# Growth pattern of infants with gastroschisis in the neonatal period

Authors: Nigel J Hall,1,2 Melanie Drewett,2 David M Burge, 2 Simon Eaton3

1. University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK
2. Department of Paediatric Surgery and Urology, Southampton Children’s Hospital
3. Developmental Biology and Cancer Programme, UCL Great Ormond Street Institute of Child Health, London, UK

Corresponding author:

Nigel J Hall

University Surgery Unit, Mailpoint 816

Faculty of Medicine, University of Southampton

Southampton General Hospital

Tremona Road

Southampton SO16 6YD

Tel: 023 8120 6146

E-mail: n.j.hall@soton.ac.uk

## Abstract

**Background / Aim:** Early postnatal growth patterns may have significant long term health effects. Although preterm infants on parenteral nutrition (PN) exhibit poor growth, growth pattern of term or near-term infants requiring PN is not well reported. We aimed to investigate this in infants born with gastroschisis.

**Methods:** Retrospective review of all infants with gastroschisis requiring PN treated at a single centre over a 4 year period. Growth and clinical data were retrieved, and weight SDS scores for corrected gestational age calculated. Weight SDS (mean±SD) were compared at clinically relevant timepoints and multi-level regression used to model growth trends over time.

**Main Results:** During the study period 61 infants with gastroschisis were treated; all were included. Infants were small for gestational age at birth for weight (SDS score -0.87±0.85). Weight SDS decreased significantly during the first 10 days of age (mean decrease 0.81±0.56; p<0.0001) and between birth and discharge (mean decrease 0.81±0.56; p<0.0001). Despite tolerating full enteral feeds, weight SDS velocity was negative around the time of transition from parenteral to enteral feed. There was evidence of ‘catch up’ growth between 3 and 6 months of age.

**Conclusion:** Despite nutritional support with PN, infants with gastroschisis demonstrate significant growth failure during the newborn period. Further efforts are required to understand the underlying mechanisms, improve nutritional support and to evaluate the long term consequences of postnatal growth failure in this population.

Abstract 234 words

## Introduction

Parenteral nutrition (PN) has become part of the everyday clinical treatment of many patients who require nutritional supplementation. In newborn infants, PN has made a significant contribution towards improving survival of both preterm infants whose intestine is too immature to absorb adequate enteral nutrition and term infants with congenital intestinal anomalies.

Despite such nutritional support with PN, preterm infants fail to exhibit expected weight gain based on existing growth charts (1). Despite improvement in neonatal care two large cohorts of preterm infants (the EPICure cohort in 1995 and the EPICURE II cohort in 2006), showed no significant improvement in post-natal weight gain and evidence of significant growth failure prior to discharge in both cohorts (2). This raises questions about the adequacy of current nutritional practice. The potential clinical effects of this growth ‘failure’ include a likely increase in infant length of stay and a detrimental neurodevelopmental outcome. There is also an increasing body of evidence supporting a link between early neonatal nutrition and subsequent health outcomes in later life including cardiovascular disease, obesity and diabetes (3-6). A follow-up study of the first EPICure cohort demonstrated evidence of altered cardiovascular outcomes compared with controls at an age as young as 11 years (7, 8). Early neonatal nutrition (and growth failure) may be a contributing factor.

Whilst the growth of preterm infants requiring PN has been reported in a number of cohorts (1, 2, 9, 10), that of term or near term infants requiring PN is less well documented (11). It is not known whether term infants receiving PN demonstrate a similar growth ‘failure’ to their preterm counterparts, or whether they grow satisfactorily and at a rate similar to enterally fed infants.

The purpose of this study was to define the postnatal growth pattern of term and near-term infants with gastroschisis (GS) treated in a single neonatal surgical unit. GS is a congenital abdominal wall defect resulting in the prenatal evisceration of intestine. It is an isolated anomaly in the vast majority of cases with co-existing morbidities being rare. Infants with GS exhibit a period of intestinal failure in the newborn period, presumed to be a result of antenatal intestinal damage and typically lasting from weeks to months (12-14). During this period of limited enteral tolerance, infants with GS receive nutritional support with PN. As such, infants with GS may be considered to have isolated intestinal failure and represent an ideal population in which to study the effects of PN on growth in term and near-term infants. Based on our clinical observations, we hypothesised that current nutritional practice using contemporary PN would result in growth failure of infants with GS.

