GROWTH OF EXTREMELY LOW BIRTH WEIGHT INFANTS AT A TERTIARY HOSPITAL IN A MIDDLE- INCOME COUNTRY

Tendai Mabhandi; MBCHB (UZ)
Student Number: 1330266
Degree: MMed Paediatrics
Email; tenbha@gmail.com

SUPERVISORS

Tanusha Ramdin; MBCHB, FCPaed (SA)
Email; tanusharamdin@yahoo.com

Daynia Elizabeth Ballot; MBCHB, FCPaed (SA), PhD
Email; Daynia.ballot@wits.ac.za

Department of Paediatrics

Charlotte Maxeke Johannesburg Academic Hospital

Johannesburg, 2019

Declaration

I Tendai Mabhandi declare that this research report is my own unaided work. It is being submitted for the Degree of Masters in Medicine (Paediatrics) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

(Signature of candidate)

16th day of June 2019 at Johannesburg

Publications arising from this study

This study has been accepted for publication by BioMed Central Paediatrics journal whose submission guidelines are attached.

Acknowledgments

None.

Contents

Mabhandi et al. BMC Pediatrics (2019) 19:231
https://doi.org/10.1186/s12887-019-1568-6

BMC Pediatrics

RESEARCH ARTICLE Open Access

Growth of extremely low birth weight infants at a tertiary hospital in a middle-income country

Tendai Mabhandi*, Tanusha Ramdin and Daynia Elizabeth Ballot

Abstract

Background: Survival of extremely low birth weight (ELBW; birth weight less than 1000 g) infants has improved significantly since the 1990s. Consequently, growth monitoring in ELBW infants has gained more relevance.

Methods: We conducted this study to describe the growth of ELBW infants at a tertiary hospital, to audit macronutrient intake and explore the association of prematurity complications with growth. This was a retrospective study on 92 ELBW infants born at Charlotte Maxeke Johannesburg Academic Hospital. The association between good growth (regaining birth weight in 21 days or less and subsequent growth velocity > 15 g/kg/day) and complications of prematurity was explored.

Results: Only 11infants (13%) had a discharge weight above the 10th centile when the Fenton growth chart was used compared to 20 infants (22.4%) when the Intergrowth 21st Project growth standard was used. The mean weight velocity was 13.5 g/kg/day and the mean number of days to regain birth weight was 18.2 days. Factors associated with poor growth were late-onset sepsis, persistent patent ductus arteriosus, continuous positive airway pressure for more than 2 days, invasive ventilation, oxygen on day 28 and being kept nil per os. Protein and caloric intake correlate positively with growth velocity. Unlike the Fenton Growth Charts, use of the Intergrowth 21st Project growth standards revealed the association between neonatal factors and poor growth.

Conclusion: Growth outcome in infants is poor at 36 weeks postmenstrual age at our institution. Intergrowth 21st Project growth standards were superior to Fenton Growth Charts, however a multicentre study is required before adoption.

Keywords: Extremely low birth weight, Neonate, Growth, Nutrition

Background

Survival of extremely low birth weight (ELBW) infants has improved significantly since the 1990s owing to advances in obstetric and neonatal care [1]. Consequently, growth monitoring of ELBW infants has gained more interest. Poor growth among ELBW infants has been well documented [2]. Although ELBW infants have compensatory growth into their early adult years, they remain shorter than their predicted mid-parental heights [3]. Low birth weight infants have also been noted to have a poor neurocognitive outcome [4]. There is growing evidence among ELBW infants that inadequate nutrition during the early weeks of life leads to persistent growth faltering that may lead to permanent detrimental effects [5]. A study on 148 ELBW infants showed that increased protein and caloric intake in the first week of life was associated with a better neurodevelopmental outcome at 18 months [6].

Nutrition in ELBW infants is surrounded by several challenges. In a low resource setting, ITN (Intravenous Total Nutrition) may not be readily available due to cost limitations [7]. Furthermore, difficult venous access, suspected or established diagnosis of necrotizing enterocolitis (NEC), sepsis and metabolic derangements frequently interfere with ITN and enteral feeds administration [8, 9].

There is little information in South Africa on the growth of ELBW infants and their caloric intake while in hospital. A previous prospective study on very low birth

* Correspondence: Tendai.Mabhandi@students.wits.ac.za
Johannesburg, South Africa

weight (VLBW) infants admitted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) showed that infants had initial poor growth followed by catch-up growth but with persistent deficits at 20 months [10]. Another study at CMJAH concluded that VLBW infants had a weight velocity approaching recommended values [11]. A study conducted in Cape Town on ELBW infants showed that weight velocity was approaching the generally accepted standard [12], however, weight Z-score and macronutrient intake were not described in the study. Therefore, the present study aimed to review growth and audit macronutrient intake of ELBW infants in the setting of a tertiary hospital.

Methods

Aim

This was a pilot study to review the growth of ELBW infants at CMJAH from birth to 36 weeks post-menstrual age, audit their macronutrient intake and explore the association of prematurity complications with growth.

Study design

The study was a retrospective longitudinal description of growth and macronutrient intake in ELBW infants at CMJAH.

Participant characteristics

Inclusion criteria

All ELBW infants admitted at CMJAH within 72 h of birth between 01 January 2015 and 31 March 2017 were included in the study.

Exclusion criteria

Infants who were transferred to other hospitals or demised before discharge, those with chromosomal abnormalities and major congenital abnormalities were excluded.

Study process

The study was a secondary analysis of an existing database managed using Research Electronic Data Capture (REDCAP), hosted by the University of Witwatersrand [13] and a review of relevant hospital records. Weight was captured weekly until discharge. The volume of feeds, intravenous (IV) fluids and ITN was captured daily for the first 28 days of life. The number of days to regain birth weight was captured and the mean weight velocity was calculated from the day birth weight was regained to 36 weeks postmenstrual age. Mean weight velocity was calculated using the exponential method [14] as shown below;

$$\text{Weight velocity} = 1000\ \text{X}\ \ln\left(\text{Weight}^{36\ \text{weeks}}/\text{Weight}^{\text{Birth weight regained}}\right)/\text{Time interval}$$

The Fenton's Growth Chart [15] and Intergrowth 21st Project growth standards [16, 17] were used as reference for normal growth. For the Intergrowth 21st Project growth standards, the Intergrowth 21st Project newborn charts were used to derive the birth weight Z-scores and the Intergrowth 21st Project postnatal growth charts were used to derive the Z-scores at 36 weeks. An infant born with a birth weight below the 10th centile was referred to as small for gestational age (SGA) [18]. The delta Z-score from birth to 36 weeks postmenstrual age was determined for each infant. To avoid under-representation of infants with good growth, infants discharged before 36 weeks postmenstrual age had their discharge weight Z-score analyzed as that at 36 weeks. Delta Z-score was calculated using the formula below;

$$\text{Delta Z–score} = \text{Weight Z–score at 36 weeks} - \text{Weight Z–score at birth}$$

For the purpose of computation of macronutrients, the nutritional content of the various types of feeds, IV fluids and ITN was derived from product inserts and previous studies (Table 1) [19]. Daily caloric intake in kcal/kg/day was calculated for each infant during the first 28 days for life using the formula below, where volume is in milliliters (mls), weight in grams and the figure 1000 converts grams to kilograms;

$$\text{Daily caloric intake} = \frac{1000\ \text{X}\ \text{Volume}^{\text{Fluid/ITN/Feed}}\ \text{X}\ \text{Calories per ml}^{\text{Fluid/ITN/Feed}}}{\text{Current heaviest weight}}$$

Mean weekly caloric intake for each week and mean caloric intake over 28 days was calculated. A mean caloric intake of at least 110 kcal/kg/day was classified as good caloric intake. Daily protein and lipid intake were calculated using a similar formula to the daily caloric intake.

