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RESEARCH ARTICLE

Change in the prevalence of extra-uterine growth restriction in very low birthweight infants, following the introduction of a written nutrition protocol, in a tertiary neonatal unit

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Background: Advances in neonatal medicine, resulting in improved survival, have brought the concept of extra-uterine growth restriction (EUGR), defined as postnatal growth failure secondary to protein and energy deficits, to the forefront as an important cause of morbidity, particularly in very low birthweight (VLBW) neonates.
Objectives: This study's main objective was to determine the prevalence of EUGR in Steve Biko Academic Hospital in VLBW infants.
Methods: This was a pre- (epoch 1) and post- (epoch 2) intervention study. The intervention was the introduction of a written nutritional protocol in the neonatal unit in mid-November 2017. Three definitions were used to identify EUGR, namely: (1) discharge weight < 10th percentile, (2) a change by −1.28 *z*-score in weight at discharge, and (3) the discharge weight percentile below the nadir percentile.
Results: The prevalence of EUGR in epoch 1 was 85.7%, 63.5%, and 88.0% using the above definitions, respectively. The prevalence of EUGR in epoch 2 was 73.9%, 65.8%, and 89.4% using the above definitions, respectively. EUGR using the three definitions combined was present in 95.2% and 92.8% of infants in epochs 1 and 2, respectively. None of the differences in EUGR prevalence between the two epochs were significant.
Conclusion: The prevalence of EUGR was not significantly different between the two epochs, although it had been proposed that the introduction of a written nutritional protocol would have decreased the prevalence of EUGR in epoch 2. One of the reasons proposed for this finding was poor adherence to the nutritional protocol during epoch 2.

Keywords: postnatal growth failure, extra-uterine growth restriction, EUGR, very low birthweight, VLBW, premature, prematurity

Introduction

Advances in neonatal medicine, resulting in improved survival, have brought the concept of extra-uterine growth restriction (EUGR), defined as postnatal growth failure[1,2] secondary to protein and energy deficits, to the forefront as an important cause of morbidity, particularly in very low birthweight (VLBW) and extremely low birthweight (ELBW) neonates. The National Institute of Child and Human Development (NICHD) Neonatal Research network reported that 97% of VLBW neonates and 99% of ELBW neonates suffered from EUGR at 36 weeks corrected age in 1996,[3] with the incidence of EUGR being inversely proportional to birth weight and gestational age (GA).[1,4,5] The Vermont Oxford Network (VON) recently reported the EUGR prevalence at 50.3% in a cohort of VLBW neonates from 2000 to 2013.[6] However, there is a paucity of South African (SA) data, with four published studies reporting on postnatal growth of infants at or before discharge who weighed < 1 500 g at birth,[7–10] with one study reporting on two different groups of infants.[8] All studies were performed in tertiary neonatal units in the public sector.[7–10] Only one of these studies on ELBW infants reported on EUGR, with a prevalence of 81% (weight for gestational age ≤ 10th percentile on day 49 of life).[9]

Intrauterine nutrition is provided via the placenta, where amino acids are actively transported to the foetus for protein accretion, and glucose and lipids are delivered at a rate equivalent to utilization and needs.[4] However, once born prematurely, enteral protein delivery is limited due to the fear of intolerance, with the sole source of energy being intravenous glucose for many neonates. This early nutritional deprivation, often seen in the NICU, neither meets nor sustains the ideal rate of growth, which should be similar to third-trimester intrauterine growth.[1] This leads to growth failure and long-term adverse outcomes of growth,[4] neurodevelopmental impairment,[1] and possibly adult-onset disease, such as hypertension, coronary heart disease, and non-insulin-dependent diabetes.[1] Beyond these effects, poor postnatal growth has negative implications for the health system with increased length of hospital stay and risk of health-care-associated infections (HAI), as well as increased health costs.[7]

Although there is no clear consensus on the exact definition of EUGR, it refers to poor growth resulting from severe nutritional deficiencies in the first few weeks of life in premature neonates.[5] Definitions for EUGR include: (1) a weight < 10th percentile (< −1.28 *z*-score) at any postmenstrual age (PMA), most commonly evaluated at 36–40 weeks PMA or at discharge,[2,5,11,12] and (2) a weight change of more than −1.28 *z*-score from birth to the time point of evaluation.[13] Severe EUGR is defined as weight < 3rd percentile for PMA.[6] However, using a weight < 10th percentile to define EUGR may be inappropriate as there is a normal physiological process of extracellular water loss early after delivery.[14] These infants often grow parallel to, but below the birthweight percentile, which may be normal according to preterm infant growth guidelines recommending growth rates similar to the foetus.[12] Therefore, this study included a definition describing a change in growth over time where the lowest weight percentile (nadir) is compared with the discharge percentile. EUGR is diagnosed if the discharge percentile is below the nadir percentile. This approach is recommended by Fenton et al.[12] EUGR is often assessed prior to 37 weeks PMA and does not consider catch-up growth that occurs between 36–40 weeks PMA, thereby over-diagnosing EUGR in these infants.[12]

