Table IV** (available at www.jpeds.com). The median time to regain birth weight was 8 days (IQR 5, 13). At birth, 36% (48 infants) and 41% of infants (54 infants) had a birth weight or length z score < −1.28 at birth (10th percentile, or SGA), respectively. At discharge, 59% (78 infants) and 59% (78 infants) had a weight and length z score < −1.28. Compared with birth, the odds of having a weight or length z score <-1.28 at discharge were 3 ($P < .001$) and 2.2 ($P = .003$) times higher, respectively.

Table III. Growth failure at each time point in infants with gastroschisis

Growth parameter and date	Mild growth failure	Moderate growth failure	Severe growth failure
Weight z score			
14 d n =120	21%	4%	0%
30 d n = 90	16%	11%	0%
Discharge n = 125	13%	12%	3%
Length z score			
14 d n = 120	15%	14%	2%
30 d n = 90	17%	17%	8%
Discharge n = 125	16%	15%	11%

Number of observations provided at each time point. Growth failure was categorized by changes in weight or length z score at each time point from birth: mild 0.8-1.19, moderate 1.2-1.99, and severe ≥2.

Weight, length, and HC z scores were all significantly less than zero at birth, 14 and 30 days, and discharge ($P = .001$ for all). Weight and length z scores at 14 and 30 days and discharge were significantly less than birth weight and length, respectively ($P = .001$ for all). However, when HC z scores at later time points were compared with birth HC, there was no difference ($P = .28$ at 14 days, $P = .54$ at 30 days, and $P = .17$ at discharge). Weight and length z score from birth to 30 days demonstrated a significant decrease over time (−0.10 z score units/week and −0.11 z score units/week, respectively, $P < .001$ for all). In contrast, there was not a significant change in HC from birth to 30 days (−0.02 z score units/week, $P = .66$).

There was not a significant increase in the incidence of weight ($P = .32$) or length growth failure over time ($P = .06$), but there was a significant increase in both weight and length growth failure over time ($P = .04$). At 14 days, 6% of infants (8 infants) with gastroschisis had both weight and length growth failure. By NICU discharge, 15% (19 infants) had both weight and length growth failure. Change in weight z score from birth to 30 days was significantly different between those who had the primary outcome compared with those who did not have the primary outcome (−0.13 vs −0.07 z score units/week, $P = .004$, **Figure 1**). Likewise, change in length z score from birth to 30 days was significantly different between the two groups (−0.54 vs 0.16 z score units/week, $P = .026$, **Figure 1**). However, change in HC z score from birth to 30 days was similar between those who had the primary outcome compared with those who did not (−0.005 vs 0.0067 z score units/week, $P = .086$, **Figure 1**). In contrast, median weight and HC growth velocity were similar when the group of infants with the primary outcome was compared with the group of infants without the primary outcome ($P = .32$ for weight and $P = .16$ for HC, respectively) (**Table V**; available at www.jpeds.com). However, there was a significant difference in median linear growth velocity. Linear velocity in infants with growth failure was 0.58 cm/week, and linear velocity in infants without growth failure was 1 cm/week ($P = .01$).

Gestational age was associated with growth failure; more mature infants had a decreased odds of growth failure (OR 0.70 for each gestational age week, 95% CI 0.55-0.89, $P = .004$). An increase in 1 SD for birth weight z score was associated with an increased the risk for growth failure (OR 1.83, 95% CI 1.78-2.83, $P = .007$). The odds of developing growth failure was 28% greater if the infant was not SGA vs SGA (OR 0.78, 95% CI, $P = .02$) (**Table VI**; available at www.jpeds.com). Weight z score trajectories for SGA infants and infants without SGA are shown in **Figure 2**. Of