Definitions of complications of prematurity were based on those used in the Vermont Oxford Network (www.vtoxford.org). The need for ventilation (invasive and non-invasive), as well as complications of prematurity including NEC, retinopathy of prematurity (ROP), late onset sepsis (> 72 h after birth), oxygen on day 28 of life and patent ductus arteriosus (PDA) were recorded. Necrotizing enterocolitis and PDA were defined in this study as follows;

- NEC was defined as NEC grade 2 or 3 according to modified Bells' staging [20]
- ROP was defined as stage 2 or more [21]

Table 1 Daily infant nutritional requirements and nutritional composition of feeds and parenteral nutrition

	Daily infant Requirement (per kg weight)	Neonatolyte (per dL)	ITN 101 per dL	ITN 102 per dL	ITN 105 per dL	Breastmilk per dL	Prenan per dL	Breastmilk Fortifier (FM85) (per 1 g)
Energy (kcal)	105–130	40	38.3	62.4	46.2	67	80	4.4
Dextrose (g)	–	10	9.57	10.41	6.3	–	–	–
Protein (g)	3.5–4.5 g	0	1.91	2.08	2.1	1.0	2.3	0.4
Lipid (g)	5 – 7 g	0	0	2.08	2.1	3.5	4.2	0.2

- PDA was defined as a hemodynamically significant PDA on echocardiography [22]

CMJAH neonatal unit

The unit's feeding protocol was as follows: Prescription of feeds was at the discretion of the attending physician. Although exclusive breastfeeding was unit protocol, no donor breast milk was available. Hence, the infant formula Prenan (Nestle) was provided for those ELBW infants whose mothers were unwilling or unable to breastfeed. Newly born infants were started on intravenous fluids (usually Non-K Neonatolyte) at 80 to 100mls/kg/day on the first day of life. Feeds were introduced on the second day of life starting at 20mls/kg/day. Feeds were gradually increased by 20 to 30mls/kg/day replacing intravenous fluids until 160 to180mls/kg/day of full enteral feeds was reached. Upon reaching full enteral feeds, each feed of breastmilk was fortified with 1 g FM85 (Nestle). Enteral feeds were discontinued if there was evidence of feeding intolerance. Infants who were not on full feeds for more than 48 h due to any reason had ITN prescribed for them provided no contraindications to ITN administration were present. Infants were weighed twice a week on an electronic scale (NAGATA BW-20, Taiwan). In the absence of ongoing complications requiring hospital care, infants were discharged upon attaining 1600 g. Infants with respiratory distress syndrome (RDS) were offered nasal continuous positive airway pressure (NCPAP) and surfactant. Upon delivery, infants with RDS were transferred to a Transitional Unit where they were offered NCPAP if available. This was done while the infant awaited transfer to their final destination, the Premature Unit, where NCPAP was usually available.

Statistical analysis

Data was entered into a Microsoft Excel Spreadsheet for data cleaning. The final dataset was exported into IBM SPSS 25 for analysis. The distribution of continuous variables was explored. Those variables with a normal distribution were described using mean and standard deviation (SD) while those with a skewed distribution were described using median and interquartile range (IQR). Categorical variables were described by frequencies and percentages.

An infant with good growth was defined as that infant who regained birth weight in 21 days or less and had a weight velocity of at least 15 g/kg/day [23, 24]. An infant with poor growth was defined as that infant who regained birth weight after 21 days and/or had a growth velocity less than 15 g/kg/day. The association of growth with complications of prematurity was assessed in three ways as follows;

- Comparison of occurrence of prematurity complications between infants with good and those with poor growth.
- Comparison of the occurrence of prematurity complications between infants who attained a weight above 10th centile at 36 weeks and those who failed to attain such a weight.
- Delta Z-scores from birth to 36 weeks were analyzed as a continuous variable.

For continuous variables, student t-test was used for variables with normal distribution and Mann Whitney U-test for ranked data or those variables with a skewed distribution. The Chi-squared test of independence was used for categorical variables.

Results

Sample characteristics

There were 2829 infants with birth weight less than 1500 g infants captured on the database. Of these, 886 were ELBW infants. After excluding those outside the study period, 325 infants remained. Ten infants were transferred to other hospitals and 181 infants died in hospital. Therefore, 134 infants were eligible for the study. Forty-two infants had missing records leaving a final sample of 92. For derivation of weight Z-scores and centiles, 89 were included because 3 infants had a gestational age less than 24 weeks and therefore could not be plotted on the Intergrowth 21st Project newborn charts. Characteristics of the sampled infants are displayed in Table 2.

Table 2 Characteristics of sample population

	N = 92
Baseline characteristics	
Females, frequency (percentage)	47 (51.1%)
Birth weight in grams, mean (SD)	867 (81.4)
Birth weight Z -score, mean (SD)	0.4 (1.1)
Gestational age at delivery in weeks, mean (SD)	27.6 (2.0)
Duration of hospital stay in days, mean (SD)	69.1 (17.1)
Postmenstrual age at discharge in weeks, mean (SD)	36.7 (2.7)
Kangaroo care, frequency (percentage)	46 (50.0%)
Predominantly breastfed at discharge	49 (52.3%)
Prenatal factors	
Chorioamnionitis, frequency (percentage)	2 (2.2%)
Antenatal steroids, frequency (percentage)	51 (55.4%)
Postnatal complications	
Patent dictus arteriosus, frequency (percentage)	13 (14.1%)
Sepsis after day 3 of life, frequency (percentage)	53 (57.6%)
Invasive ventilation, frequency (percentage)	17 (18.5%)
Continuous positive airway pressure for more than 2 days, frequency (percentage)	29 (31.5%)
Nil per os (excluding the first day of life), frequency (percentage)	61 (66.3%)
Retinopathy of prematurity, frequency (percentage)	79 (85.7%)
Oxygen on day 28 of life, frequency (percentage)	68 (73.9%)
Postnatal steroids, frequency (percentage)	49 (53.3%)
Necrotizing enterocolitis	7 (7.6%)
Surgery for necrotizing enterocolitis, frequency (percentage)	1 (1.1%)
Other surgery	4 (4.3%)

Growth

The mean birth weight was 867 g (SD = 81.4) with a mean birth weight Z-score of −0.45 (SD = 1.01) and − 0.72 (SD = 1.20) as per Fenton Growth Chart and Intergrowth 21st Project newborn weight charts respectively. Table 3 displays the mean birth weight Z-score, weight Z-score at 36 weeks and delta Z-score as per the Fenton Growth Chart and Intergrowth 21st Project growth standard. The mean percentage weight loss was 7.38% (SD = 5.82) and the mean number of days to regain birth weight was 18.2 days (SD = 10.2). Mean weight velocity was 13.5 g/kg/day (SD = 3.1) for the full length of hospital stay. At 36 weeks postmenstrual age, the mean weight for males was 1494 g (SD = 297) with a mean weight Z-score of − 2.81 (SD = 1.16) and − 3.18 (SD = 1.84) as per Fenton Growth Chart and Intergrowth 21st Project growth standard respectively. Among females, at 36 weeks the mean weight was 1569 g (SD = 201) with a mean weight Z -score of − 2.21 (SD = 1.02) and − 1.95 (SD = 1.36) as per Fenton Growth Chart and Intergrowth 21st Project growth standard respectively. An independent samples t-test showed a significant difference in mean weight Z-scores between birth and 36 weeks postmenstrual age, $p < 0.001$. This was true for both reference growth charts. Therefore, infants were significantly lighter for postmenstrual age at 36 weeks compared to the time of birth. Table 4 shows how growth parameters varied across different birth weight categories.

Table 3 shows that a statistically significant increase in infants labeled as small for gestational age was observed with the Intergrowth 21st Project growth standard compared to the Fenton Growth Chart. There was a larger number of infants who plotted above the 10th centile on the Intergrowth 21st Project standards compared to the Fenton Growth Chart, but this was not statistically significant. There was no statistically significant difference between the Z-scores derived from Fenton Growth Chart and Intergrowth 21st standard for birth weight, weight at 36 weeks and delta Z score.

Figures 1 and 2 shows how the mean weekly weight for females and males respectively markedly differed from both the Fenton Growth Chart and Intergrowth 21st Project growth standards. Many infants who regained birth weight in 21 days or less did not have an adequate weight velocity afterwards and the vice versa is true as shown in Table 5. Only 25 infants (27.2%) had good growth (regained their birth weight in 21 days or less and subsequently had a weight velocity above 15 g/kg/day) (Table 5).

Table 3 Birth weight Z-score and endpoint outcomes at 36 weeks according to Fenton Growth Chart and Intergrowth 21st Project standard. *P* values expressing the difference between these charts are shown. Chi squared test used for the variables "small for gestational age" and "weight above 10th centile at 36 weeks". Student t-test used for the variables "Delta Z-score", "Birthweight Z-score" and "Weight Z-score at 36 weeks"

	Number of infants plotted	Fenton Growth Chart	Intergrowth 21st Project	*P* value
Small for gestational age, n (%)	89	13 (14.6%)	27 (30.3%)	0.012
Birth weight Z-score, mean (SD)	89	−0.45 (1.01)	− 0.72 (1.20)	0.107
Weight Z-score at 36 weeks, mean (SD)	89	− 2.50 (1.13)	−2.57 (1.72)	0.725
Delta Z-score, mean (SD)	89	−2.05 (0.87)	−1.87 (1.30)	0.250
Weight above 10th centile at 36 weeks, n (%)	89	11 (12.4%)	20 (22.5%)	0.075

Table 4 Birth weight categories and corresponding growth parameters. Weight velocity was calculated from the day birth weight was regained to 36 weeks postmenstrual age

Birth weight	Total number of infants	Infants with good growth (N/%)	Infants with discharge weight > 10th centile (N/%)	Median Gestational age (min - max)	Mean Delta Z-score from birth to 36 weeks (SD)	Mean number of days to regain birth weight (SD)	Mean weight velocity (SD)
600–699	3	0 (0%)	0 (0%)	23 (23–28)	−2.8 (0.7)	10.6 (9.2)	11.6 (2.0)
700–799	13	6 (46.2%)	2 (15.4%)	27 (24–29)	−2.1 (0.9)	14.7 (7.4)	14.0 (3.6)
800–899	35	12 (34.3%)	4 (11.4%)	28 (25–34)	−2.0 (0.8)	19.7 (9.4)	14.0 (3.3)
900–999	41	7 (17%)	5 (12.2%)	28 (23–32)	−2.2 (1.3)	18.5 (11.3)	13.0(2.8)

