**Abstract**

Background: Extrauterine growth restriction (EUGR) is multifactorial in etiology and predisposes infants to multiple morbidities that can be significantly ameliorated by adequate nutrition and appropriate longitudinal growth. Current strategies to reduce the risk of EUGR include optimization of parental nutrition, varying schedules of feeding advances, and caloric supplementation. Very low birthweight (VLBW) preterm infants are particularly affected by EUGR, therefore ensuring adequate postnatal growth is an essential component in improving the long-term health outcomes for VLBW infants. The objectives of this observational study were to examine potential risk factors for growth failure among premature infants that did not respond to caloric and volume supplementation.

Methods: We conducted a retrospective chart review of all infants born at the University of Massachusetts level III NICU from January 2016 to June 2020. Growth was tracked using PediTools electronic gestational age and growth calculators. (17) We reviewed the EMRs of infants who met the criteria for EUGR at the time of hospital discharge for a variety of potential factors affecting growth.

Results: Overall, a total of 448 infants were screened with a final study cohort of 358 infants, of which 13% were discharge with EUGR. Analysis of demographic and clinical characteristics of infants with EUGR before and after nutritional intervention showed no statistically significant differences between the two cohorts. Pre-protocol, only weight percentiles and z-scores were statistically significant. Post-protocol, the change in z-score was also statistically significant. The only factor found to be statistically significantly different between was Necrotizing enterocolitis (NEC). Timing of EUGR in the pre-protocol groups occurred between 33-35 weeks, while in the post-protocol group EUGR occurred between 32 and 37 weeks (Figure 2).

Conclusions: Our findings confirmed the presence of several factors that have been previously shown to increase risk for EUGR, including male sex, lower gestational age, lower birth weight, and the occurrence of NEC. It also identified an additional risk factor, that of being born “constitutionally small”. In the post-protocol cohort, the change in z-score was statistically significant in addition to birth weight percentile and z-score and discharge weight percentile in z-score. The window in which EUGR occurred as well as the interquartile range was significantly widened post-protocol. These data suggest that the volume supplementation protocol successfully addressed the causes of EUGR in some infants, but other mechanisms may have occurred in infants who were still discharged with EUGR post-protocol.

**Background**

Extrauterine growth restriction (EUGR) is multifactorial in etiology and predisposes infants to multiple morbidities that can be significantly ameliorated by adequate nutrition and appropriate longitudinal growth. (1-4) Premature infants who experience EUGR are at risk for developmental delays, behavioral problems, and cardiometabolic dysregulation. (5) Current strategies to reduce the risk of EUGR include optimization of parental nutrition, varying schedules of feeding advances, and caloric supplementation (12-15). Major contributors to the development of EUGR include delayed time to full volume and calorie enteral feeds as well as insufficient protein and caloric intake, particularly in the first weeks of life (8). Other factors associated with EUGR include prenatal factors, gestational age and weight at birth, respiratory distress syndrome, necrotizing enterocolitis bronchopulmonary dysplasia, and male sex. (9-11) However, the directionality of association between these factors and EUGR is unclear in many cases.

Very low birthweight (VLBW) preterm infants are particularly affected by EUGR. (1) Many VLBW infants demonstrate poor longitudinal growth patterns during their hospitalization in a neonatal intensive care unit, leading to EUGR that persists long after discharge. (3,6) Every year, approximately one-quarter of premature infants born appropriate for gestational age, and more than three quarters of premature infants born small for gestational age, are discharged from the neonatal intensive care unit with EUGR. (10) Ensuring adequate postnatal growth is an essential component in improving the long-term health outcomes for VLBW infants. (1-4)

The objectives of this observational study were to examine potential risk factors for growth failure among premature infants that did not respond to caloric and volume supplementation. We first compared the demographic and clinical characteristics of infants with and without EUGR. Next, we compared the infants with EUGR prior to and after the institution of the caloric and volume supplementation protocol. Finally, we investigated the predetermined causes of EUGR within the study cohort. The primary comparison groups were infants with growth failure before and after the targeted nutrition protocol was implemented, on which extensive analysis was performed.

**Methods**

We conducted a retrospective chart review of all infants born at the University of Massachusetts level III NICU from January 2016 to June 2020. Inclusion criteria were infants born either appropriate for gestational age (AGA) or large for gestational age (LGA) at this NICU and ≤ 32 0/7 weeks gestational age. Any infants born SGA (defined as <10th percentile on the Fenton growth curve (16)), infants born with congenital anomalies, infants who did not follow nutritional protocol guidelines due to other clinical concerns, infants whose nutrition and growth parameters were not available due to lack of documentation, infants who received the majority of their care and nutrition at outside institutions, or infants who died prior to discharge were excluded.