The growth velocity in VLBW neonates follows a specific course as compared with that of full-term neonates,[15] and understanding this is imperative to providing the necessary nutritional support required to duplicate intrauterine growth similar to that of a foetus of similar GA.[13] Although weight loss is expected after delivery, birthweight should be regained by 14 days of life in preterm infants[16] and the days to regain birthweight significantly predict poor postnatal growth.[1] The appropriate weight gain velocity for preterm infants is uncertain, with ESPGHAN suggesting different ranges for different gestational ages; this therefore requires further research.[17] However, to prevent the development of EUGR, current recommendations are to attain weight gain velocity of 15–20 g/kg/day in premature neonates.[1] Fenton et al. recommend a weight gain velocity of 15 g/kg/day for VLBW infants.[18] Of the SA studies available, four reported a growth velocity below 15 g/kg/day (10–14.5 g/kg/day).[7–10] Growth velocity met the recommended rate (15 g/kg/day) in the one group of infants in the one study.[8] It is, however, difficult to compare these studies directly as four studies used the original fortifier (OF) (1 g fortifier [0.2 g protein] per 20 mL breast milk)[7–10] and the one study with adequate growth in the one group of infants used the reformulated fortifier (RF) (1 g fortifier [0.4 g protein] per 25 mL breast milk).[8] Additionally, weight gain velocity was calculated at different time points in the various studies and using different methods, making results difficult to compare.

Even though there are no standardised guidelines on feeding the preterm infant, the concept of ‘early aggressive nutrition’, aimed at preventing an early catabolic state, includes earlier introduction of enteral feeds, and the provision of parenteral nutrition (PN) containing amino acids, glucose, and lipids from the first day of life.[4] To stimulate development of the immature gastrointestinal tract, to enable early establishment of enteral nutrition and prevent EUGR, premature neonates should be initiated on minimal enteral feeds (MEF) at a rate of 10–20 mL/kg/day from birth and maintained for the first few days of life.[4] Evidence guides the advancement of enteral feeds by 30–40 mL/kg/day in neonates below 1 500 g without increasing the risk of necrotising enterocolitis (NEC).[19] Breast milk alone does not provide adequate amounts of macronutrients and selected micronutrients for the premature neonate, and fortification of expressed breast milk (EBM),[4] once tolerating volumes of 100 mL/kg/day, has become standard practice for neonates < 1 500 g.[1]

Additional factors associated with the development of EUGR include small for gestational age (SGA), male gender, assisted ventilation on the first day of life,[5] need for respiratory support on day 28 of life,[5] respiratory distress syndrome (RDS),[2] prolonged hospital stay,[2] and co-morbidities such as bronchopulmonary dysplasia (BPD),[2] NEC,[5] and late onset sepsis.[2,16]

The prevalence of EUGR in the Steve Biko Academic Hospital (SBAH) neonatal unit is unknown and this study will provide valuable data regarding the growth of neonates in this unit. The results between the two studied groups (epochs 1 and 2) may also provide information on whether a particular feeding protocol makes a difference in the growth velocity of the studied neonates, or if the other identified factors play a more significant role in the development of EUGR. Adding to the data reported by the four SA studies performed in tertiary public hospital neonatal units will provide valuable information on the problem of EUGR in South Africa (SA).

Methods

This was a retrospective pre- (epoch 1) and post- (epoch 2) intervention study conducted in the neonatal unit of SBAH, a tertiary institution in Tshwane. A written nutritional protocol was the intervention introduced into the unit in mid-November 2017. Data were collected in a retrograde manner prior to August 2014 for epoch 1 (January 2013 to July 2014) and in a forward consecutive manner from January 2018 to September 2018 for epoch 2. During August 2014 to mid-November 2017 there were verbal instructions on nutrition and this period was therefore not included in epoch 1. The nutritional protocol used during epoch 2 recommended the initiation of MEF at 10–20 mL/kg/day for all VLBW infants. Advancement of feeds was started on day four of life by 15–20 mL/kg/day in ELBW infants and 30–35 mL/kg/day in infants weighing 1 000–1 499 g until the infants reached a volume of 150 mL/kg/day. Some infants’ enteral feed volume was increased up to 180 mL/kg/day depending on growth velocity. Initiation of PN (full intravenous volume) including fat, carbohydrates and amino acids was recommended on the first day of life for all VLBW infants and adjusted daily depending on the tolerance of enteral feeds. Mother’s own milk and donor expressed breast milk were the preferred feeding choices. Fortification changed from OF in epoch 1 to RF in epoch 2.

A web-based application called PediTools: Fenton 2013 Growth Calculator for Preterm Infants,[20] based on the revised Fenton growth charts for preterm infants,[21] was used to determine the exact weight percentiles and *z*-scores. Infants plotting below the 10th percentile, or a decrease by 1.28 *z*-score at discharge, or if the discharge percentile was below the nadir percentile were defined as having EUGR in this study. Weight gain velocity in g/kg/day was calculated using the 2-Point Average Weight model (2-PM).[22] Weight gain velocity = $[1\ 000 \times (W_n - W_1)] \div \{(D_n - D_1) \times [(W_n + W_1)/2]\}$, where W = weight in grams; D = day; 1 = the beginning of the time interval in days (nadir); n = the end of the time interval in days (discharge).[22]

All inborn infants with a birthweight < 1 500 g admitted to the neonatal unit during the specified time periods were eligible for inclusion. Outborn infants weighing < 1500 g were also included provided they were admitted within 24 hours of delivery. Infants that were discharged, transferred, or died within the first 13 days of life were excluded. Infants that were readmitted after transfer out were only included once (first admission). Lastly, infants with congenital abnormalities were excluded as they were expected to have poorer postnatal growth.