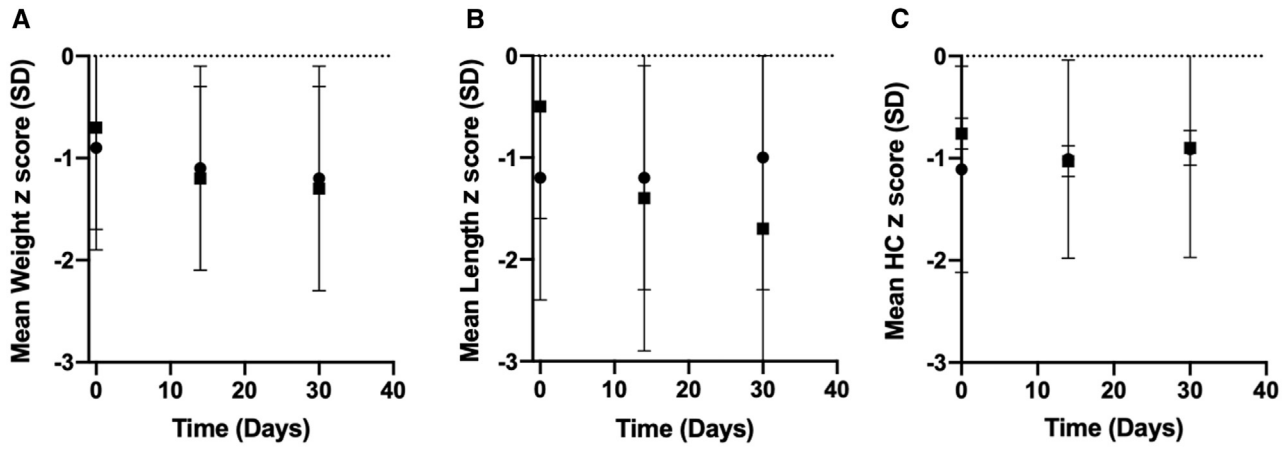

Figure 1. **A,** Mean weight, **B,** length, and **C,** HC z scores from birth to 30 days. Circles represent those who had no growth failure (weight or length) at discharge. Squares represent those who had growth failure (weight or length) at discharge. Error bars represent SD. The change in weight z score from birth to 30 days was significantly different between those who developed growth failure at discharge compared with those who did not (−0.13 vs −0.07 z score units/week, $P = .004$). The change in length z score from birth to 30 days was significantly different between these 2 groups (−0.54 vs 0.16 z score units/week, $P = .023$). There was no significant difference in HC score changes from birth to 30 days between groups (−0.0050 vs 0.0067 z score units/week, $P = .086$).

note, infants born SGA had a significantly higher median gestational age than infants born appropriate for gestational age (37.1 [IQR 36.7-37.1] vs 36.3 [IQR 34.4-37.9], $P = .001$). Weight growth failure was not associated with sepsis, necrotizing enterocolitis, or age at first feed and full feeds. There were no significant associations for length growth failure at discharge.

Discussion

In this multisite study of 125 infants with gastroschisis, growth failure, specifically, linear growth failure, was common. The incidence of infants with both weight and length growth failure increased during the hospital stay. Our data suggest that growth failure may be detected prior to hospital discharge and bring up the possibility that improved nutritional practices and clinical strategies should be considered.

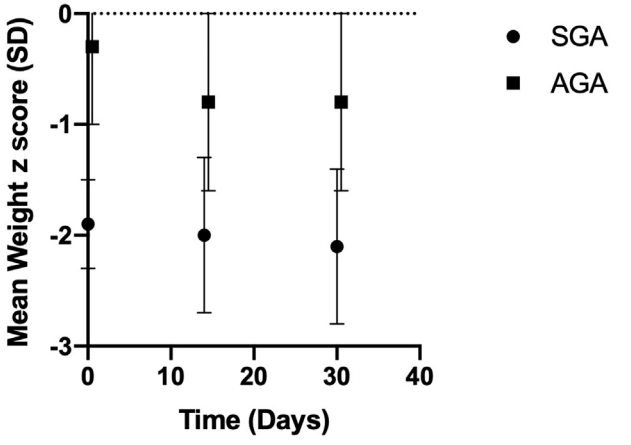

Figure 2. Mean weight z score from birth to 30 days in infants who are SGA vs infants who are appropriate for gestational age. *AGA*, appropriate for gestational age.