## Methods

With institutional approval, we performed a retrospective review of all infants with GS treated at a single neonatal surgical centre over a 4 year period. Growth and clinical data were retrieved from the case notes, an online clinical data capture database routinely in use for all infants in our region (South East Neonatal Database [SEND]) and from a prospectively maintained departmental database. Standard deviation scores (SDS) for corrected gestational age were calculated for weight and head circumference using the LMSgrowth add-in (15) for Microsoft Excel 2010 (Microsoft Corporation). As recommended, we used the UK\_WHO\_preterm dataset due to the gestational age at birth of our population. This dataset comprises data from the British 1990 reference data, reanalysed 2009 and the 2006/2007 WHO Child Growth Standards. A SDS of 0 is equivalent to 50th centile, -1 to 16th centile and -2 to 2nd centile.

We calculated weight SDS for individual infants at clinically relevant time points. These were (i) birth; (ii) 10 days chronological age; (iii) the day on which they last received PN (indicative of successful transition to exclusive enteral feeds); (iv) discharge from hospital and (iv) during out-patient follow up. For the purposes of follow-up duration we restricted our dataset to 6 months of chronological age as the number of datapoints after this was limited. The 10-day time point was chosen as it is recognised that there is a period of fluid redistribution following birth meaning that weight SDS at 10 days of age may be a more reliable indicator of subsequent growth potential than birth weight. Since not all infants were weighed on the 10th day of life, we used a weight taken on the 9th, 10th or 11th day of life as being representative of the 10th day of life and used the corresponding SDS.

Data Analysis

SDS for weight for the cohort over time are presented as mean ± standard deviation (SD). SDS for individual infants were compared between time points using a series of paired T-tests (it was not possible to perform a repeated measures ANOVA due to a small amount of missing data). In order to correct for multiple comparisons, a Bonferroni correction was performed; as six possible comparisons were made between time points, the cut-off for significance between individual time points was set at 0.05/6 = 0.0083).

To illustrate the data graphically we generated smoothed ‘growth curves’ for the entire cohort showing a mean SDS and 95% confidence interval. These were generated by calculating a weight SDS on each and every day for each infant. When a weight was not measured on a specific day, we assumed a linear change in weight SDS between consecutive time points when a weight was available and imputed weight SDS on the basis of this linear change. Weight SDS imputed in this way were not used for statistical analysis.

To determine the effect of a variety of relevant processes on change in SDS, we centred the growth curves on different clinically relevant milestones (e.g. stopping PN, discharge home). This enabled us to investigate the pattern of growth at these time points more precisely than if we were to interrogate the data based on chronological age alone since all infants achieve these milestones at different ages. This analysis only included infants who had received PN.

Clinical management

The clinical and nutritional care of infants did not change during the study period. The preference in our unit is to use a preformed silo (Medicina®) to facilitate reduction of abdominal viscera into the abdominal cavity followed by non-surgical closure at the bedside whenever safe and feasible. Infants in whom such an approach was not deemed possible (predominantly for anatomical reasons) underwent either primary closure under general anaesthesia or staged reduction using a surgically applied silo followed by surgical closure of the abdomen. The nutritional practice in our unit did not change during the study period and consisted of provision of total parenteral nutrition (TPN) starting on day 2-3 once the infant was clinically stable aiming to provide 100-120 kCal/kg/day in a volume of 150ml/kg/day. Infants were placed ‘nil by mouth’ until surgical closure of the abdomen had been achieved and there were signs of intestinal motility judged by reducing volumes and clearance of bile in nasogastric aspirates. At this time enteral feeds were commenced and advanced as tolerated aiming to achieve a volume of at least 150mL/kg/day in divided feeds. If an infant was not thriving on this volume then additional volume was offered. Mothers who wished to provide breast milk for their infant were encouraged to do so; infants of those who did not or could not received a term formula milk. As enteral feeds were advanced the volume of PN administered was reduced appropriately. Once the clinical team judged that enteral feeds of more than 100mL/kg/day were being tolerated (i.e. without vomiting, significant abdominal distension and with passing of regular stool), PN was discontinued. Infants were discharged home once they had demonstrated weight gain on full enteral feeds and were reviewed regularly in a neonatal surgical out-patient clinic. The period during which infants received PN includes a period where infants were being exclusively fed with PN and a period during which they received at least some enteral feed and some PN, the proportion on any given day determined by their clinical progress.