Data were extracted from the electronic medical record (EMR) and stored on a secure server. Data collected included demographic and anthropometric characteristics, dietary intake, laboratory values, hospital length of stay, and illness severity. Maternal data extracted from the EMR included maternal parity, age, and mode of delivery.

Growth was tracked using PediTools electronic gestational age and growth calculators. (17) We reviewed the EMRs of infants who met the criteria for EUGR at the time of hospital discharge for a variety of potential factors affecting growth, including delayed return to birthweight, timing of growth failure, hyponatremia, and NEC. Delayed return to birthweight was defined as infant weight below birthweight at 10 days of life. NEC was defined as the presence of bloody stools or clinical signs requiring antibiotic treatment for 7 days or more. Hyponatremia was defined as two consecutive serum sodium levels of less than 135 milliequivalents per liter. An infant was defined as constitutionally small if their birthweight was below the 15th percentile for gestational age. Aerodigestive issues were defined as abnormal suck and swallow on modified barium swallow or speech-language pathologist exam. Timing of growth failure was determined by examining the weight-for-age percentile on the first day of each gestational age week throughout hospitalization. Inadequate nutritional intake was defined as clinical signs of increased energy requirements and/or limited parenteral macronutrient content due to hypertriglyceridemia or hyperinsulinemia. Total fluid volumes were calculated daily by dividing total intake in milliliters by the daily weight. Birthweight was used until the daily weight exceeded the infant’s birthweight.

**Statistical Analysis**

 The primary comparison groups were infants with growth failure before and after the targeted nutrition protocol was implemented. For these infants, multiple demographic, maternal, and clinical factors were compared. P values were obtained using chi square tests of association for categorical variables and t-tests for continuous variables. A larger secondary analysis compared sex, GA at birth, birth and discharge weight z-scores and %tiles, and changes from birth to discharge among 4 groups of infants: those with/without intervention and those with/without growth failure. For continuous variables, analysis of variance (ANOVA) F-test was used to obtain p values for comparing means among all four groups. Furthermore, Tukey’s post-hoc pairwise comparison test was used to compare between two groups. For categorical variables, a categorical model was used instead to test the difference in proportions among four groups. Two-group comparison was made by method of contrast. P values for categorical variables were obtained from categorical model Chi-square test. P values for all other continuous variables were obtained from Analysis of Variance (ANOVA) F-test and Tukey's multiple comparison test. Finally, logistic regression was used to derive odds ratio (OR) of growth failure for infants experienced intervention vs those not, adjusted for sex, GA at birth, and birthweight percentile.

We then investigated potentially growth-related factors among infants who had growth failure. The proportion of each dichotomized factor was compared between two cohorts: those with/without intervention, using Contingency Table Chi-square test, or Fisher’s exact test in case the cell sizes for the contingency table were small.

To find what factors were associated with weight loss from birth to discharge among infants with growth failure, we modeled the change in weight %tile (birth weight – discharge weight) using multivariate ordinary least square with predetermined predictors listed in Figure 1. The change in weight percentile was defined as weight percentile at birth minus weight percentile at discharge, therefore a positive number indicates a weight loss.

**Results**

Overall, a total of 448 infants were screened, of which 395 were eligible for this study. A further 37 infants were excluded based on SGA birthweight, leaving a final study cohort of 358 infants. Of the remaining infants, 53 were discharged with EUGR (14.8%) and 305 were discharged without EUGR.

Analysis of demographic and clinical characteristics (Table 1) of infants with EUGR before and after nutritional intervention showed no statistically significant differences between the two cohorts. Pre-protocol, only weight percentiles and z-scores were statistically significant. Post-protocol, the change in z-score was also statistically significant. We investigated potentially growth-related factors among infants who had EUGR. The only factor found to be statistically significantly different between was NEC (Figure 1). Timing of growth failure between these two groups was also compared. Of note, timing of EUGR in the pre-protocol groups occurred between 33-35 weeks, while in the post-protocol group EUGR occurred between 32 and 37 weeks (Figure 2).

Logistic regression analysis was used to derive odds ratio (OR) of growth failure for infants who received the nutritional intervention vs those who did not, adjusted for sex, GA at birth, and birthweight %tile. Odds of growth failure was reduced by 53% (OR=0.47, 95% CL 0.24-0.95) for infants in the intervention program, compared to those not in the program (Table 3).

 To determine potential factors associated with weight loss from birth to discharge among infants with EUGR, we modeled the change in weight %tile (birth weight – discharge weight) using multivariate ordinary least square regression analysis with possible predictors listed in Table 4. Birth weight %tile, NEC, and “constitutionally small” were associated with greater weight loss (p<0.05), while GA at birth was associated with less weight loss (p=0.05).