Macronutrient intake during the first 28 days if life

The mean number of days to reach full enteral feeds was 15.9 days (SD = 6.3) and by the seventh day of life, enteral feeds contributed more than 50% of caloric intake. A plateau of 90–92% mean enteral caloric contribution was reached from the twentieth day. During the first 28 days of life, the mean number of days in which infants received at least 160mls/kg/day of enteral feeds was 12.1 days (SD = 6.3). Thirty-four infants had an adequate caloric intake (above 110 kcal/kg/day). Mean caloric intake during the first 28 days was 97.0 kcal/kg/day (SD = 14.4). A mean caloric intake above 80 kcal/kg/day was reached on day 8, by day 14 the mean caloric intake was above 110 kcal/kg. There was a steady increase in mean weekly caloric intake from 65, 7 kcal/kg/day (SD = 18.7) in the first, 101 kcal/kg/day (SD = 8.6) in the second, 118 kcal/kg/day (SD = 5.0) in the third to 123 kcal/kg/day (SD = 2.9) in the fourth week. The mean protein intake was 2.5 g/kg/day (SD = 0.7) with a mean daily intake above 3.0 g/kg/day being reached on the twentieth day of life. The mean lipid intake was 4.4 g/kg/day (SD = 1.1) with a mean daily intake above 5 g/kg/day being reached at the fourteenth day of life.

Pearson correlational analysis showed that during the first 28 days of life, weight velocity increased with a shorter duration to attain full feeds ($r = -0.38$) and

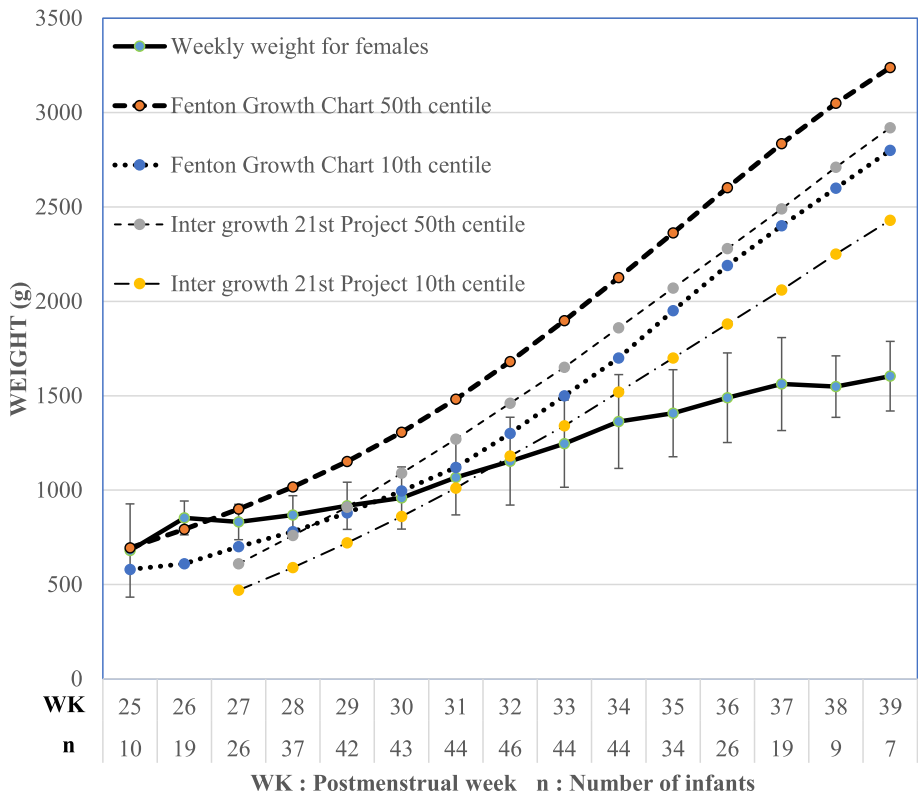

Fig. 1 Growth curve for females with standard deviation indicated for each mean weekly weight. Fenton Growth Chart and Intergrowth 21st Project centile lines shown as reference

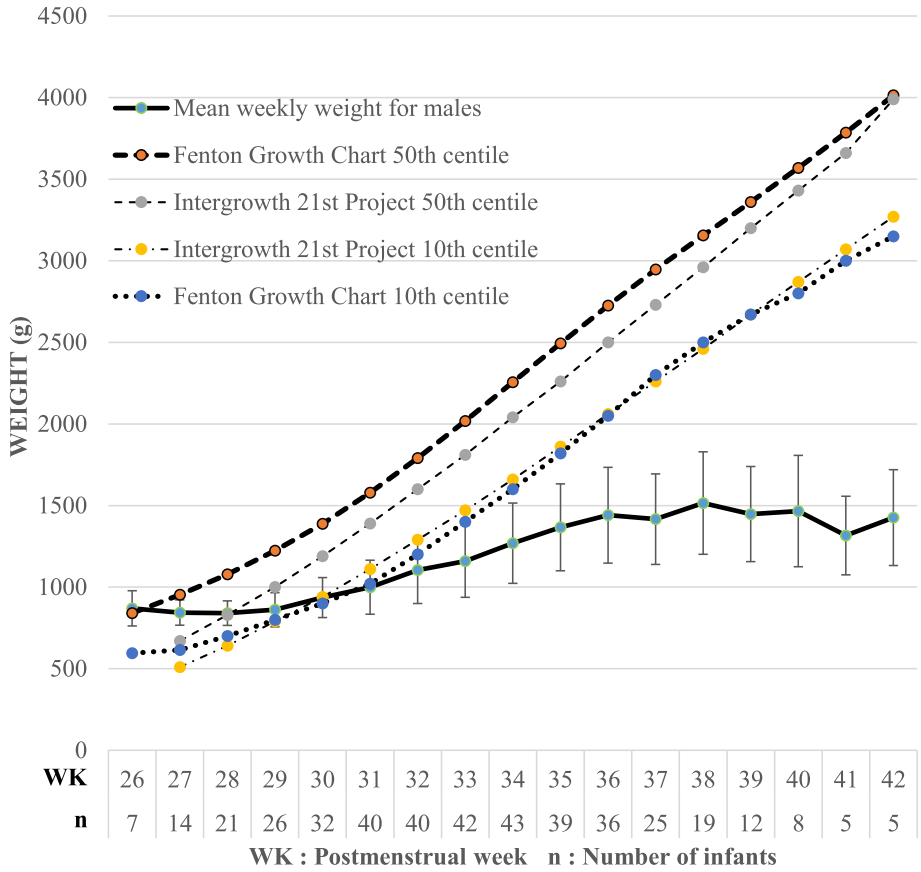

Fig. 2 Growth curve for males with standard deviation indicated for each mean weekly weight. Fenton Growth Chart and Intergrowth 21st centile lines shown as reference

the longer the infant remained on feeds of at least 160mls/kg/day ($r = 0.44$). Increases in protein ($r = 0.38$), lipid ($r = 0.42$) and caloric intake ($r = 0.38$) were associated with an increase in weight velocity during the first 28 days of life.

Complications of prematurity

A comparison was done between the group classified as "good growth" ($n = 25$) and that classified as "poor growth" ($n = 67$). Complications of prematurity which showed a significant association with poor growth were CPAP for more

Table 5 Distribution of growth parameters (number of days to regain birth weight and weight velocity) among infants and the resultant discharge weight centile

	Weight velocity > 15 g/kg/day, regained birth weight in 21 days or less	Weight velocity > 15 g/kg/day, regained birth weight after 21 days	Weight velocity < 15 g/kg/day, regained birth weight in 21 days or less	Weight velocity < 15 g/kg/day, regained birth weight after 21 days
Number of infants	25	6	34	27
Infants with weight > Fenton Growth Chart 10th centile at 36 weeks, N (%)	6 (24%)	2 (33.3%)	3 (8.8)	0 (0%)
Infants with weight > Intergrowth 21st Project 10th centile at 36 weeks, N (%)	10 (40%)	3 (50%)	6 (17.6%)	1 (3.7%)
Mean weight velocity, g/kg/day (SD)	16.6 (1.4)	17.5 (2.1)	12.1 (1.9)	11.5 (2.6)
Mean number of days to regain birth weight, days (SD)	14.6 (5.0)	24.3 (2.1)	10.8 (7.0)	29.4 (7.1)

Table 6 Neonatal characteristics associated with poor growth. Univariate analysis with Chi-squared test or Fischer's exact used as appropriate