## Results

During the study period 64 infants with GS were treated at our institution. Three infants transferred into our unit following initial management in other surgical centres were excluded. A total of 949 separate weight measurements were identified in 61 infants. Eight infants were transferred out to other units during the study period. Data for these infants were included up until the point of transfer and weight at discharge home was obtained in all but two. Thirty infants were male and mean gestational age at birth was 36.0±2.3 weeks. Mean birth weight was 2.36±0.54kg corresponding to a mean weight SDS of -0.87±0.85. Three infants met the criteria of having complex gastroschisis as defined by Molik et al (16); the remainder had simple gastroschisis.

Five infants never received PN but were started initially on enteral feeds due to favourable clinical progression. All but these five infants received PN until a mean age of 29.8±21.3 days. Eighteen infants received PN until greater than 30 days of age, 2 until greater than 60 days and 1 for more than 90 days. Mean age at discharge home was 35.6±24.8 days.

*Growth pattern during first 6 months*

The overall pattern of change in weight SDS from birth until age 6 months, including the periods of TPN, mixed PN/enteral feeds, and exclusive enteral feeds pre discharge is shown in Figure 1. Mean weight SDS fell from -0.87±0.85 at birth to a nadir of -2.24±1.13 at 71 days of age. There was evidence of catch up growth from 3 to 6 months of age with rising weight SDS during this time period.

Figure 1 Weight SDS change over time (whole cohort) Mean (95%CI) Smoothed curves were generated by linear regression as described in the methods.