For continuous parameters, both the two-sample t-test (evenly distributed data) and Mann–Whitney test (skewed data) were used to determine significance. Medians with interquartile ranges were reported for skewed data and means with standard deviations reported for evenly distributed data. For frequencies and prevalence, Fisher's exact test was used. For the univariate analysis for associations, Pearson's chi-square test was used to determine significance. Odds ratios (OR) with 95% confidence intervals were determined using logistic regression and reported where significant. Where there was missing data, these infants were not included in the statistical analysis. Ethical approval from the Faculty of Health Sciences of the University of Pretoria was obtained prior to data collection (reference: 420/2020).

Results

There were a total of 681 admissions of infants weighing < 1 500 g at birth during the study period (epoch 1 and epoch 2). A total of 318 infants were excluded according to the above-mentioned exclusion criteria, with 363 infants remaining who were eligible for possible inclusion (Figure 1). Thereafter, 189 infants were excluded for incomplete data/missing records. Thus, a total of 174 infants were included in this study. Of the 174 included infants, 63 infants were in epoch 1 and 111 infants were in epoch 2.

As itemised in Table 1, infants from epoch 1 had a mean birthweight of 1 125 g and those from epoch 2 had a mean birthweight of 1 108 g, with no significant difference ($p = 0.611$). ELBW infants comprised 28.6% of epoch 1 and 31.5% of epoch 2, but this was not significant ($p = 0.734$). Significantly more infants in epoch 1 were SGA at delivery (28.6% vs 15.3%, $p = 0.049$). The median birthweight percentile and mean *z*-score was significantly different between epoch 1 and epoch 2 (21st vs 33rd, $p = 0.002$; and −0.9 vs −0.4, $p = 0.001$).

Infants from epoch 1 and epoch 2 had a mean GA of 30 and 29 weeks, respectively, which was significantly different ($p = 0.008$). There were more infants in epoch 2 that were < 28 weeks' gestation compared with epoch 1 (18.9% vs 14.3%), and also more between 28 weeks and 31^6 weeks' gestation (70.3% vs 57.1%), which was significant ($p = 0.032$). There was no significant difference in gender, number of foetuses, place of delivery, HIV exposure, length of admission, duration of supplemental oxygen use, or the use of invasive ventilation between the two epochs. However, significantly more infants' mothers received antenatal corticosteroids (ANCS) (71.2% vs 55.6%, $p < 0.001$) and significantly more infants received nasal continuous positive airway pressure (nCPAP) (90.1% vs 61.9%, $p < 0.001$) in epoch 2.

Data regarding the growth parameters of infants from both epochs are presented in Table 2. The mean weight loss for epochs 1 and 2 was 43 and 61 g, respectively, which was not significantly different ($p = 0.094$). The mean weight loss percentage for epoch 1 was 3.5% and for epoch 2 was 5.3%; these were significantly different ($p = 0.038$). A similar number of infants lost ≤ 10% and > 10% bodyweight in epoch 1 and 2 (89.5% vs 88.3% and 10.5% vs 11.7%, respectively), therefore, this was not significant ($p = 1.000$). Infants in epoch 2 regained birthweight significantly quicker (12.9 days vs 15.6 days, $p = 0.002$). The median weight gain velocity from nadir to discharge was the same (12 g/kg/day, $p = 0.732$) for epochs 1 and 2. The majority of infants in epoch 1 and 2 gained < 15 g/kg/day (70.2% vs 75.7%). However, more infants from epoch 1 gained weight appropriately (≥ 15 g/kg/day), compared with epoch 2 (29.8% vs 24.3%) but this was not significant ($p = 0.463$).

The median weight at transfer out of the neonatal unit, usually to a kangaroo-mother-care (KMC) facility (hereafter to be called discharge), were 1 490 g and 1 500 g for epoch 1 and 2, respectively, with no significant difference ($p = 0.161$). The median discharge weight *z*-score was significantly lower in epoch 1 (−2.4 vs −1.9, $p = 0.037$), but was not significant when comparing the median discharge weight percentiles (1st vs 2nd, $p = 0.069$). The median change in *z*-score between birth and discharge weight for epochs 1 and 2 was the same (−1.5, $p = 0.841$); however the median change in percentile from birth to discharge weight was significantly different between epochs 1 and 2 (−16 vs −27, $p = 0.002$).