Our findings validate previous finding by other investigators.[4,15,19-21] Growth failure during initial hospital stay in infants with gastroschisis was investigated in 2 single-site, retrospective studies. These studies had a sample size of 60 and 90 infants, respectively. In both studies, 30% of infants with gastroschisis had a weight z score less than 1 at discharge.[15,20] This is comparable with our study; 28% of infants had a weight z score <0.8 at discharge. In contrast to these studies, we investigated growth in larger group of infants who were cared for at 6 different sites. Each site utilized a standardized obstetrical, surgical, and medical approach for the management of gastroschisis. We also investigated longitudinal measurements for weight, length, HC, and growth velocity.

Weight velocity is commonly used to assess growth in the NICU. Growth velocity is calculated in g/kg/day, which accounts for birth weight, or g/day.[4,23] When using g/kg/day, some investigators use birth weight, and others will use the physiologic nadir for this calculation.[29] We opted to report g/kg/day, accounting for birth weight, to be consistent with the growth failure definitions published by Goldberg et al.[23] Although the infants in this study had a median gestational age of 37 weeks, many infants were born prematurely and were SGA or growth restricted. We compared z score changes with velocities for weight, length, and HC. There was no significant difference in weight velocity between gastroschisis infants who developed growth failure and infants with gastroschisis who did not develop growth failure. In this study, the median weight growth velocity for infants with gastroschisis was 5.8 g/kg/day, which is far below the

recommended growth velocity of at least 15 g/kg/day.[23] In contrast, infants with gastroschisis who developed growth failure had a significantly different and worse linear velocity compared with infants without growth failure.

In preterm infants, poor linear growth and microcephaly are associated with neurodevelopmental delays.[30-33] Fetuses with gastroschisis have smaller occipitofrontal circumference and crown-heel length compared with healthy control fetuses matched for gestational age.[34] In preterm infants, smaller occipitofrontal circumference and shorter fetal lengths have been associated with a decreased amount of white matter on magnetic resonance imaging.[35] In this study, HC z score did not change over time, and HC velocity was similar for infants with gastroschisis with growth failure and those without growth failure. Although it is unclear why HC was spared, we hypothesize that these infants were not severely malnourished or stunted. Studies in preterm infants with postnatal growth failure reported similar findings.[31,36,37]

Increased energy and protein provisions are associated with improved somatic growth and a decreased risk for cerebral palsy in very low birth weight infants.[38-43] It is possible that some infants with gastroschisis and growth failure develop an energy and protein deficit. Providing sufficient parenteral protein beginning at birth and not prematurely discontinuing parenteral nutrition may be an important nutritional practice to consider in infants with gastroschisis. Fortification of enteral nutrition may also improve growth. However, some infants with gastroschisis may not tolerate bovine fortification. Given our results, we have recently amended our clinical guidelines to include recommendations for parenteral nutrition and enteral nutrition fortification.

Gestational age, SGA, and birth weight z score were associated with weight growth failure at discharge. As expected, infants with gastroschisis who were born less mature had a higher risk of growth failure. Studies that have demonstrated that late-preterm infants are at risk for growth failure and later disabilities.[44] SGA and IUGR infants are at high risk for growth failure.[45,46] In our study, there was a high incidence of SGA and IUGR; 43% and 32% of the infants had SGA or IUGR, respectively. Unexpectedly, SGA was associated with a decreased risk for growth failure. This is inconsistent with our hypothesis and prior research.[45,46] This may be explained by the fact that SGA infants had a significantly higher gestational age at birth compared with infants who were born appropriate for gestational age. In this study, there was a 30% reduction in growth failure for each additional week of gestation. It is also possible that clinicians caring for infants who are born SGA may pay more attention to growth and nutrition compared with infants born appropriate for gestational age.