**Discussion**

Reducing the risk of EUGR has become a significant area of both clinical and quality improvement research. Previously, clinicians at the University of Massachusetts Memorial Medical Center NICU were able to significantly reduce EUGR at discharge through multiple quality improvement initiatives that targeted early enteral feeding, more rapid caloric fortification, and volume advancement. (18) The EUGR rate at discharge subsequently showed a significant reduction from 22% to 9% after implementing a targeted volume increase protocol between 31 0/7 and 34 0/7 weeks PMA (19). The goal of the present study was to examine the characteristics of infants who failed the volume and caloric supplementation protocols to identify potential causes of continued EUGR in infants born AGA.

Our findings confirmed the presence of several factors that have been previously shown to increase risk for EUGR, including male sex, lower gestational age, lower birth weight, and the occurrence of NEC. It also identified an additional risk factor, that of being born “constitutionally small”. Previously, it was understood that infants born SGA were more likely be discharged with EUGR, but to our knowledge no studies had identified that infants born just above the 10th percentile on the Fenton growth curve were at higher risk for EUGR.

In our analysis comparing infants with EUGR before and after nutritional intervention, we found two changes in statistical significance. First, in the post-protocol cohort, the change in z-score was statistically significant in addition to birth weight percentile and z-score and discharge weight percentile in z-score. Additionally, the time at which EUGR occurred was also impacted by the volume supplementation protocol. The window in which EUGR occurred as well as the interquartile range was significantly widened according to our data. These data suggest that the volume supplementation protocol successfully addressed the causes of EUGR in some infants, but other mechanisms may have occurred in infants who were still discharged with EUGR post-protocol.

**Study strengths and limitations**

Strengths of this study include the large, longitudinal sample size as well as the high degree of granular nutritional data collected. Limitations of the study include retrospective data collection, lack of randomization, and failure to collect matching granular nutritional data on the non-EUGR infants. Lack of certain data in both maternal and paternal history is also a potential limitation. One potentially significant limitation is the use of discharge weight less than the 10th percentile as the definition of EUGR. Recent literature has suggested that defining EUGR as a decrease in z-score of more than 0.8 addresses the issue of infants born SGA, as by this definition each infant acts as its own control.

**Conclusions**

Future directions of research include comparison of granular nutritional data for the entire cohort to elucidate other potential causes of EUGR, use of different working definitions of EUGR, and tracking of the z-score through hospitalization to identify infants at risk for EUGR earlier so that interventions have a greater chance of success.

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Figure 1- Study population. Infants born less than or equal to 32 weeks with weight above the 10th percentile on the Fenton growth curve with discharge weight less than the 10th percentile on the Fenton growth curve were considered to have EUGR.

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| Table 1. Comparison among EUGR infants (N=53) |
|   | Pre-Protocol (N=27)  | Post-Protocol (N=26) | p-value |
|   | N (%) | N (%) |
| Male | 12 (44) | 16 (62) | 0.21 |
| White | 15 (55) | 17 (65) | 0.46 |
| Hispanic | 6 (22) | 8 (31) | 0.48 |
| Public Insurance | 17 (63) | 11 (42) | 0.13 |
| Multiple Birth | 8 (30) | 7 (27) | 0.82 |
| Maternal HTN | 16 (60) | 12 (46) | 0.34 |
| Maternal Diabetes | 2 (7) | 4 (15) | 0.36 |
| C-Section | 19 (70) | 20 (77) | 0.59 |
| BPD Moderate-Severe | 8 (30) | 9 (35) | 0.7 |
| PDA Requiring Treatment | 4 (15) | 3 (12) | 0.72 |
| Severe IVH | 0 (0) | 1 (4) | 0.3 |
| ROP | 8 (30) | 9 (35) | 0.7 |
|   | Mean ± SD | Mean ± SD | p-value |
| Birth GA | 29.7 ± 2.31 | 28.4 ± 2.71 | 0.08 |
| Birth Weight (g) | 1115 ± 250 | 998 ± 270 | 0.1 |
| Maternal Age | 29.7 ± 5.3 | 29.5 ± 6.2 | 0.89 |
| Ventilator Days | 4 ± 9 | 7 ± 16 | 0.4 |
| CGA at Discharge | 39.5 ± 9.6 | 39.6 ± 3.9 | 0.96 |

Table 1: Comparison of demographic and clinical characteristics of infants with EUGR before and after implementation of a volume supplementation feeding protocol to establish baseline equivalence between the two groups.