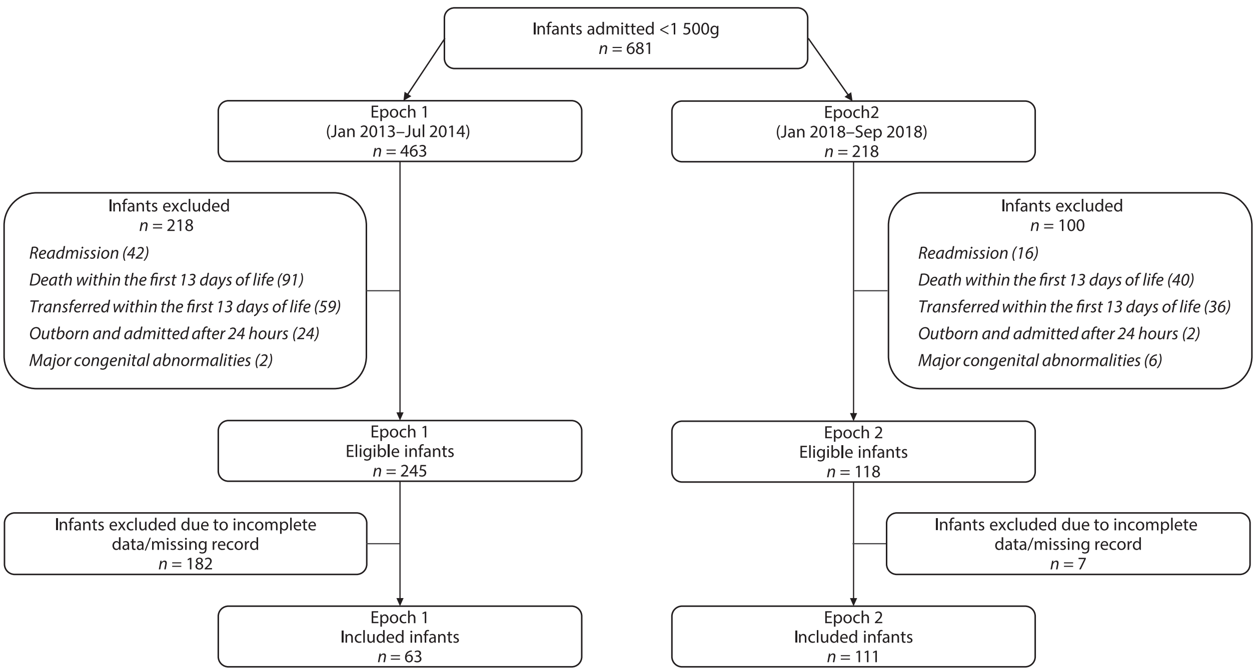

Figure 1: Infant exclusions and distribution per epoch.

Table 1: Infant variables for epoch 1 and epoch 2

Variable	Epoch 1 (*n* = 63)	Epoch 2 (*n* = 111)	*p*-value
Mean birthweight (g) (SD)	1 125 (218)	1 108 (196)	0.611
Median birthweight percentile (IQR)	21 (7–39)	33 (17–55)	**0.002**
Mean birthweight *z*-score (SD)	−0.9 (0.9)	−0.4 (0.9)	**0.001**
ELBW, *n* (%)	18 (28.6)	35 (31.5)	0.734
SGA present, *n* (%)	18 (28.6)	17 (15.3)	**0.049**
Mean gestational age (weeks) (SD)	30 (3)	29 (2)	**0.008**
Male gender, *n* (%)	29 (46.0)	60 (54.1)	0.346
Multiple foetuses, *n* (%)	14 (22.2)	33 (29.7)	0.155
Inborn, *n* (%)	58 (92.1)	104 (93.7)	0.452
HIV-exposed, *n* (%)	14 (22.2)	26 (23.4)	0.632
Median length of admission (days) (IQR)	35 (22–55)	35 (24–50)	0.971
Median duration of supplemental oxygen (days) (IQR)*	7 (2–19)	10 (4–29)	0.118
Received nCPAP, *n* (%)	39 (61.9)	100 (90.1)	**<0.001**
Invasive ventilation, *n* (%)†	6 (9.7)	22 (19.8)	0.090
Maternal ANCS, *n* (%)	35 (55.6)	79 (71.2)	**<0.001**

*Total observations = 161 (*n* = 4 and 9 missing from epochs 1 and 2, respectively); †total observations = 173 (*n* = 1 missing from epoch 1). Abbreviations: ANCS = antenatal corticosteroids, ELBW = extremely low birthweight, g = grams, IQR = interquartile range, nCPAP = nasal continuous positive airway pressure, SD = standard deviation, SGA = small-for-gestational age. *p*-values in bold are statistically significant ($p < 0.05$).

The prevalence of EUGR in epoch 1 was 85.7%, 63.5% and 88.0% using the definitions: (1) weight < 10th percentile at discharge, (2) a change of −1.28 *z*-score in weight at discharge, and (3) the discharge weight percentile below the nadir weight percentile, respectively. The prevalence of EUGR in epoch 2 was 73.9%, 65.8%, and 89.4% using the same definitions, respectively. EUGR using any of the three definitions was present in 95.2% of infants in epoch 1 and 92.8% of infants in epoch 2. None of the differences in EUGR between the two epoch's were significant. Severe EUGR, defined as a discharge weight < 3rd percentile, was present in 63.5% of infants in epoch 1 and 50.5% of infants in epoch 2, but this difference was not significant ($p = 0.114$).