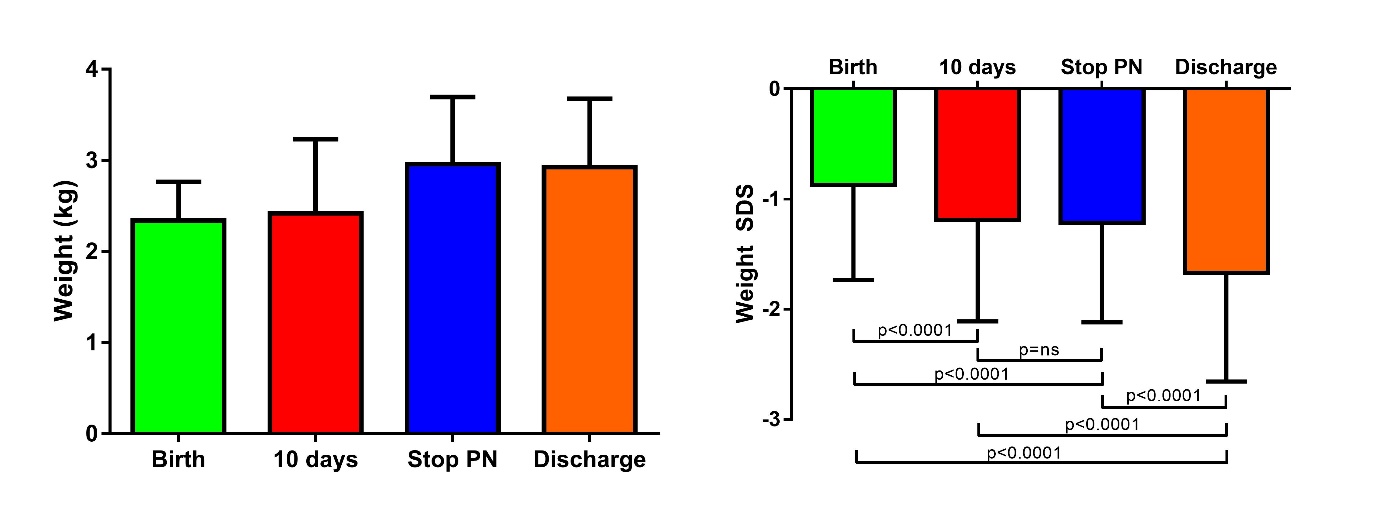


*Weight at clinically relevant milestones in infants who received PN (n=56)*

Mean weight and weight SDS at pre-specified milestones is shown in Figure 2. Mean weight SDS at birth was -0.87 and fell to -1.19±0.92 at 10 days of age. Mean SDS at the time of stopping PN was -1.22±0.90 and at time of discharge home was -1.67±0.99. Weight SDS at 10 days of age was significantly lower than birth weight SDS (mean difference 0.35±0.37; p<0.0001). Weight SDS at the time of stopping PN was significantly lower than birth weight (mean difference 0.34±0.46; p<0.0001) but similar to weight SDS at 10 days of age (mean difference 0.0007±0.38; p=0.91). Discharge weight SDS was significantly lower than weight SDS at birth (mean difference 0.84±0.58; p<0.0001), 10 days of age (mean difference 0.54±0.59) and at the time of stopping PN (mean difference 0.48±0.41; p<0.0001).

Figure 2 Change in weight (A) and weight SDS (B) across time points. Weight SDS scores were compared between time points by paired t-tests, using a Bonferroni-corrected p-value cutoff of p<0.083 (=0.05/6).

A B



*Growth pattern whilst on PN (n=56)*

Change in weight SDS whilst receiving at least some PN is shown in Figure 3A. This period includes a period where infants were being exclusively fed with PN and a period during which they received at least some enteral feed and some PN, the proportion on any given day determined by their clinical progress. The graph has been limited to 60 days of age as only 2 infants received PN for longer than this time. The graph illustrates growth pattern achieved during nutritional support with PN. To investigate change in weight SDS over time whilst on PN, mean change in weight SDS during 5 day time periods were calculated and plotted against age. These data are shown in Figure 3B and demonstrate that weight SDS fell during the first 10 days of life and increased progressively during the next 15 days before stabilising after 25 days of age.

Figure 3A Growth pattern whilst on PN (mean, 95%CI)

Figure 3B Mean change in weight SDS per day in 5 day time periods from birth (data points are mean (SEM))

A B



*Change in weight SDS around the time of discontinuing PN*

Growth pattern around the time of discontinuing PN and establishing full enteral feeds is illustrated in Figure 4A which is centred at the time of discontinuation of PN. Change in weight SDS per day around the same time point is shown in Figure 4B. These data demonstrate that there was a progressive fall in weight SDS during the transition from PN to enteral feed which was maximal immediately following discontinuation of PN. This fall continued whilst the infants were on full enteral feed but the magnitude of this fall decreased over time, with weight SDS appearing to stabilise by approximately 30 days after discontinuing PN.

Figure 4A Change in weight SDS around the time of discontinuing PN (Mean and 95%CI)

Figure 4B Mean change in weight SDS per day in 5 day time periods centres on the time of discontinuation of PN (data points are mean (SEM))

A B

## Discussion

Our main aim was to document growth and change in weight over time in a population of near term infants since there is a paucity of data relating to this population particularly when compared to preterm infants. We used a cohort of infants with a single diagnosis of GS to remove the variability that may be attributable to diagnosis. The majority of infants with GS are born without co-existing morbidities and therefore GS represents a condition in which there is a temporary, isolated intestinal failure. The mean gestational age at birth was 36 weeks and all but 5 infants received PN.