Although the median surgical closure was 2 days of age, feeds were initiated at a mean of 12 days of age in this study. This delay in feeding is most likely secondary to underlying intestinal dysmotility. Chronic inflammation and intestinal dysbiosis may contribute to dysmotility and poor growth in neonates with gastroschisis. In the pediatric population, inflammation has been linked to abnormalities in the growth hormone/ insulin-like growth factor 1 axis.[47] In fetuses with gastroschisis, the intestinal exposure to amniotic fluid causes an inflammatory bowel "peel" that may cause feeding intolerance and prolonged parenteral nutrition courses, which may in turn, may cause growth failure.[48]

This inherent inflammation in neonates with gastroschisis may be exacerbated by the enteral diet. Although the majority of the infants received human milk when enteral feeds were started, 56% of infants were receiving some formula at discharge. In term infants fed an exclusively human milk diet compared with those who received formula, infants who received a human milk diet had lower concentrations of fecal calprotectin and alpha-1 antitrypsin levels, markers of inflammation, at 3 months of life.[49] Some mothers may not be able to provide a sufficient amount of human milk, or there may be contraindications to human milk. In very low birth weight infants, the prolonged use of unfortified donor milk has been associated with poor growth.[44] However, when donor milk is used as a "bridge," and a standardized approach to donor milk fortification is used, a human milk diet improves overall growth and neurodevelopment, and decreases the risk of sepsis, necrotizing enterocolitis, and hospital re-admissions.[50-52]

We recognize the limitations of our study. Data was collected retrospectively and, as a result, there is some missing data. We did not assess growth or neurodevelopment beyond the NICU. Assessments of linear growth were not uniform. However, all but one site used length boards, which is the preferred method for measuring length in infants. We did not collect data on albumin concentrations, blood urea nitrogen, and urine sodium concentrations, which are markers of nutritional status. Last, we are unable to comment on specific components of parenteral and enteral nutrition. The UCFC gastroschisis clinical pathway provides limited guidance on nutritional management. As result, it is unclear if the growth patterns observed in our study are secondary to variability in nutritional practices.

Because this study enrolled a large group of infants from several large children's hospitals in the state of California and participating centers utilized a standardized approach to the management of gastroschisis, we believe our results are generalizable. These findings suggest that clinicians may need to develop a multidisciplinary nutritional approach to prevent and treat growth failure in infants with gastroschisis. ■

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References

1. Corkins MR, Guenter P, DiMaria-Ghalili RA, Jensen GL, Malone A, Miller S, et al. Malnutrition diagnoses in hospitalized patients: United States, 2010. JPEN J Parenter Enteral Nutr 2014;38:186-95.
2. Irving SY, Daly B, Verger J, Typpo K, Brown A, Hanlon A, et al. The association of nutrition status expressed as body mass index z score with outcomes in children with severe sepsis: a secondary analysis from the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study. Crit Care Med 2018;46:e1029-39.