Variable		Poor growth	Good growth	n	*P*-value
PDA	Yes	13(100%)	0(0%)	13	0.017
	No	54(68.4%)	25(31.6%)	79	
Sepsis after day 3 of life	Yes	45(84.9%)	8(15.1%)	53	0.002
	No	22(56.4%)	17(43.6%)	39	
Invasive ventilation	Yes	16(94.1%)	1(5.9%)	17	0.034
	No	51(68.0%)	24(32.0%)	75	
CPAP more than 2 days	Yes	26(89.7%)	3(10.3%)	29	0.014
	No	41(65.1%)	22(34.9%)	63	
Nil per os (excluding the first day of life)	Yes	49(80.3%)	12 (19.7%)	61	0.023
	No	18(58.1%)	1341.9%)	31	
Oxygen on day 28 of life	Yes	54(79.4%)	14(20.6%)	68	0.017
	No	13(54.2%)	11(45.8%)	24	

than 2 days, invasive ventilation, oxygen on day 28 of life, late-onset sepsis, PDA and being kept nil per os (excluding the first day of life) (Table 6). No single complication of prematurity was independently associated with neither a weight above the 10th centile at 36 weeks nor a significant difference of delta Z-score between birth and 36 weeks when the Fenton Growth Chart was used. However, use of the Intergrowth 21st Project growth standards showed a significant difference in delta Z-score between infants who were receiving oxygen by day 28 ($p = 0.024$), those with PDA ($p = 0.001$) and sepsis after day 3 ($p = 0.050$) compared to those who did not have such complications. Being kept NPO ($p = 0.123$), receiving for CPAP more than 2 days ($p = 0.069$), antenatal steroids ($p = 0.219$) and invasive ventilation ($p = 0.254$) did not show a significant difference in delta Z-scores compared to those who did not have such complications. A Chi squared test showed a significant association between infants having a weight at 36 weeks less than the 10th centile and those who had sepsis after day 3 of life when the Intergrowth 21st Project growth standards were used ($p = 0.021$).

Discussion

This study details the pathological growth pattern in ELBW infants leading to an undesirable weight at 36 weeks postmenstrual age. In the present study, infants regained birth weight in 18.3 days and had a mean weight velocity of 13.5 g/kg/day. Although a recommendation on the minimum acceptable weight velocity does not exist [24], the mean weight velocity in the present study was comparable to previous studies [11, 12] and approaches the frequently used minimum of 15 g/kg/day [24]. The present study shows that many infants who regained birth weight in 21 days or less did not have an adequate weight velocity afterwards and vice versa. This resulted in failure of most infants to attain a weight above the 10th centile at 36 weeks on both the Fenton Growth Chart and Intergrowth 21st Project Postnatal Chart. Findings by Dejhalla et al. among 21 ELBW infants with an uncomplicated hospital stay showed much better outcomes with 71% of infants having a weight above the 10th centile on discharge [25]. The study excluded infants with blood culture proven sepsis, necrotizing enterocolitis and neonatal surgery among other complications. This highlights the importance of identifying the neonatal characteristics associated with growth.

The mean caloric intake in the present study is comparable to previous studies but lags in protein intake [6, 25]. Indeed, during the first few days of life, infants in the present study had a more rapid advancement of caloric intake and enteral feeds compared to the study by Dejhalla et al. whose infants had a better outcome. The determining factor could have been the protein intake, in the study by Dejhalla et al., a protein intake of 3.0 g/kg/day was reached by the tenth day compared to the twentieth day in the present study.

CPAP duration exceeding 2 days, invasive ventilation, oxygen on day 28, late-onset sepsis, being kept nil per os and PDA were associated with poor growth (number of days to regain birth weight and weight velocity). In a South African study by Mudahemuka et al., the growth of 69 VLBW infants who survived to discharge from the neonatal unit was reviewed. In the study, a growth velocity < 14 g/kg/day was associated with antenatal steroids and the number of days nil per os without ITN correlated negatively with the discharge weight Z-score [11]. In the present study, no association was demonstrated between growth and antenatal steroids, however the definition of good growth velocity was different from that use by Mudahemuka et al. Alejandro et al. demonstrated multiple neonatal characteristics associated with

a significant decline in Z-score from birth to discharge including mechanical ventilation and PDA among 130 infants with a birth weight less than 1500 g [26]. These findings approximate the results of the present study, however, the use of discharge weight Z-score as an endpoint by Alejandro et al. presents a possibly significant difference in study design.

In the present study, a greater portion of infants were considered small for gestation age using the Intergrowth 21st Project growth standards compared to the Fenton Growth Chart. The increase in number of infants plotting above the 10th centile at 36 weeks using the Intergrowth 21st standards approaches statistical significance. These findings are consistent with a study conducted by Funda et al. on 248 infants in Turkey comparing the Fenton Growth Chart to Intergrowth 21st Project standards [27]. Funda et al. did not find any increased risk for early morbidity in the new small for gestational age infants identified by the Intergrowth 21st Project growth standards. However, in the present study, although no neonatal factors were associated with a weight > 10th centile at 36 weeks when the Fenton Growth Chart was used, this was not the case with the Intergrowth 21st Project growth standards. When Intergrowth 21st Project growth standards were used, the decline in Z-score from birth to 36 weeks was significantly larger among infants with PDA, sepsis after day 3 of life and those who remained on oxygen at day 28 of life. This suggests that Intergrowth 21st Project growth standards may provide a better association between growth and neonatal complications in our population compared to the traditionally used Fenton Growth Chart. This finding reverberates the concern that intrauterine growth may not be the appropriate standard for extrauterine growth in premature infants, furthermore, whether the Fenton Growth Chart is suitable for our population [17].

Study limitations

This was a retrospective study and infants were managed as per attending physicians' discretion. The method by which gestational age was determined was not standardized. A larger sample would have allowed a better description of rare complications of prematurity and infants who attended follow-up clinic at 12 months corrected age as only a few infants were picked up. Thirty-six infants (40.4%) were discharged before 36 weeks had their discharge weight Z-score analyzed as the one at 36 weeks, however, the resulting error was assumed to be small since the mean postmenstrual age at discharge was 36.7 weeks. Infants discharged before 36 weeks had a mean postmenstrual age of 34.5 weeks (SD = 1.1) at the time of discharge.

However, this study provides a detailed description of macronutrient intake, such detail has rarely been described in South Africa and other middle and low-income countries. The present study also explores the usefulness of the Intergrowth 21st Project growth standards compared with the traditionally used Fenton Growth Charts.

Conclusion and recommendations

The growth of ELBW infants at CMJAH is suboptimum. Multiple complications of prematurity are associated with poor growth and nutritional intake correlates positively with weight velocity. There is need for a multifaceted approach to address characteristics associated with poor growth. Respiratory complications of prematurity can be reduced by increased coverage of antenatal steroids. Infants are likely receiving NCPAP after a significant delay at CMJAH neonatal unit, there is a need to avail enough NCPAP units in the Transitional Unit. A protocol addressing both volume and nutritional requirements during initiation of enteral feeds is needed. Consideration should be given to start ITN by 24 h rather than the current 48 h in infants not on full enteral feeds. Small enteral feeds can also be introduced on the first day of life. Chorioamnionitis is likely underreported, more vigilant surveillance and treatment in pregnant mothers could prevent premature delivery. Strong consideration should be given for the use of Intergrowth 21st Project growth standards as reference for normal postnatal growth in premature infants instead of the Fenton Growth Chart currently in use. Unlike the Fentons Growth Charts, use of the Intergrowth 21st Project growth standards revealed the association between neonatal factors and poor growth. A large multicenter prospective study is needed to assess the extent to which changes brought about by the Intergrowth 21st Project growth standards correlate with long term outcomes.

Abbreviations

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; CPAP: Continuous positive airway pressure; ELBW: Extremely low birth weight (birth weight less than 1000 g); ITN: Intravenous total nutrition; NEC: Necrotising enterocolitis; RDS: Respiratory distress syndrome; REDCAP: Research electronic data capture; ROP: Retinopathy of prematurity; VLBW: Very low birth weight (birth weight less than 1500 g)

Acknowledgments

None.

Authors' contributions

TM conceptualized and designed the study, collected data and carried out the data analysis, drafted the initial manuscript and approved the final manuscript. DEB conceptualized and designed the study, assisted with data analysis, reviewed and revised the manuscript, and approved the final manuscript. TR conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript.