Our rationale for documenting growth in this population was to challenge whether contemporary nutritional practice for this population is adequate and appropriate. There is an increasing body of evidence to suggest a link between early life nutrition and later life health outcomes including neurodevelopmental outcome and risk of cardiovascular disease, diabetes and obesity (3, 6, 17-20). Previous investigations have primarily focussed on term infants who are enterally fed and preterm infants. Documenting the growth pattern of term or near-term infants who receive PN has rarely been performed (11). Further we wished to investigate anecdotal clinical observations and report these to the wider clinical nutritional community. These included progressive downward crossing of growth centiles despite nutritional supplementation with PN in this population and poor growth (including on occasion weight loss) during the period of transition from parenteral to full enteral nutrition.

Overall these data demonstrate that infants with GS are born small for gestational age (mean weight SDS at birth was -0.87) and that the weight SDS continues to fall during early life, both during the first 10 days of life in which fluid shifts are expected, but also subsequently (Figure 1). In this cohort of infants weight SDS did not increase until between 3 and 6 months of age suggesting that ‘catch-up’ growth may be occurring at this time. We limited our study to 6 months of age since there was a paucity of data beyond this time point. The fall in weight SDS during early life is during a time when the majority of infants were receiving at least some nutritional support with PN and certainly all under close medical scrutiny. These findings therefore challenge the adequacy of current nutritional practices for this population.

There are a number of potential explanations for our findings, some of which we have attempted to investigate by analysing change in weight SDS between clinically relevant milestones. During the immediate postnatal period the majority of infants received PN in accordance with our institutional guidelines. Once there was clinical evidence that the intestine may tolerate enteral feed, these were commenced and increased at a rate determined by the clinical status on a daily basis, as is usual in all neonatal surgical centres. We observed that during this time period of complete or partial nutritional support with PN, weight SDS initially decreased. Unfortunately using our methodology it was not possible to differentiate between periods of total PN (i.e. no enteral feed) and partial PN (some enteral feed). It is therefore not possible to conclude whether this decrease is due to inadequacy of PN regime, or that the infant was not able to achieve nutritional benefit from the enteral feed being given, or indeed perhaps both.

Prior to this study we had observed that infants tended to cross downwards across centile lines and in some cases actually lose weight around the transition from PN to enteral feeds. Our data demonstrate that this is indeed the case (Figure 4) and that decrease in weight SDS continued in this population for at least 30 days. These observations raise the possibility that PN is being discontinued too early and/or that infants may not be able to absorb adequate nutrition from the administered enteral feed in order to thrive at the time at which PN is discontinued. The time at which PN is discontinued was typically once the infant was tolerating at least 100ml/kg/day of enteral feed. The decision to stop PN is typically made based on the overall progress of the infant, their anticipated ability to tolerate further increases in enteral feed quickly and other clinically relevant factors. It is possible that prolonging PN until a higher volume of enteral feed is tolerated may alter wight trajectory around the time of stopping PN. However any prolongation of PN needs to be weighed against the risks of PN and central venous access, most notably in this population, the risk of sepsis.

It is generally assumed that an infant who can tolerate a certain volume of enteral feed will gain nutritional benefit from it. A possible explanation for our observations however is that although infants can take feed into their gastrointestinal tract and do not vomit large amounts of it, they may not be able to digest or absorb it adequately to realise its full nutritional benefit. This raises the possibility of there being an ongoing intestinal pathology in this group of infants that may at least in part contribute to poor weight gain. Although outside the remit of this study we have recently raised the possibility of a high incidence of cow’s milk protein intolerance in infants with GS (21). Poor nutrient absorption may be a component of this clinical entity in which case an alternate feed type, such as a partially hydrolysed or amino acid based formula may be appropriate for this population. Further study would be necessary to demonstrate if the use of an alternate enteral formula would improve growth during the period of PN administration and after stopping PN altogether. However it is striking that SDS at discharge home was lower than SDS at the time of stopping PN despite the infant being fully enterally fed and apparently tolerating enteral feed. Our observations of decrease in weight SDS around the time of stopping PN is similar to that reported in preterm infants during the transition phase from PN to enteral feed (22). Inadequate protein supply as opposed to inadequate calorie intake has been proposed as a causative factor in the preterm population. Investigation of substrate provision was not possible in our cohort.