3. Mabhandi T, Ramdin T, Ballot DE. Growth of extremely low birth weight infants at a tertiary hospital in a middle-income country. BMC Pediatr 2019;19:231.
4. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics Apr 2006;117:1253-61.
5. Wiedmeier JE, Joss-Moore LA, Lane RH, Neu J. Early postnatal nutrition and programming of the preterm neonate. Nutr Rev 2011;69:76-82.
6. Van Dommelen P, Van der Pal S, Gravenhorst J. The effect of early catch-up growth on health and well-being in adults. Ann Nutri Metab 2014;65:220-6.
7. Taine M, Charles MA, Beltrand J, Rozé JC, Léger J, Botton J, et al. Early postnatal growth and neurodevelopment in children born moderately preterm or small for gestational age at term: a systematic review. Paediatr Perinat Epidemiol 2018;32:268-80.
8. Nair N, Merhar S, Wessel J, Hall E, Kingma P. Factors that influence longitudinal growth from birth to 18 months of age in infants with gastroschisis. Am J Perinatol 2019;37:1438-45.
9. Puligandla PS, Janvier A, Flageole H, Bouchard S, Mok E, Laberge JM. The significance of intrauterine growth restriction is different from prematurity for the outcome of infants with gastroschisis. J Pediatr Surg 2004;39:1200-4.
10. Vu LT, Nobuhara KK, Laurent C, Shaw GM. Increasing prevalence of gastroschisis: population-based study in California. Pediatrics 2008;152:807-11.
11. Laughon M, Meyer R, Bose C, Wall A, Otero E, Heerens A, et al. Rising birth prevalence of gastroschisis. J Perinatol 2003;23:291-3.
12. Amin SC, Pappas C, Iyengar H, Maheshwari A. Short bowel syndrome in the NICU. Clin Perinatol 2013;40:53-68.
13. Henrich K, Huemmer HP, Reingruber B, Weber PG. Gastroschisis and omphalocele: treatments and long term outcomes. Pediatric Surg Int 2008;24:167-73.
14. South AP, Marshall DD, Bose Cl, Laughon LL. Growth and neurodevelopment at 16 to 24 months of age for infants born with gastroschisis. J Perinatol 2008;28:702-6.
15. Minutillo C, Rao S, Pirie S, McMichael J, Dickinson JE. Growth and developmental outcomes of infants with gastroschisis at one year of age: a retrospective study. J Pediatr Surg 2013;48:1688-96.
16. Van Manen M, Hendson L, Wiley M, Evans M, Taghaddos S, Dinu I. Early childhood outcomes of infants born with gastroschisis. J Pediatr Surg 2013;48:1682-7.
17. Harris E, Minutillo C, Hart S, Warner T, Ravikumara M, Nathan E, et al. The long term physical consequences of gastroschisis. J Pediatr Surg 2014;49:1466-70.
18. Giudici L, Bokser VS, Maricic MA, Golombek SG, Ferrario CC. Babies born with gastroschisis and followed up to the age of six years faced long-term morbidity and impairments. Acta Paediatr 2016;105:275-80.
19. Hijkoop A, Ijsselstijn, Wijnen RMH, Tibboel D, Rosmalen JV, Cohen-Overbeek TE. Prenatal markers and longitudinal follow-up in simple and complex gastroschisis. Arch Dis Child Fetal Neonatal Ed 2019;103:126-31.
20. Hong CR, Zurakowski D, Fullerton BS, Ariagno K, Jaksic T, Mehta NM. Nutrition delivery and growth outcomes in gastroschisis. J Parenteral Nutr 2018;42:913-9.
21. Strobel KM, Purdy I, Romero T, Calkins KL. Growth from birth to 30 months for infants born with congenital gastrointestinal anomalies and disorders. [published online ahead of print, 2020 Mar 13]. *Am J Perinatol* 2020. https://doi.org/10.1055/s-0040-1705136
22. DeUgarte D, Calkins KL, Guner Y, Kim J, Kling K, Kramer K, et al. Adherence to and outcomes of a University-Consortium gastroschisis pathway. J Pediatr Surg 2020;55:45-8.
23. Goldberg DL, Becker PJ, Brigham K, Carlson S, Fleck L, Gollins L, et al. Identifying malnutrition in preterm and neonatal populations: recommended indicators. J Acad Nutr Dietetics 2018;118:1571-82.
24. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obst Gynecol 1996;87:163-8.
25. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
26. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:13-59.
27. Centers for Disease Control and Prevention. WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age. Published 2010. Accessed October 21, 2014. http://www.cdc.gov/growthcharts/who_charts.htm#TheWHOGrowthCharts
28. Patel AL, Engstrom JL, Meier PP, Kimura RE. Accuracy of methods for calculating postnatal growth velocity for extremely low birth weight infants. Pediatrics 2005;116:1466-73.
29. Cormack BE, Embleton ND, van Goudoever JB, Hay WW Jr, Bloomfield FH. Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies. Pediatr Res 2016;79:810-20.
30. Pfister KM, Ramel SE. Linear growth and neurodevelopmental outcomes. Clin Perinatol 2014;41:309-21.
31. Ramel SE, Demerath EW, Gray HL, Younge N, Boys C, Georgieff MK. The relationship of poor linear growth velocity with neonatal illness and two-year neurodevelopment in preterm infants. Neonatology 2012;102:19-24.
32. Fuentefria RN, Silveira RC, Procianoy RS. Neurodevelopment and growth of a cohort of very low birth weight preterm infants compared to full-term infants in Brazil. Am J Perinatol 2018;35:152-62.
33. Neubauer V, Griesmaier E, Pehbock-Walser N, Pupp-Peglow U, Kiechl-Kohlendorfer U. Poor postnatal head growth in very preterm infants is associated with impaired neurodevelopment outcome. Acta Paediatrica (Oslo, Norway 1992) 2013;102:883-8.
34. Payne NR, Simonton SC, Olsen S, Arnesen MA, Pfleghaar KM. Growth restriction in gastroschisis: quantification of its severity and exploration of a placental cause. BMC Pediatr 2011;11:11-90.
35. Watanabe Y, Itabashi K, Taki M, Miyazawa T, Nakano Y, Murase M. Body length and occipitofrontal circumference may be good indicators of neurodevelopment in very low birthweight infants: secondary publication. Acta Paediatr 2018;107:975-80.
36. Modi M, Saluja S, Kler N, Batra A, Kaur A, Garg P, et al. Growth and neurodevelopmental outcome of VLBW infants at 1 year corrected age. Indian Pediatr 2013;50:573-7.
37. Bocca-Tjeertes I, Bos A, Kerstjens J, de Winter A, Reijneveld S. Symmetrical and asymmetrical growth restriction in preterm-born children. Pediatrics 2014;133:e650-6.
38. Prado EL, Larson LM, Cox K, Bettencourt K, Kubes JN, Shankar AH. Do effects of early life interventions on linear growth correspond to effects on neurobehavioural development? A systematic review and meta-analysis. Lancet Glob Health 2019;7:e1398-413.
39. Dogra S, Thakur A, Garg P, Kler N. Effect of differential enteral protein on growth and neurodevelopment in infants <1500 g: a randomized controlled trial. J Pediatr Gastroenterol Nutr 2017;64:e126-32.
40. Gerritsen L, Lindeboom R, Hummel T. Prescribed protein intake does not meet recommended intake in moderate- and late-preterm infants: contribution to weight gain and head growth. [published online ahead of print, 2020 Mar 3]. *Nutr Clin Pract* 2020. https://doi.org/10.1002/ncp.10464
41. Schneider N, Garcia-Rodenas CL. Early nutritional interventions for brain and cognitive development in preterm infants: a review of the literature. Nutrients 2017;9:187.
42. Maggio L, Cota F, Gallini F, Lauriola V, Zecca C, Romagnoli C. Effects of high vs standard early protein intake on growth of extremely low birth weight infants. J Pediatr Gastroenterol Nutr 2007;44:124-9.
43. Biasini A, Marvulli L, Neri E, China M, Stella M, Monti F. Growth and neurological outcome in ELBW preterms fed with human milk and extra-protein supplementation as routine practice: do we need further evidence? J Matern Fetal Neonatal Med 2012;25:72-4.
44. Gupta P, Mital R, Kumar B, Yadav A, Jain M, Upadhyay A. Physical growth, morbidity profile and mortality among healthy late preterm neonates. Indian Pediatr 2017;54:629-34.
45. Marks K, Reichman B, Lusky A, Zmora E. Fetal growth and postnatal growth failure in very-low-birthweight infants. Acta Paediatrica 2006;95:236-42.
46. Cooke RJ. Postnatal growth and development in the preterm and small for gestational age infant. Nestle Nutr Workshop Ser Pediatr Program 2010;65:85-98. discussion 96-8.