Table 3 demonstrates the feeding variables for infants from both epochs. The mean day of life that the first enteral feed was received was not significantly different between epochs 1 and 2 (1.5 days vs 1.7 days, $p = 0.302$). The mean day of life it took to reach 100 and 150 mL/kg/day of enteral feeds was also not significantly different between the two epochs (7.9 days for each epoch, $p = 0.988$ and 11.4 days vs 10.9 days, $p = 0.546$, respectively). The mean number of days it took to reach 150 mL/kg/day from the day of starting enteral feeds was also not significantly different between epochs 1 and 2 (9.9 days vs 9.2 days, $p = 0.454$). During epoch 2, only 16% of infants weighing 1 000–1 499 g and 54.3% of infants weighing 500–999 g reached full enteral feeds (150 mL/kg/day) by the recommended day 7 and day 11 of life, respectively. The day of life that human milk fortifier (HMF) was added was significantly different between epochs 1 and 2 (15.5 days vs 12.6 days, $p = 0.021$); however, the volume of enteral feeds when HMF was added was the

Table 2: Growth parameters of included infants

Parameter	Epoch 1 (*n* = 63)	Epoch 2 (*n* = 111)	*p*-value
Mean weight loss (g) (SD)*	43 (60)	61 (68)	0.094
Mean weight loss percentage (%) (SD)*	3.5 (4.5)	5.3 (5.8)	**0.038**
Mean time to regain birthweight (days) (SD)†	15.6 (5.8)	12.9 (4.9)	**0.002**
Median weight gain velocity (g/kg/day) (IQR)*	12 (10.0–15.7)	12 (10.0–14.7)	0.732
Median discharge weight (g) (IQR)	1 490 (1440–1730)	1 500 (1325–1715)	0.161
Median discharge *z*-score (IQR)	−2.4 (−1.6 – −3.6)	−1.9 (−1.3 – −2.9)	**0.037**
Median discharge percentile (IQR)	1 (0–6)	2 (0–10)	0.069
Median change in *z*-score (IQR)	−1.5 (−0.9 – −2.3)	−1.5 (−1.1 – −2.2)	0.841
Median change in percentile (IQR)	−16 (−6 – −31)	−27 (−12 – −44)	**0.002**
EUGR definition 1, *n* (%)	54 (85.7)	82 (73.9)	0.086
EUGR definition 2, *n* (%)	40 (63.5)	73 (65.8)	0.869
EUGR definition 3, *n* (%)‡	44 (88.0)	93 (89.4)	0.789
EUGR combined, *n* (%)	60 (95.2)	103 (92.8)	0.748
Severe EUGR, *n* (%)	40 (63.5)	56 (50.5)	0.114

*Total observations = 168 (*n* = 6 missing from epoch 1); †total observations = 163 (*n* = 11 missing from epoch 1); ‡total observations = 154 (*n* = 13 unable to classify as both nadir weight percentile and discharge weight percentile plot as 0; *n* = 6 and 1 missing from epochs 1 and 2, respectively). Abbreviations: EUGR = extra-uterine growth restriction, g = grams, IQR = interquartile range, SD = standard deviation; EUGR definitions: (1) weight < 10th percentile at discharge, (2) a change of − 1.28 *z*-score in weight at discharge, and (3) discharge weight percentile below the nadir weight percentile. *p*-values in bold are statistically significant ($p < 0.05$).

Table 3: Feeding variables for included infants

Variable	Epoch 1 (*n* = 63)	Epoch 2 (*n* = 111)	*p*-value
Mean DOL received 1st enteral feed (days) (SD)*	1.5 (1.1)	1.7 (1.2)	0.302
Mean DOL reached 100 mL/kg/day enteral feeds (days) (SD)†	7.9 (3.2)	7.9 (3.9)	0.988
Mean DOL reached 150 mL/kg/day enteral feeds (days) (SD)‡	11.4 (3.6)	10.9 (5.7)	0.546
Full enteral feeds by day 11 (500–999 g), *n* (%)	No recommendation	19 (54.3)	-
Full enteral feeds by day 7 (1 000–1 500 g), *n* (%)	No recommendation	12 (16.0)	-
Mean DOL HMF added (days) (SD)§	15.5 (7.3)	12.6 (6.1)	**0.021**
Mean volume when HMF added (mL/kg/day) (SD)¶	149 (12.9)	149 (11.7)	0.944
Received PN, *n* (%)	30 (47.6)	109 (98.2)	**<0.001**
Mean DOL PN initiated (days) (SD)**	2.2 (1.6)	0.6 (0.9)	**<0.001**
Median DOL PN stopped (days) (IQR)††	11 (8–13)	8 (7–11)	**0.014**
Received DEBM, *n* (%)	12 (19.1)	12 (10.8)	0.170
Received top-up formula, *n* (%)	6 (9.5)	8 (7.2)	0.576
EFF, *n* (%)	0 (0.0)	1 (0.9)	1.000