Funding

None.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethics approval for this study was granted by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. This was a retrospective study, the need for consent to participate was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 24 December 2018 Accepted: 3 June 2019
Published online: 11 July 2019

References
1. Horbar JD, Badger GJ, Carpenter JH, Fanaroff AA, Kilpatrick S, LaCorte M, et al. Trends in mortality and morbidity for very low birth weight infants, 1991–1999. Paediatrics. 2002;110(1):143–51.
2. Niklasson A, Engström E, Hård A-L, Wikland KA, AJPr H. Growth in very preterm children: a longitudinal study. Pediatr Res. 2003;54:899–905.
3. Saigal S, Stoskopf BL, Streiner DL, Burrows EJP. Physical growth and current health status of infants who were of extremely low birth weight and controls at adolescence. Pediatrics. 2001;108:407–15.
4. Kelleher KJ, Casey PH, Bradley RH, Pope SK, Whiteside L, Barrett KW, et al. Risk factors and outcomes for failure to thrive in low birth weight preterm infants. Pediatrics. 1993;91(5):941–8.
5. Embleton NE, Pang N, Cooke RJJP. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatric. 2001;107(2):270–3.
6. Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M, et al. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics. 2009;123(5):1337–43.
7. Sowande OA, Ogundoyin OO, Adejuyigbe OJSP. Pattern and factors affecting management outcome of neonatal emergency surgery in Ile-Ife, Nigeria. Surg Pract. 2007;11(2):71–5.
8. Chaudhari S, Kadam S. Total parenteral nutrition in neonates. Indian Pediatr. 2006;43(11):953.
9. Neu J. Gastrointestinal development and meeting the nutritional needs of premature infants. Am J Clin Nutr. 2007;85(2):629S–34S.
10. Mackay CA, Ballot De Fau - Cooper PA, Cooper PA. Growth of a cohort of very low birth weight infants in Johannesburg, South Africa. BMC Pediatr. 2011;11:50.
11. Mudahemuka JC, Ballot D. Birth weight recovery among very low birth weight infants surviving to discharge from Charlotte Maxeke Johannesburg Academic Hospital. S Afr J Child Health. 2014;8(4):149–53.
12. Lango MO, Horn AR, Harrison MC. Growth velocity of extremely low birth weight Preterms at a tertiary neonatal unit in South Africa. J Trop Pediatr. 2013;59(2):79–83.
13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.
14. 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(6):1466–73.
15. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13(1):59.
16. Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. Lancet. 2014;384(9946):857–68.
17. Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Ismail LC, et al. Postnatal growth standards for preterm infants: the preterm postnatal follow-up study of the INTERGROWTH-21st project. Lancet Glob Health. 2015;3(11):e681–e91.
18. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967;71(2):159–63.
19. Mimouni FB, Lubetzky R, Yochpaz S, Mandel D. Preterm Human Milk macronutrient and energy composition: a systematic review and meta-analysis. Clin Perinatol. 2017;44:1557–9840 Electronic.
20. 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):1.
21. Agarwal K, Jalali S. Classification of retinopathy of prematurity: from then till now. Community Eye Health. 2018;31(101):S4.
22. Kindler A, Seipolt B, Heilmann A, Range U, Rudiger M, Hofmann SR. Development of a diagnostic clinical score for hemodynamically significant patent ductus arteriosus. Front Pediatr. 2017;5:280.
23. Hossain M, Islam M, Shahidullah M, Akhter H. Pattern of change of weight following birth in the early neonatal period. Mymensingh Med J. 2006;15(1):30–2.
24. 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 Diet. 2018;118(9):1571–2.
25. Dejhalla M, Lahage N, Parvez B, Brumberg HL, La Gamma EF. Early postnatal growth in a subset of convalescing extremely-low-birth-weight neonates: approximating the "index fetus" ex utero. J Pediatr Gastroenterol Nutr. 2015;61(3):361–6.
26. Avila-Alvarez A, Solar Boga A, Bermúdez-Hormigo C, Fuentes Carballal J. Extrauterine growth restriction among neonates with a birthweight less than 1500 grams. An Pediatr (English Edition). 2018;89(6):325–32.
27. Tuzun F, Yucesoy E, Baysal B, Kumral A, Duman N, Ozkan H. Comparison of INTERGROWTH-21 and Fenton growth standards to assess size at birth and extrauterine growth in very preterm infants. J Matern Fetal Neonatal Med. 2018;31(17):2252–7.

Publisher's Note

Appendix A: Approved research protocol

GROWTH OF EXTREMELY LOW BIRTH WEIGHT INFANTS AT A TERTIARY HOSPITAL IN A MIDDLE-INCOME COUNTRY

Dr. Tendai Mabhandi MBCHB (UZ)

Student number 1330266

Degree: MMed Paediatrics

Supervisors

Dr. T Ramdin MBCHB, FCPaed (SA)

Prof. DE Ballot MBCHB, FCPaed (SA), PhD

Contents

Abbreviations

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ELBW	Extremely Low birth weight (Birth weight less than 1000g)
ITN	Intravenous Total Nutrition
NCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotising Enterocolitis
RDS	Respiratory Distress syndrome
VLBW	Very Low Birthweight (Birth weight less than 1500g)
ROP	Retinopathy of prematurity
CLD	Chronic lung disease

1. Introduction

Survival of extremely low birth weight (ELBW) infants has improved significantly since the 1990s [1]. This was a result of advances in perinatal care including antenatal steroids [2], surfactant therapy for respiratory distress syndrome (RDS) [3] and early nasal continuous positive airway pressure (NCPAP) [4]. Consequently, growth monitoring in preterm infants has gained more interest and relevance.

Very low birth weight infants (VLBW; birth weight less than 1500 grams) have atypical growth compared to term infants [5]. Long-term follow-up studies observed lower weight, height and inadequate neurocognitive outcome when compared to normal birth weight infants [6,7,8]. Conversely, too rapid weight gain is associated with cardiovascular disease, diabetes mellitus, hypertension and obesity in adulthood [9]. Investigators have seen that atypical growth patterns are much more common among ELBW infants [10,11,12]. Although ELBW infants have compensatory growth into their early adult years, they remain shorter than their predicted mid-parental heights [13].

Identifying these failing to thrive ELBW infants is important as they are more likely to have poorer neurocognitive outcome [14]. Indeed, there is growing evidence among ELBW infants that inadequate nutrition during the early weeks of life result in persistent growth faltering that may lead to permanent detrimental effects [15,16]. However enteral feeds in ELBW infants should be advanced slowly to avoid necrotising enterocolitis. Therefore, early intravenous total nutrition (ITN) should be provided to ELBW infants because it leads to better neurodevelopmental outcome and growth [17,18, 19]. A study of 148 ELBW infants showed that increased protein and caloric intake in the first week of life was associated with a better neurodevelopmental outcome at 18months [20].

The growth of ELBW infants should approximate intrauterine growth rate. Quantitatively, normal singleton foetal growth increases from approximately 5g/day at 14 – 15weeks of gestation to 10 g/day at 20weeks. Growth rate increases further reaching 30 – 35g/day at 32 – 34weeks followed by slowing rate as the foetus approaches term [21]. Adequate nutritional support is vital if this growth rate is to be realised. Where protein to energy ratio is sufficient (3 to 3.6g/100kCal), energy intake above 100kCal/kg is generally adequate [22]. While high intakes of 140 to 150 kcal/kg/day are safe in the short term, evidence shows this leads to excessive fat deposition [22]. Individual energy requirements will differ according to clinical condition and physical activity. For premature infants on enteral feeds, the average daily energy requirement is 120 kcal/kg per day [23]. In ELBW infants on ITN, 80 to 100kcal/kg/day is required because of less exposure to cold stress, less faecal energy loss and somewhat less physical activity. Preterm infants with chronic illnesses may need as much as 150kcal/kg/day [24].

Nutrition in ELBW infants is surrounded by several challenges. In a low resource setting, ITN may not be readily available due to cost limitations [25]. Furthermore, venous access is often difficult in these small infants, limiting ITN use in such situations. Necrotising Enterocolitis (NEC) increases in frequency with declining birth weight [26]. Extremely low birth weight infants have the highest frequency of NEC [27] and consequent discontinuation of oral feeds. During this time the infant may have contraindications to ITN use, for example, severe metabolic acidosis, sepsis and deranged liver function.

There is little information in South Africa on the growth of ELBW infants and their caloric intake while in hospital. A previous prospective study on VLBW infants admitted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) showed that infants had initial poor growth followed by catch-up growth but with persistent deficits at 20months [28]. Another study at the same hospital concluded that during admission, VLBW infants were

having growth velocity less than but approaching recommended values [29]. However, both studies do not have ELBW infants as a subcategory and no information on caloric intake is provided.

2. Aim

To review the growth of ELBW infants at CMJAH from birth to 9 – 12 months of age, corrected for the degree of prematurity and audit caloric intake in the first 28 days of life.

3. Objectives

- To describe the growth of ELBW infants admitted at CMJAH from birth up to 9 – 12 months of age, corrected for the degree of prematurity.
- To explore complications of prematurity that are associated with poor growth.
- To describe the effect of growth on neurodevelopmental outcome.
- To conduct an audit of caloric intake during the first 28 days of life.

4. Subjects and Methods

- This will be a pilot study to evaluate growth in ELBW infants.
- The study will be a retrospective longitudinal description of growth and caloric intake in ELBW infants at CMJAH.

4.1 Inclusion criteria

- All ELBW infants admitted at CMJAH within 72hrs of birth between 01 January 2015 and 31 March 2017 will be eligible for inclusion.

4.2 Exclusion criteria

- Those ELBW infants who died in hospital and those who did not attend follow up clinic post discharge at 9 – 12 months of age will be excluded.

- Infants with major congenital abnormalities of the gastrointestinal tract or other chromosomal abnormality will be excluded.