An additional observation that we have made in caring for these infants that is difficult to quantify using a retrospective methodology is that around the time of transition from parenteral to enteral nutrition there appears to be a change in the body shape of many infants often with a redistribution of subcutaneous fat or shedding of oedema. The cause of this is unclear but we now know that this time period is associated with a change in growth velocity and speculate that these phenomena may be related. One possible explanation is that there is a difference in the way the body handles intravenous and enteral nutrition, particularly fluid and lipid . A prospective evaluation of change in body composition around the time of transition from PN to enteral nutrition may help to investigate this phenomenon further.

One challenge regarding the assessment of weight and weight SDS in the immediate postnatal period relates to the use of weight SDS calculated at birth. Specifically concern has been raised that comparing weight SDS at any given time with the weight SDS at birth may be misleading and may be interpreted as demonstrating poor growth when in fact growth has been adequate (23). For this reason the current WHO growth charts for full term infants do not include datapoints for the first 2 weeks of life and recommend that full term infants are not plotted on growth charts during this 2 week period. It is recognised that in full term infants there is a period of fluid redistribution during which infants lose both weight SDS and weight. However for preterm infants (defined as <37 weeks gestation) no such recommendation exists and until recently it was not known how the weight of preterm infants changed in the immediate postnatal period (9). Additionally assumptions made regarding the post-natal growth pattern in term infants relate to a healthy population receiving enteral milk feeds, many of whom (if breast fed) actually receive very little volume of milk during the first few days of life. Whether such assumptions should apply to a population of infants who receive intravenous fluid and PN from birth onwards is not known.

Given the possibility that a comparison of weight SDS at a given time point with weight SDS at birth may overestimate poor growth (23), we compared weight SDS at subsequent time points with weight SDS at 10 days of age. We did indeed demonstrate a significant reduction in weight SDS between birth and 10 days of age suggesting that this population of infants do behave similarly to their healthy counterparts. Further we observed that weight SDS at the time of stopping PN was similar to that at 10 days of age (Figure 2B) suggesting that during the period of complete or partial PN support, and beyond 10 days of age, nutritional support is in fact adequate. The data in Figure 3B confirm this and in fact demonstrate that weight SDS increased during this time period. However, there remained a significant decrease in weight SDS between that at 10 days of age and that at discharge. This supports the hypothesis that overall this group of infants do not achieve adequate growth using current enteral nutritional practices.

We acknowledge a number of limitations to this study some of which are inherent in the retrospective design. . Firstly it is possible that infants who were growing well were not reviewed as regularly as those who were not, particularly following discharge from hospital, and that we have over-estimated decrease in weight SDS following discharge as a result. We have not been able to account for other contributory factors that may have resulted in infants receiving less nutritional support than anticipated, particularly whilst on PN. These include temporary lack of central venous access and episodes of sepsis during which PN may not have been given. Whilst we have focussed on weight and weight SDS in this report we had originally intended to include other important anthropometric measures such as head circumference and length. Unfortunately we were precluded from making meaningful analysis of these due to a paucity of measurements. It was not routine practice to measure length regularly on our unit during the study period. Since this time we now regularly measure all three anthropometric measures at least weekly on all infants in our unit. We used the UK\_WHO preterm dataset as a reference standard for this study which is recommended for all infants born at less than 37 weeks gestation. Whilst it is possible that infants with gastroschisis may not be expected to follow standard weight trajectories, we are unaware of any gastroschisis specific growth standards and therefore believe the reference standard we have used to be the most appropriate currently available.

In summary we have documented pattern of growth in a cohort of infants with GS during the first 6 months of life. Whilst we have raised more questions than we have provided answers, we believe we have identified justification to investigate further the nutritional support these infants receive and their growth related outcomes. As a result of this study we plan to review our nutritional practice and subsequently review the effects of this on growth outcomes in a more detailed manner prospectively.

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*Contributor statement*

NJH conceived the study, contributed to study design, collected data, analysed data and wrote the first draft of the manuscript. MD and DMB contributed to study design, collected data and critically appraised and revised the manuscript. SE contributed to study design, analysed data and critically appraised and revised the manuscript

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