Total observations = 163 (*n* = 11 missing from epoch 1); †total observations = 132 (*n* = 42 missing from epoch 1); ‡total observations = 166 (*n* = 7 and 1 missing from epochs 1 and 2, respectively); §total observations = 140 (*n* = 28 and 6 missing from epochs 1 and 2, respectively); ¶total observations = 141 (*n* = 28 and 5 missing from epochs 1 and 2, respectively); **total observations = 136 (*n* = 36 and 2 missing from epochs 1 and 2, respectively); ††total observations = 133 (*n* = 36 and 5 missing from epochs 1 and 2, respectively). Abbreviations: DEBM = donor-expressed breast milk, DOL = day of life, EFF = exclusive formula feeding, HMF = human milk fortifier, PN = parenteral nutrition, SD = standard deviation. *p*-values in bold are statistically significant ($p < 0.05$).

same (149 mL/kg/day, $p = 0.944$). Significantly more infants received PN in epoch 2 (98.2% vs 47.6%, $p < 0.001$). PN was also initiated significantly earlier in epoch 2 (0.6 days vs 2.2 days, $p < 0.001$), with significantly more infants receiving PN on the day of birth in epoch 2 (60.6% vs 18.5%, $p < 0.001$). PN was also stopped significantly sooner in infants in epoch 2 (8 days vs 11 days, $p = 0.014$). The use of donor-expressed breast milk (DEBM), exclusive formula feeding, and the use of top-up formula was not significantly different between epochs 1 and 2.

For the calculation of associations, all infants with EUGR in epochs 1 and 2 were grouped together. One significant association was that of birthweight, with infants weighing 500–999 g having a lower odds ratio (OR) of developing EUGR compared with infants weighing 1 000–1 499 g (87.0% vs 96.7%, $p = 0.016$; OR 0.2, 95% CI 0.06–0.82, $p = 0.024$). EUGR was more common with increasing GA (86.7% at < 28 weeks, 93.9% at 28^0–31^6 weeks, 100% at ≥ 32 weeks), but this was not significant ($p = 0.340$). Significantly more infants that had a lower weight gain velocity (< 15 g/kg/day) also had EUGR compared with those who grew appropriately at ≥ 15 g/kg/day (99.2% vs 77.3%, $p < 0.001$). The OR for EUGR was 36.2 times higher in those that gained < 15 g/kg/day (95% CI 4.5–292.6, $p < 0.001$). EUGR was less common in infants that regained their birthweight within the first 7 days of life, with the highest rate of EUGR in those that regained birthweight after 21 days of life (82.4% vs 100%); however, this was not significant ($p = 0.218$). EUGR was also more common in infants with a longer hospital stay, but this was not significant ($p = 0.340$). All infants that were SGA at delivery had EUGR on discharge, but this was not significant ($p = 0.086$). EUGR was significantly more common in infants that did not receive maternal ANCS (100% vs 90.4%, $p = 0.045$). No association could be found for gender, the number of foetuses, HIV exposure, the presence of RDS, the use of nCPAP, the need for invasive ventilation, days requiring supplemental oxygen, BPD, NEC, patent ductus arteriosus (PDA), or healthcare-associated infections. With regard to the specific infant feeding practices in the unit (listed in Table 3), no associations could be found for EUGR in this study.

Discussion

This study failed to demonstrate any difference in EUGR between the two epochs, despite having a written nutritional protocol in place during epoch 2.

The infants in both epochs 1 and 2 were of similar weight at birth, but more infants in epoch 1 were SGA at delivery. This is due to the significantly different GA at delivery, with epoch 1 infants having a higher GA (30 weeks vs 29 weeks). This also explains why the birthweight percentiles and *z*-scores are significantly lower in epoch 1. However, the reason why proportionally more infants in epoch 1 were SGA at delivery cannot be explained by the available data. We postulate that perhaps, during epoch 1 (2013/2014), more premature infants with a lower gestational age died secondary to limited resources, leaving more SGA infants to be included in the study. The fact that significantly more infants in epoch 2 received ANCS and nCPAP may reflect better antenatal care and more resources available in the neonatal unit (nCPAP machines).

The mean absolute weight loss was higher in epoch 2 (61 g vs 43 g); however, this was not significant. This correlated with a higher percentage weight loss from birth (5.3% vs 3.5%), which was significant. Percentage weight loss was higher in the two studies from Gauteng and the one study performed in Cape Town (7.4%, 7.7% and 10.7%, respectively).[7,9,10] The reduced percentage weight loss in our study may be explained by the fact that all infants were eligible to receive enteral feeds and PN from the first day of life, which is in contrast to the one study from Gauteng (2013) where infants were kept nil per os (NPO) for at least the first 24 hours and only received a 10% dextrose solution intravenously. PN was administered only to infants with surgical conditions of the gastrointestinal tract and NEC.[7] In another study from Gauteng, infants were initiated on a 10% dextrose solution intravenously on the first day of life and enteral feeds were only introduced on the second day of life at 20 mL/kg/day. PN was administered only to infants kept NPO for more than 48 hours.[10] Similarly, infants that received PN were excluded from the Cape Town study, and infants in this study received only a 10% dextrose solution intravenously, until on full enteral feeds. Additionally, 14% of infants had not received any feeds by day three of life, with some infants taking 10–14 days to initiate enteral feeds.[9] Although infants in epoch 2 regained their birthweight significantly quicker (12.9 days vs 15.6 days), their weight gain velocity to discharge was the same as for epoch 1 (12 g/kg/day). It would be expected that, as the infants in epoch 2 regained their birth weight sooner, they should have had a higher growth velocity. This might be explained by the growth velocity not being sustained over time in epoch 2, with increased weight gain initially while receiving PN, which may have slowed after stopping the PN. The same two studies from Gauteng and the one study from Cape Town reported regain of birthweight at 16, 18, and 18 days, respectively, which was longer than it took infants in the most recent epoch in our study (12.9 days).[7,9,10]