4.3 Data capture and sources

This is a secondary analysis of an existing database and review of relevant patient records. Data is collected for all patients admitted to CMJAH on discharge from hospital for the purpose of clinical audit. Demographic, labour room and clinical characteristics are collected by attending physicians. The data is entered into a computerized database using Research Electronic Data Capture (REDCAP) hosted by University of Witwatersrand (Harris et al). Basic demographic, labour room and clinical information will be obtained from the database for each patient. Additional information regarding the weight gain and nutritional intake will be obtained by scrutinizing patient records. The need for ventilator support (mechanical ventilation and NCPAP), as well as complications of prematurity including NEC, retinopathy of prematurity (ROP), late onset sepsis (>72hrs after birth), chronic lung disease (CLD) and patent ductus arteriosus (PDA), will be recorded for each patient. Data will be entered into a Microsoft Excel Spreadsheet for data cleaning. The final dataset will be exported into IBM SPSS 25 for analysis

4.4 Sample size

This is a pilot study, so a convenience sample which will include all ELBW infants born during the period under study (01 January 2015 to 31 March 2017) and attended follow-up clinic at 9 – 12 months of age will be used. From January 2015 the records department at CMJAH has been storing patient records digitally by scanning all the pages in a discharged patient's file. Since this project requires meticulous recording of variables daily during the

first 28 days of life and weekly weight until discharge, patient records prior to January 2015 are unlikely to be suitable due to missing data. To ensure all selected patients have attended follow-up clinic at 9 – 12 months of age, records later than 31 March 2017 will be excluded. On average, thirty ELBW infants per year attend follow-up clinic at 9 – 12 months of age. Therefore about 68 ELBW infants are expected to meet the above criteria.

4.5 CMJAH Neonates unit

- At CMJAH neonatal unit the target growth rate for ELBW infants is 15 to 20g/kg/day once the infant has regained their birth weight

- Feeds are prescribed by the attending physician, guided by the unit protocol. The enteral feed of choice if breastmilk. Breast milk for ELBW infants is fortified using FM85 (Nestle). The infant formula Prenan (Nestle) is provided for those ELBW infants whose mothers are unwilling or unable to breastfeed.

- Newly born ELBW infants at CMJAH are started on intravenous fluids (usually Non-K Neonatolyte) at 80 to 100mls/kg/day on the first day of life. Feeds are introduced on the second day of life starting at 20mls/kg/day. Feeds are gradually increased by 20 to 30mls/kg/day replacing intravenous fluids until 160 to180mls/kg/day of full enteral feeds is reached.

- As per unit protocol, intravenous total nutrition (ITN) is started on all ELBW infants not on full enteral feeds for 48hours.

- All ELBW infants are weighed twice a week on an electronic scale.

- Enteral feeds are discontinued if there is evidence of feeding intolerance (gastric aspirates greater than 20% of the previous day's intake, more than 50% of previous feed or bilious vomiting)

- Post discharge, ELBW infants are seen every three months at follow-up clinic. Weight, height and skull circumference are measured at each visit. These parameters are converted into Z-scores using World Health Organisation growth charts.

- Neurodevelopment is assessed at follow up clinic using the Bayley Scales of Infant Development [30]. Development is assessed in three sub-scales – cognitive, motor and language. A score of less than 85 on the Bayley Scale of Infant Development is classified "at risk" and a score less than 70 is classified as "delayed". For the purpose of the study, an ELBW with a score below 70 on all three sub-scales will be classified as delayed.

5. Definitions

Definitions of complications of prematurity are based on those used in the Vermont Oxford Network (www.vtoxford.org).

NEC will be defined as NEC grade 2 or 3 according to modified Bells' staging [31]

ROP will be defined as stage 2 or more

CLD will be defined as supplemental oxygen at 28 days of life

6. Data analysis

Data will be described using standard statistical methods. IBM SPSS 25 will be used to analyse the data. The distribution of continuous variables will be explored. Those variables with a normal distribution will be described using mean and standard deviation (SD) while those with a skewed distribution will be described using mean and interquartile range (IQR). Categorical variables will be described using frequency and percentages.

The following variables will be determined:

1. Birth weight for gestational age.

   The birth weight for each ELBW infant will be plotted for gestational age. Weight for gestational age (WFGA) above 90th centile is classified as large for gestational age (LGA), WFGA between 10th and 90th centile is appropriate for gestational age (AGA) and WFGA below 10th centile is small for gestational age (SGA).

2. Percentage of birth weight lost.

   The nadir of each ELBW infant's weight will be recorded and used to calculate the percentage of birth weight lost. This should not be greater than 20% [30].

3. The number of days to regain birthweight.

   The number of days to regain birth weight is noted. This should be approximately 14 days in preterm infants [32].

4. Growth velocity in hospital

   Growth velocity will be calculated week on week once the infant has regained birth weight. Growth velocity above 14g/kg/day will be considered as adequate (28).

5. Average caloric intake for the first 28 days.

   Daily caloric intake will be calculated by reviewing the total intravenous fluid and feed intake of each ELBW infant. The different intravenous fluids and infant formulas have a known caloric content. The caloric content of breast milk will be estimated from a standard table [33]. The volume of intravenous fluid or feed will be multiplied by the caloric content and added together to determine the daily caloric intake. The average caloric intake for each ELBW infant for the first 28 days of life will be computed.

6. The total duration of no enteral feeding.

7. Duration of ventilatory support.

8. Duration of hospitalization.

9. Weight, height and head circumference at 9 to 12 months of corrected age.

   These measurements are recorded at follow-up clinic. These values will be plotted on World Health Organisation (WHO) Growth Charts at the corrected age for each ELBW infant and converted to Z-scores. A Z-score of 0 corresponds to 0 standard deviation and a Z-score of 1 corresponds to 1 standard deviation (SD). Weight for age less than -3 Z-score will be considered as failure to thrive, height for age less than -2.5 Z-score will be considered as stunting and head circumference Z-score less than -2 Z-score will be considered as microcephaly.

10. Neurodevelopmental outcome at 9 to 12 months corrected age.

    Those ELBW infants with all three scales less than 70 will be considered as delayed neurodevelopment.

Adequate weight gain will be classified as birth weight recovery in less than 21 days and growth velocity greater than 15g/kg/day (28). Extremely low birth weight infants with adequate weight gain will be compared with those with inadequate weight gain. Univariate analysis will be done using Chi-square analysis for categorical variables and unpaired t-test or Mann-Whitney u test for continuous variables as appropriate. A p-value <0,05 will be considered to be statistically significant. Binary logistic regression will be used to calculate adjusted odds ratio for significant variables. Similar analysis will be done for weight, height, head circumference and neurodevelopmental outcome at 9 to 12 months of age.

7. Ethics

The study will be presented to the Human Research Ethics Committee for ethics clearance. Permission will be requested from CMJAH Chief Executive Officer to grant a waiver of informed consent since this will be a retrospective study.

8. Timing

	Nov/Dec 2017	Feb/Mar 2018	Apr 2018	May 2018	Jun 2018	Jul 2018	Aug 2018	Sep 2018	Oct 2018	Nov 2108	Dec 2018
Literature review											
Preparing protocol											
Protocol assessment											
Ethics application											
Collecting data											
Data analysis											
Writing up – thesis											
Writing up – paper											

9. Funding

The project will cost approximately R500. This will be incurred in printing of the research protocol, data collection sheets and the synopsis. The cost will be met by the researcher.

10. Study limitations

Since the project will be retrospective and observational in nature, confounding variables cannot be completely eliminated without controls.

11. References

1. Horbar J.D., Badger G.J., Carpenter J.H, Fanaroff AA, Kilpatrick S, LaCorte M, Phibbs R, Soll RF. Trends in mortality and morbidity for very low birth weight infants. Pediatrics 2002:110, 143-151

2. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017:3, CD004454.

3. Suresh GK, Soll RF. Overview of surfactant replacement trials. J Perinatol 2005:25 Suppl 2, S40.

4.Dunn MS, Kaempf J, de Klerk A, Reilly M, Howard D, Ferrelli K, O'Conor J, Soll RF. Vermont Oxford Network DRM Study Group. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011:128, 5.

5. Kimble KJ, Ariagno RL, Stevenson DK, Sunshine P. Growth to age 3 years among low birth weight sequelae free survivors of modern neonatal intensive care. J Pediatr 1982:100, 622 – 624.

6. Kitchen W.H., Doyle L.W., Ford G.W., Callanan C. Very low birth weight and growth to age 8 years: I weight and height. Am J Dis Child 1992:146, 40-45

7. Ford G.W., Doyle L.W., Davis N.M., Callanan C. Very low birth weight and growth into adolescence. Arch Pediatr Adolesc Med 2000:154, 778-784

8. Ericson A., and Kallen B. Very low birth weight boys at the age of 19. Arch Dis Child Fetal Neonatal Ed 1998:78, F171-F174

9. Hales CN, Ozanne SE. The dangerous road of catch up growth. J Physiol 2003:547, 5 – 10.

10. Hack M., Schluchter M., Carter L., Rahman M., Cuttler L., Borawski E. Growth of very low birth weight infants to age 20 years. Pediatrics 2003:112, 30-38

11. Niklasson A., Engstrom E., Hard A.L., Wikland KA, Hellstrom A. Growth in very preterm children: a longitudinal study. Pediatr Res 2003:54, 899-905

12. Farooqi A., Hagglof B., Sedin G., Gothefors L, Serenius F. Growth in 10-12 year old children born at 23 to 25 weeks' gestation in the 1990s: a Swedish national prospective follow-up study. Pediatrics 2006:118, 1452-1465

13. Saigal S., Stoskopf B.L., Streiner D.L., Burrows E. Physical growth and current health status of infants who were extremely low birth weight and controls at adolescence. Pediatrics 2001:108, 407-415

14. Kelleher K.J., Casey P.H., Bradley R.H., Pope SK, Whiteside L, Barrett KW, Swanson ME, Kirby RS. Risk factors and outcomes for failure to thrive in low birth weight preterm infants. Pediatrics 1993:9, 941-948

15. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001:107, 270.

16. Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol 2007:31, 48.

17. Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. Am J Clin Nutr 2013: 97, 816.

18. Wilson DC, Cairns P, Halliday HL, Reid M, McClure G, Dodge JA. Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 1997:77, F4.

19. Ehrenkranz RA, Das A, Wrage LA, Poindexter BB, Higgins RD, Stoll BJ, Oh W; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res 2011:69, 522.

20. Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M, Nye J, Vohr BR. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics 2009:123, 1337.

21. Resnik R. Intrauterine growth restriction. Obstet Gynecol 2002:99, 490.

22. Van GoudoeverJB, Sulkers EJ, Lafeber HN, Sauer PJ. Short-term growth and substrate use in very low birth weight infants fed formulas with different energy contents. Am J Clin Nutr 2000;71:816–21.

23. Bai-Horng Su. Optimizing Nutrition in Preterm Infants. Pediatrics and Neonatology 2014:55, 5-13.

24. Weinstein MR, Oh W. Oxygen consumption in infants with bronchopulmonary dysplasia. J Pediatr 1981:99, 958.

25. Sowande OA, Ogundoyin OO, Adejuyigbe O. Pattern and factors affecting management outcome of neonatal emergency surgery in Ile-Ife, Nigeria. Surg Pract 2007:11, 71-75.

26. Sankaran K, Puckett B, Lee DS, Seshia M, Boulton J, Qiu Z, Lee SK; Canadian Neonatal Network. Variation in incidence of necrotizing enterocolitis in Canadian neonatal intensive care units. J Pediatr Gastroenterol Nutr 2004:39, 366

27. Rees CM, Eaton S, Pierro A. National prospective surveillance study of necrotizing enterocolitis in neonatal intensive care units. J Pediatr Surg 2010: 45, 1391

28. CA Mackay, DE Ballot, PA Cooper. Growth of a cohort of very low birth weight infants in Johannesburg South Africa. BMC Pediatrics 2011:**11**, 50

29. JC Mudahemuka, DE Ballot. Birth weight recovery among very low birth weight infants surviving to discharge Charlotte Maxeke Johannesburg Academic Hospital. S Afr J of Child Health, 2014;8(4):149-153

30. Bayley N. Bayley Scales of Infant and Toddler Development: Administration Manual 3rd Edition ed. United States of America: Psychorp; 2006. 266 p.

31. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Annals of surgery. 1978;187(1):1-7.

32. RD Christensen, E Henry, TI Kiehn, JL Street. Pattern of daily weights among low birth weight neonates in the neonatal intensive care unit: data from a multihospital health care system. Journal of Perinatology (2006):26, 37–43

33. Mimouni FB, Lubetzky R, Yochpaz S, Mandel D. Preterm Human Milk Macronutrient and Energy Composition: A Systematic Review and Meta-Analysis. Clin Perinatol. 2017 Mar;44(1):165-172

Appendix B: Data sheet

Patient No. 01 Datasheet A

Demographics	
Gender (M or F)	
Gestational age in weeks	
Number of days in hospital	
Vital weights	
Birth weight (g)	
Lowest weight (g)	
Discharge weight (g)	
Number of days to regain birth weight	
Complications of prematurity	
Number of days not on feeds	
Necrotising enterocolitis (yes or no)	
Number of days on invasive ventilation	
Number of days on NCPAP	
Chronic lung disease (yes or no)	
Retinopathy of prematurity (yes or no)	
Positive blood culture (yes or no)	
Patent ductus arteriosus (yes or no)	
Surgery (yes or no)	
Follow up at 9 to 12 months of age	
Weight (g)	
Height (cm)	
Head circumference (cm)	
Neurodevelopmental outcome (Normal, At risk or Delayed)	

Patient No 1. Datasheet B

	Weight in grams	5% clear fluid (mls/hr)	10% clear fluid (mls/hr)	ITN 105 mls/hr	ITN 102 (mls/hr)	ITN 100 (mls/hr)	ITN 101 mls/3hrs	EBM mls/3hrs	EBM + 1g FM85 (mls/3hrs)	EBM +0.5g FM85 (mls/3hrs)	Prenan mls/3hrs	Nan mls/3hrs
Day 1												
Day 2												
Day 3												
Day 4												
Day 5												
Day 6												
Day 7												
Day 8												
Day 9												
Day 10												
Day 11												
Day 12												
Day 13												
Day 14												
Day 15												
Day 16												
Day 17												
Day 18												
Day 19												
Day 20												
Day 21												
Day 22												
Day 23												
Day 24												
Day 25												
Day 26												
Day 27												
Day 28												
Wk 5												
Wk 6												
Wk 7												
Wk 8												

Appendix C: Caloric content of feeds, fluids and ITN

Caloric content in intravenous fluids and infant formula

Fluid	Kcal/dL
5% Clear solutions	20
10% Clear solutions	40
ITN 102	62.32
ITN 105	46.18
ITN 101	38.28
ITN 100	49.5
Infant formula	Kcal/dL
Prenan	80
Nan	67
Breastmilk fortifier	Kcal/g
FM-85	4.4

- 5% clear solution contains 5g of dextrose per 100mls. An example is Paediatric Maintalyte solution
- 10% clear solutions contain 10g of dextrose per 100mls. An example in Neonatolyte
- 1g of dextrose releases 4kcal

The composition of preterm breastmilk [31]

Duration post delivery	**Kcal/dL**
Day 1 – 3	58.8 (+-) 7.9
Day 4 – 7	67.9 (+-) 14.1
Week 2	69.1 (+-) 10.1
Week 3 – 4	70.8 (+-) 9.3

Appendix D: Ethic clearance certificate

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr Tendai Mabhandi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180301

NAME: (Principal Investigator)	Dr Tendai Mabhandi
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital Neonatal Intensive Care and High Care Unit
PROJECT TITLE:	Growth of Extremely Low Birthweight Infants at a Tertiary Hospital in a Middle Income Country
DATE CONSIDERED:	06/04/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot and Dr Tanusha Ramdin
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	12/04/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 29/04/18

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix E: TURNITIN report

00820433:ELBW_article_BMC.odt

ORIGINALITY REPORT

9%	2%	8%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Handbook of Growth and Growth Monitoring in Health and Disease", Springer Nature America, Inc, 2012 Publication	3%
2	A Laher, D E Ballot, T Ramdin, T Chirwa. "A review of antenatal corticosteroid use in premature neonates in a middle-income country", South African Medical Journal, 2017 Publication	2%
3	preview-mhnpjournal.biomedcentral.com Internet Source	2%
4	Deborah K. Steward, Karen F. Pridham. "Growth Patterns of Extremely Low-Birth-Weight Hospitalized Preterm Infants", Journal of Obstetric, Gynecologic & Neonatal Nursing, 2002 Publication	2%

Exclude quotes On

Exclude matches < 2%

Appendix F: BioMed Central Paediatrics journal author guidelines

Research article

Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

BMC Pediatrics strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors

    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval.

See our editorial policies for more information.

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication.

You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication).

See our editorial policies for more information on consent for publication.

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].
- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here.

BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:

Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]

Competing interests

All financial and non-financial competing interests must be declared in this section.

See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office.

Please use the authors initials to refer to each authors' competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

See our editorial policies for a full explanation of acknowledgements and authorship criteria.

If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the "Acknowledgements" section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.

Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

Authors' information

This section is optional.

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

Examples of the Vancouver reference style are shown below.

See our editorial policies for author guidance on good citation practice

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Preparing main manuscript text

Back to top

Quick points:

- Use double line spacing
- Include line and page numbering
- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF
- Do not use page breaks in your manuscript

File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- TeX/LaTeX (use BioMed Central's TeX template)

Please note: editable files are required for processing in production. If your manuscript contains any non-editable files (such as PDFs) you will be required to re-submit an editable file when you submit your revised manuscript, or after editorial acceptance in case no revision is necessary.

Additional information for TeX/LaTeX users

Please use BioMed Central's TeX template and BibTeX stylefile if you use TeX format. Submit your references using either a bib or bbl file. When submitting TeX submissions, please submit both your TeX file and your bib/bbl file as manuscript files. Please also convert your TeX file into a PDF (please do not use a DIV file) and submit this PDF as a supplementary file with the name 'Reference PDF'. This PDF will be used by our production team as a reference point to check the layout of the article as the author intended.

The Editorial Manager system checks for any errors in the Tex files. If an error is present then the system PDF will display LaTex code and highlight and explain the error in a section beginning with an exclamation mark (!).