47. Cirillo F, Lazzeroni P, Catellani C, Sartori C, Amarri S, Street ME. MicroRNAs link chronic inflammation in childhood to growth impairment and insulin-resistance. Cytokine Growth Factor Rev 2018;39:1-18.
48. Guibourdenche J, Berrebi D, Vuillard E, de Lagausie P, Aigrain Y, Oury JF, et al. Biochemical investigations of bowel inflammation in gastroschisis. Pediatr Res 2006;60:565-8.
49. Ossa JC, Yáñez D, Valenzuela R, Gallardo P, Lucero Y, Farfán MJ. Intestinal inflammation in chilean infants fed with bovine formula vs. breast milk and its association with their gut microbiota. front cell infect microbiol 2018;8:190.
50. Ginovart G, Gich I, Gutiérrez A, Verd S. A fortified donor milk policy is associated with improved in-hospital head growth and weight gain in very low-birth-weight infants. Adv Neonatal Care 2017;17:250-7.
51. Asbury MR, Unger S, Kiss A, Ng DVY, Luk Y, Bando N, et al. Optimizing the growth of very-low-birth-weight infants requires targeting both nutritional and nonnutritional modifiable factors specific to stage of hospitalization. Am J Clin Nutr 2019;110:1384-94.
52. Trang S, Zupanic JAF, Unger S, Kiss A, Bando N, Won S, et al. Cost-effectiveness of supplemental donor milk versus formula for very low birth weight infants. Pediatrics 2018;141:141.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Pregnancy in Women with Galactosemia