Although the median discharge weight *z*-score was significantly lower in epoch 1 (−2.4 vs −1.9), it was the change in *z*-score (> −1.28) that was being assessed, which was the same in the two epochs (−1.5), resulting in a similar prevalence of EUGR using this definition. This study performed poorly against the most recent study from Gauteng in the group of infants receiving RF, as in epoch 2 of our study, where the change in *z*-score from birth to study exit was −1.2.[8] The other three studies reported the highest negative change in *z*-scores of −1.57, −1.6, and −2.05 where infants received OF.[7,9,10] Although the mean change in weight percentile from nadir to discharge was significantly different between the two epochs (−16 vs −27) in our study, a change in percentile is not one of the described definitions of EUGR, and therefore cannot be used to classify infants as having EUGR.

EUGR had a high prevalence in both epochs 1 and 2 in this study, irrespective of which of the three definitions was used. Only the first definition of EUGR commonly used (discharge weight < 10th percentile) had a lower prevalence in epoch 2 (73.9% vs 85.7%), but this was not significant. Also, when combining the three definitions, EUGR was less prevalent in epoch 2 (92.8% vs 95.2%), but this was also not significant. The prevalence of EUGR in this study during epoch 2 (combining all three definitions) was slightly better than that reported by the NICHD Neonatal Research network in 1996[3] (92.8% vs 97%), though is much higher than that reported by VON in 2000–2013[6] (92.8% vs 50.3%). The prevalence of EUGR was higher in this study compared with the study performed in Cape Town (92.8% vs 81%).[9] However, severe EUGR was present in approximately half of infants in epoch 2 in this study, which is less than the 63% reported in ELBW infants in the Cape Town study.[9] It is the opinion of the authors that the most accurate definition for EUGR would be a change in *z*-score of −1.28 from nadir weight to discharge weight. Unfortunately, in this study, the birthweight *z*-score was used for comparison with the discharge *z*-score, which does not account for the normal physiological water loss after delivery. However, when using this definition, the prevalence of EUGR is the lowest of all the definitions used in this study (63.5% and 65.8% in epochs 1 and 2, respectively) and is more comparable to, if not better than, other studies.

Infants had a similar growth velocity compared with four of the other SA studies using OF,[7–10] but grew slower than the infants in the most recent study performed in Gauteng, where the second group of infants received RF.[8] These differences may additionally be attributed to the different formulae used to calculate weight gain velocity (Patel's formula vs 2-PM) and which weight was used as the baseline weight in the calculation (birthweight vs nadir weight).

Although significantly more infants in epoch 2 received PN (98.2% vs 47.6%), which was also initiated sooner (0.6 days vs 2.2 days), and had HMF added significantly sooner (12.6 days vs 15.5 days), this did not impact the prevalence of EUGR in epoch 2, despite the introduction of a written nutritional protocol. The reasons proposed for this finding are explained in the limitations section. Additionally, adherence to the nutritional protocol at the time of epoch 2 was poor. The first enteral feeds occurred at 1.7 days instead of the first day of life. It took longer than the recommended time to reach full enteral feeds of 150 mL/kg/day in infants weighing 1 000–1 499 g (7 days) and 500–999 g (11 days). Lastly, HMF was only added to enteral feeds at a volume of 149 mL/kg/day, instead of the recommended 100 mL/kg/day. We propose that the poor adherence to the nutritional protocol in epoch 2 was due to the high turnover of paediatric doctors, meaning that new doctors who were unfamiliar with the nutritional protocol were allocated to the neonatal ward every 2–4 months. Additionally, the dietitians allocated to the neonatal ward rotated regularly, with the new dietitians being unfamiliar with the nutritional protocol. However, we should not discard the fact that feeding intolerance secondary to HAI or the presence of NEC would also result in the appearance of poor adherence to the nutritional protocol, with a longer duration to reach full enteral feeds. In this study, HAI was present in 44.4% and 51.4% of infants in epochs 1 and 2, respectively. Similarly, fewer infants in epoch 1 had NEC compared with epoch 2 (3.2% vs 8.1%, respectively). These co-morbidities may have impacted the time taken to reach full enteral feeds in epoch 2, despite the use of a written nutritional protocol.