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| Table 2. Comparison Among 4 Groups (N=336)  |
| Variable | No intervention | Intervention |  |  |
| Non-EUGR (n=93) | EUGR (n=27; ) | p value  | . Non-EUGR (N=190) |  EUGR (N=26; ) | p value  |  | p value for all 4 groups |
|   | N | % | N | % |   | N | % | N | % |   |   |   |
| Male | 46 | 49 | 12 | 44 | 0.65 | 96 | 51 | 16 | 62 | 0.89 | 0.36 | 0.64 |
|   | Mean | SD | Mean | SD |   | Mean | SD | Mean | SD |   |   |   |
| GA at birth (weeks) | 29.1 | 2.2 | 29.7 | 2.3 | 0.62 | 29.2 | 2.3 | 28.4 | 2.7 | 0.40 | 0.20 | 0.25 |
| Birth weight (g) | 1279 | 356 | 1115 | 250 | 0.17 | 1330 | 393 | 998 | 270 | 0.0001 | 0.65 | <.0001 (Take all stat significant p values out to no more than 3 decimals) |
| Discharge weight (g) | 2755 | 639 | 2289 | 470 | 0.005 | 2936 | 595 | 2573 | 596 | 0.0206 | 0.31 | <.0001 |
| Birth weight z score | 0.19 | 0.70 | -0.68 | 0.52 | <.001 | 0.15 | 0.79 | -0.59 | 0.55 | <.0001 | 0.97 | <.0001 |
| Discharge weight z score | -0.44 | 0.65 | -1.67 | 0.30 | <.001 | -0.25 | 0.61 | -1.74 | 0.39 | <.0001 | 0.97 | <.0001 |
| Change | -0.62 | 0.75 | -0.99 | 0.49 | 0.11 | -0.40 | 0.79 | -1.15 | 0.80 | <.0001 | 0.87 | <.0001 |
| Birth weight %tile | 55.6 | 22.9 | 26.4 | 17.4 | <.001 | 56.3 | 22.0 | 29.2 | 18.7 | <.0001 | 0.97 | <.0001 |
| Discharge weight %tile | 34.7 | 22.2 | 5.3 | 2.6 | <.001 | 40.6 | 21.3 | 4.9 | 2.5 | <.0001 | 1.00 | <.0001 |
| Change | -20.9 | 24.4 | -21.1 | 16.8 | 1 | -15.7 | 19.9 | -24.2 | 20.0 | 0.21 | 0.95 | 0.08 |

Table 1: Comparison of demographic and clinical characteristics among 4 groups of infants: those with/without intervention and those with/without growth failure.

Figure 2: Potential contributory factors to EUGR in infants before and after implementation of a volume supplementation feeding protocol



Figure 3: Box-whisker plot of timing of growth failure before and after implementation of a volume supplementation feeding protocol

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| Table 3. Odds ratio of EUGR based on Logistic Regression (N=336) |
| Risk factor | OR | 95% CL |
| Intervention | 0.47 | 0.24 | 0.95 |
| Male | 1.30 | 0.65 | 2.58 |
| GA at birth (weeks) | 0.86 | 0.74 | 1.00 |
| Birth weight %tile | 0.93 | 0.90 | 0.95 |

Table 3: Odds ratio of EUGR based on simple logistic regression of predetermined risk factors listed in Figure 2.

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| Table 4. Multivariate Ordinary Least-square Regression Model for Predicting Change in Weight %tile from Birth to Discharge among Infants with EUGR (N=53) |
| Parameter | Estimate | SE | 95% CL |
| Intercept | 3.00 | 5.22 | -7.23 | 13.24 |
| intervention | -0.27 | 0.65 | -1.55 | 1.01 |
| GA at birth (weeks) | -0.32 | 0.16 | -0.64 | 0.00 |
| male | 0.58 | 0.61 | -0.60 | 1.77 |
| Birth weight %tile | 0.97 | 0.02 | 0.92 | 1.01 |
| NEC | 2.98 | 0.90 | 1.21 | 4.76 |
| Delayed return to birthweight | 1.52 | 1.01 | -0.46 | 3.49 |
| Hyponatremia | 0.99 | 0.79 | -0.55 | 2.53 |
| Inadequate Intake | 0.43 | 1.18 | -1.88 | 2.74 |
| Constitutionally small | 2.74 | 0.98 | 0.82 | 4.65 |
| Aerodigestive Issues | -0.27 | 0.77 | -1.79 | 1.25 |
| Other issues | 1.17 | 0.93 | -0.66 | 2.99 |
| Note: The change in Weight %tile is defined as Weight %tile at birth minus Weight %tile at discharge. Thus a positive number indicates an weight loss. |