Roe TF, Hallatt JG, Donnell GN, Ng WG. Childbearing by a galactosemic woman. J Pediatr 1971;78:1026-30.

Galactosemia, an inborn error of galactose metabolism due to impaired activity of the enzyme galactose-1-phospate uridyltransferase, affects 1 in 16 000-50 000 newborns. Despite adherence to a galactose-restricted diet, abnormal menstrual cycles and primary ovarian insufficiency (POI) are frequent (<90%) in girls and women with galactosemia. POI represents one of the most frequent long-term complications.[1]

Fifty years ago, Roe et al reported in *The Journal* that a woman with classical galactosemia gave birth to a healthy heterozygous offspring. Subsequent reports confirmed spontaneous pregnancies indicating subfertility rather than infertility. A retrospective multicenter study reported near 50% spontaneous pregnancy rate in patients actively attempting to conceive during 2 years, substantially greater than for other cases of ovarian failure.[1]

During puberty, the number of follicles is reduced in these patients. Several mechanisms have been suggested, including direct toxicity of galactose and its metabolites. A small study demonstrated a preserved number of follicles in young girls, raising the opportunity for cryopreservation to manage subfertility.[2] The observation by Roe et al 50 years ago illustrated that spontaneous pregnancies occur despite POI. If these women attempt to conceive for a period of 27-30 months, it is estimated that >60% of couples would become pregnant.[1] The awareness of this relatively high rate of spontaneous pregnancies should be emphasized in the counseling of the patients. The years to come will reveal details about the underlying pathophysiologic mechanism, timing of the ovarian dysfunction, and new treatment strategies.

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References

1. van Erven B, Berry GT, Cassiman D, Connolly G, Forga M, Gautschi M, et al. Fertility in adult women with classic galactosemia and primary ovarian insufficiency. Fertil Steril 2017;108:168-74.
2. Mamsen LS, Kelsey TW, Ernst E, Macklon KT, Lund AM, Andersen CY. Cryopreservation of ovarian tissue may be considered in young girls with galactosemia. J Assist Reprod Genet 2018;35:1209-17.

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Table I. 2015 UCFC clinical pathway for gastroschisis

Obstetrical guidelines
- Recommend delivery at 38 wk if routine pregnancy with fetal gastroschisis without other maternal or fetal indications for delivery
- In pregnancies with fetal gastroschisis that are complicated by fetal growth restriction or suboptimal interval fetal growth, the goal gestational age for delivery is 37 wk
- Vaginal delivery is recommended with Cesarean section reserved for obstetrical indications

Surgical guidelines
- *Attempt bedside silo placement and closure without intubation or anesthesia is encouraged when feasible (a narrow fascial defect requiring lateral extension does not prohibit this approach). Routine intubation and paralysis are not recommended
- If silo is utilized, closure within 3 d is recommended when feasible
- Recommend gastric and rectal decompression as strategies to facilitate reduction