Despite associations of EUGR being reported with male gender, SGA, RDS, ventilation, prolonged oxygen supplementation, BPD, NEC, HAI, and prolonged hospital stay in other studies,[2,5,16] these associations were not found in this study. Infants with a lower birthweight (500–999 g) had lower odds of having EUGR in this study. This is different from what has been demonstrated in other studies, where ELBW infants usually have a greater risk of having EUGR.[1,4,5] Similarly, EUGR in this study was associated with a higher GA (although not significant), which is in contrast to other published studies where EUGR is inversely proportional to GA.[1,4,5] We propose that these differences in this study may be due to the fact that smaller infants were presumed to be at higher risk of EUGR and therefore greater focus was placed on managing their nutrition appropriately. We also observed that fewer infants 1 000–1 499 g reached full feeds as recommended. Lastly, this study shows that maternal ANCS use was associated with significantly less EUGR, which is similar to the 2013 study performed in Gauteng that also showed maternal ANCS use was associated with improved growth velocity (OR 0.18, 95% CI:0.05–0.6, $p = 0.005$).[7]

Limitations

Difficulty accessing files from hospital records for epoch 1 led to fewer infants being included, which may have affected the reliability of data in epoch 1. The accuracy of the anthropometric measurements, the standardisation of equipment to perform measurements, and GA estimates cannot be guaranteed due to the retrospective nature of this study. There were also missing data in the files (predominantly during epoch 1), resulting in lower numbers in some of the data analysis variables (indicated in table footnotes).

Using the birthweight as the point of reference for determining the presence of EUGR may result in an overestimation of the prevalence of EUGR when using a downward change in z-score (−1.28). However, birthweight was used as the reference point in both epochs, still enabling assessment of the change in prevalence of EUGR. In future studies, however, we recommend using the nadir *z*-score as the point of reference to determine the change in *z*-score. Also, EUGR was defined using weight only and did not consider length and head circumference.

In calculating the percentage weight loss, the nadir weight recorded for infants in this study may not be the actual nadir weight (it may be lower) as infants in this neonatal ward are weighed only three times per week, meaning that the actual nadir may have been missed, and the percentage weight loss may be higher. The composition of the HMF (FM85 Nestle®) changed between the two epochs with 1 g (0.4 g protein) of HMF being added to 25 mL EBM during epoch 2 (RF), compared with 1 g (0.2 g protein) added to 20 mL during epoch 1 (OF). The implication of this difference is that HMF would have been added at a later stage in epoch 2 due to higher EBM volumes required for dilution. Additionally, the number of feeds when HMF was added to EBM changed during the two epochs. During epoch 1, HMF was added to all eight feeds by either the mother or the nursing staff. However, the unit policy changed with the opening of the 'baby feeding unit' during epoch 2. Unfortunately, this unit was only open for 12 hours per day (07:00–19:00), limiting the amount of feeds containing HMF to five in 24 hours (HMF could not be added to the evening feeds due to the risk of bacterial overgrowth, NEC, and increasing osmolality of the feed when left to stand). The South African studies being compared used different growth standards to calculate *z*-scores (Fenton charts and INTERGROWTH 21st standards) and may therefore not be directly comparable. Growth velocity may also not be directly comparable as some studies used the 2-PM,[7] while other studies used Patel's formula.[8–10] Lastly, EUGR was assessed before the period of catch-up growth (36–40 weeks PMA) in 73.6% of infants.

Conclusion

The prevalence of EUGR was not significantly different between epoch 1 (pre-nutritional protocol) and epoch 2 (post-nutritional protocol). However, many reasons have been identified that may contribute to this finding as outlined earlier, including poor adherence to the recommendations in the nutritional protocol. Despite the high prevalence of EUGR in epoch 2 when a nutritional protocol was in place, we would still recommend that neonatal units have a written nutritional protocol to guide the feeding of VLBW infants to prevent EUGR. We also recommend that, although the high turnover of paediatric doctors cannot be avoided due to the rotational basis required to complete all sub-disciplines in paediatric training programmes, a specialist neonatal dietitian be allocated to the neonatal ward permanently. This will assist in ensuring optimal nutritional care in the neonatal unit. Additionally, all staff should be educated regularly on the nutritional protocol to ensure improved adherence to the recommendations. This should include briefings at least every two months when the paediatric doctors are rotated within the wards, but can be done more regularly if it is noticed that compliance is poor. Additionally, the nutritional protocol should be shared with paediatric doctors working overtime in the neonatal unit to ensure compliance after hours and over weekends. Compliance with the nutritional protocol should be reviewed during the week on daily ward rounds by the neonatologists working in the unit.

Further research is recommended to determine why the written nutritional protocol to guide the feeding of VLBW infants was not effective in preventing EUGR. Additionally, the definitions of EUGR, particularly a discharge weight below the 10th percentile, require revision as we observed a big difference in the prevalence of EUGR using the different definitions (with a higher prevalence of EUGR using the definition of discharge weight below the 10th percentile compared with the change in *z*-scores). It is the opinion of the authors that the most accurate definition for EUGR would be a change in *z*-score of −1.28 from nadir weight to discharge weight.

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