All relevant editable source files must be uploaded during the submission process. Failing to submit these source files will cause unnecessary delays in the production process.

TeX templates
BioMedCentral_article (ZIP format) - preferred template
Springer article svjour3 (ZIP format)
birkjour (Birkhäuser, ZIP format)
article (part of the standard TeX distribution)
amsart (part of the standard TeX distribution)

Style and language

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should consider:

- Visiting the English language tutorial which covers the common mistakes when writing in English.
- Asking a colleague who is a native English speaker to review your manuscript for clarity.
- Using a professional language editing service where editors will improve the English to ensure that your meaning is clear and identify problems that require your review. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts. BMC authors are entitled to a 10% discount on their first submission to either of these services. To claim 10% off English editing from Nature Research Editing Service, click here. To claim 10% off American Journal Experts, click here.

Please note that the use of a language editing service is not a requirement for publication in the journal and does not imply or guarantee that the article will be selected for peer review or accepted.

Data and materials

For all journals, BioMed Central strongly encourages all datasets on which the conclusions of the manuscript rely to be either deposited in publicly available repositories (where available and appropriate) or presented in the main paper or additional supporting files, in machine-readable format (such as spread sheets rather than PDFs) whenever possible. Please see the list of recommended repositories in our editorial policies.

For some journals, deposition of the data on which the conclusions of the manuscript rely is an absolute requirement. Please check the Instructions for Authors for the relevant journal and article type for journal specific policies.

For all manuscripts, information about data availability should be detailed in an 'Availability of data and materials' section. For more information on the content of this section, please see the Declarations section of the relevant journal's Instruction for Authors. For more information on BioMed Centrals policies on data availability, please see our [editorial policies].

Formatting the 'Availability of data and materials' section of your manuscript

The following format for the 'Availability of data and materials section of your manuscript should be used:

"The dataset(s) supporting the conclusions of this article is(are) available in the [repository name] repository, [unique persistent identifier and hyperlink to dataset(s) in http:// format]."

The following format is required when data are included as additional files:

"The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s))."

BioMed Central endorses the Force 11 Data Citation Principles and requires that all publicly available datasets be fully referenced in the reference list with an accession number or unique identifier such as a DOI.

For databases, this section should state the web/ftp address at which the database is available and any restrictions to its use by non-academics.

For software, this section should include:

- Project name: e.g. My bioinformatics project
- Project home page: e.g. http://sourceforge.net/projects/mged
- Archived version: DOI or unique identifier of archived software or code in repository (e.g. enodo)
- Operating system(s): e.g. Platform independent
- Programming language: e.g. Java
- Other requirements: e.g. Java 1.3.1 or higher, Tomcat 4.0 or higher
- License: e.g. GNU GPL, FreeBSD etc.
- Any restrictions to use by non-academics: e.g. licence needed

Information on available repositories for other types of scientific data, including clinical data, can be found in our editorial policies.

References

See our editorial policies for author guidance on good citation practice.

Please check the submission guidelines for the relevant journal and article type.

What should be cited?

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited.

Unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited

colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE.

Any in press articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

How to format your references

Please check the Instructions for Authors for the relevant journal and article type for examples of the relevant reference style.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

Authors may wish to make use of reference management software to ensure that reference lists are correctly formatted.

Preparing figures

Back to top

When preparing figures, please follow the formatting instructions below.

- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order. Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
- Figure keys should be incorporated into the graphic, not into the legend of the figure.

- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.
- Individual figure files should not exceed 10 MB. If a suitable format is chosen, this file size is adequate for extremely high quality figures.
- **Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures (or tables) that have previously been published elsewhere.** In order for all figures to be open access, authors must have permission from the rights holder if they wish to include images that have been published elsewhere in non open access journals. Permission should be indicated in the figure legend, and the original source included in the reference list.

Figure file types

We accept the following file formats for figures:

- EPS (suitable for diagrams and/or images)
- PDF (suitable for diagrams and/or images)
- Microsoft Word (suitable for diagrams and/or images, figures must be a single page)
- PowerPoint (suitable for diagrams and/or images, figures must be a single page)
- TIFF (suitable for images)
- JPEG (suitable for photographic images, less suitable for graphical images)
- PNG (suitable for images)
- BMP (suitable for images)
- CDX (ChemDraw - suitable for molecular structures)

For information and suggestions of suitable file formats for specific figure types, please see our author academy.

Figure size and resolution

Figures are resized during publication of the final full text and PDF versions to conform to the BioMed Central standard dimensions, which are detailed below.

Figures on the web:

- width of 600 pixels (standard), 1200 pixels (high resolution).

Figures in the final PDF version:

- width of 85 mm for half page width figure
- width of 170 mm for full page width figure
- maximum height of 225 mm for figure and legend
- image resolution of approximately 300 dpi (dots per inch) at the final size

Figures should be designed such that all information, including text, is legible at these dimensions. All lines should be wider than 0.25 pt when constrained to standard figure widths. All fonts must be embedded.

Figure file compression

- Vector figures should if possible be submitted as PDF files, which are usually more compact than EPS files.
- TIFF files should be saved with LZW compression, which is lossless (decreases file size without decreasing quality) in order to minimize upload time.
- JPEG files should be saved at maximum quality.
- Conversion of images between file types (especially lossy formats such as JPEG) should be kept to a minimum to avoid degradation of quality.

If you have any questions or are experiencing a problem with figures, please contact the customer service team at info@biomedcentral.com.

Preparing tables

Back to top

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.
- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.
- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.
- Color and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained in a table legend.
- Commas should not be used to indicate numerical values.

If you have any questions or are experiencing a problem with tables, please contact the customer service team at info@biomedcentral.com.

Preparing additional files

Back to top

As the length and quantity of data is not restricted for many article types, authors can provide datasets, tables, movies, or other information as additional files.

All Additional files will be published along with the accepted article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files, if requested, should be sent by email to the journal's editorial

email address, quoting the manuscript reference number. Please do not send completed patient consent forms unless requested.

Results that would otherwise be indicated as "data not shown" should be included as additional files. Since many web links and URLs rapidly become broken, BioMed Central requires that supporting data are included as additional files, or deposited in a recognized repository. Please do not link to data on a personal/departmental website. Do not include any individual participant details. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission. Each additional file should be cited in sequence within the main body of text.

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)
- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

For further guidance on how to use Additional files or recommendations on how to present particular types of data or information, please see How to use additional files.

Appendix G: BioMed Central Paediatrics journal acceptance letter

Gmail **Tendai Mabhandi <tenbha@gmail.com>**

Decision on your Submission to BMC Pediatrics - BPED-D-18-01115R2

BMC Pediatrics - Editorial Office <em@editorialmanager.com> Mon, Jun 3, 2019 at 2:40 PM
Reply-To: BMC Pediatrics - Editorial Office <catherine.olino@biomedcentral.com>
To: Tendai Mabhandi <tenbha@gmail.com>

BPED-D-18-01115R2
Growth of extremely low birth weight infants at a tertiary hospital in a middle-income country.
Tendai Mabhandi, MBCHB; Tanusha Ramdin, MBCHB; FCPead(SA); Daynia Elizabeth Ballot, MBCHB; FCPead(SA); PhD
BMC Pediatrics

Dear Dr Mabhandi,

I am pleased to inform you that your manuscript "Growth of extremely low birth weight infants at a tertiary hospital in a middle-income country." (BPED-D-18-01115R2) has been accepted for publication in BMC Pediatrics.

If any final comments have been submitted from our reviewers or editors, these can be found at the foot of this email for your consideration.

Before publication, our production team will also check the format of your manuscript to ensure that it conforms to the standards of the journal. They will be in touch shortly to request any necessary changes, or to confirm that none are needed.

Please do not hesitate to contact us if you have any questions regarding your manuscript and I hope that you will consider BMC Pediatrics again in the future.

If you wish to co-submit a data note to be published in BMC Research Notes (https://bmcresnotes.biomedcentral.com/about/introducing-data-notes) you can do so by visiting our submission portal http://www.editorialmanager.com/resn/. Data notes support open data (https://www.springernature.com/gp/open-research/open-data) and help authors to comply with funder policies on data sharing. Please note that this additional service is entirely optional.

Best wishes,

Nadia Liotto
BMC Pediatrics
https://bmcpediatr.biomedcentral.com/

Comments:

Dear Authors,
I noted that you have corrected the requests made by the reviewers, therefore your manuscript can be accepted for publication.

Best regard,
Nadia Liotto

--
Please also take a moment to check our website at field https://bmcpediatr.biomedcentral.com/ .
BMC Pediatrics operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

%CUSTOM_ SN_CAREERS%

Recipients of this email are registered users within the Editorial Manager database for this journal. We will keep your

information on file to use in the process of submitting, evaluating and publishing a manuscript. For more information on how we use your personal details please see our privacy policy at https://www.springernature.com/production-privacy-policy. If you no longer wish to receive messages from this journal or you have questions regarding database management, please contact the Publication Office at the link below.

_____

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/bped/login.asp?a=r). Please contact the publication office if you have any questions.