Ventilator guidelines
- Routine intubation and paralysis are not recommended for silo placement and bedside reduction

Antibiotic guidelines
- Ampicillin and gentamicin are recommended as primary choice for prophylaxis
- Discontinue antibiotics within 48 h after abdominal closure in the absence of culture-positive sepsis and clinical instability

Pain management guidelines
- *Recommend oral sucrose water for silo placement, reduction, and closure
- If narcotics are used, limit to a single dose when feasible to prevent against apnea or intubation
- Recommend nonnarcotic medications to control pain
- Discontinue opioids within 48 h after abdominal closure

Central venous access guidelines
- Peripherally inserted venous access is preferred over central-insertion of tunneled catheters
- Discontinue central venous catheters as soon as 100 kcal/kg/d of enteral feeds (or ad lib oral feeds) are achieved

Feeding guidelines
- Initiate feeds within 48 h of gastric output becoming nonbilious
- Use mother's own breastmilk if available
- Advance feeding by at least 20 cc/kg/d as tolerated

*Represents changes made in 2016.

Table IV. Mean (95% CIs) for weight, length, and HC z scores at birth, 14 and 30 days, and discharge in infants with gastroschisis

Growth parameter	Birth	14 d	30 d	Discharge
Weight	−0.82 (−1,-0.7)*	−1.2 (−1.4,-1)*,†	−1.2 (−1.4,-1.0) *,†	−1.3 (−1.5,-1.2)*,†
Length	−0.83 (−1,-0.6) *	−1.3 (−1.5,-1)*,†	−1.4 (−1.8,-1.1)*,†	−1.3 (−1.5, −1)*,†
HC	−0.83 (−1.1,-0.7)*	−1.0 (−1.2,-0.8)*	−0.93 (−1.2,-0.8)*	−0.77 (−1,-0.6)*

*$P < .05$ when compared with zero (average).
†$P < .05$ when compared with birth.

Table V. Median growth velocity (IQR) from birth to discharge in infants with gastroschisis

Growth velocity	All Infants	Growth failure	No growth failure	*P* value
Weight gain velocity (g/kg/d)	5.8 (4.3-7.0)	5.2 (4.1, 6.9)	6.1 (5.2, 7.2)	.32
Length velocity (cm/wk)	0.6 (0.5-0.8)	0.58 (0.17, 0.74)	1.0 (0.83, 1.4)	.01
HC velocity (cm/wk)	0.8 (0.4-1.1)	0.58 (0.41, 0.74)	0.67 (0.41, 0.74)	.16

Velocities were compared between infants who developed weight or length growth failure and infants who did not develop weight or length growth failure at discharge.

Table VI. Predictors of weight growth failure at discharge

Predictor	OR (95% CI)	*P* value
Gestational age (wk)	0.70 (0.55-0.89)	.004
Birth weight z score	1.83 (1.78-2.83)	.007
SGA (yes)	0.28 (0.10-0.80)	.017
IUGR (yes)	1.4 (0.62-3.3)	.40
Length of stay (d)	1.0 (0.99-1.0)	.59
Complicated gastroschisis (yes)	0.61 (0.16-2.3)	.47
Days until first feed	1.0 (0.99-1.0)	.44
Days until full feeds	1.0 (0.99-1.0)	.75
Late onset sepsis	0.54 (0.11-2.7)	.45
Silo (yes)	1.5 (0.60-4.0)	.38
Days until closure	1.0 (0.85-1.2)	.99
Site	–	.45

N/A, not applicable.
SGA is a birth weight less than the 10th percentile. IUGR is a fetal weight estimated to be less than the 10th percentile on ultrasound. Complicated gastroschisis is defined as pulmonary hypoplasia, intestinal atresia or stricture, or ischemic bowel prior to closure. Late onset sepsis is a positive blood culture after 72 hours of age.