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**DISSERTATION**

**GROWTH VELOCITY OF EXTREMELY LOW BIRTH WEIGHT  
PRETERMS AT GROOTE SCHUUR HOSPITAL NURSERY**

**INVESTIGATOR**

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**DEGREE:**

**MPHIL IN NEONATOLOGY**

**Declaration**

I declare that this dissertation is my original work and is to be presented as part fulfillment of the requirements for the M. Phil in Neonatology from the University of Cape Town, and has not been presented in any other university for any other degree, and had not been published prior registration for this degree.

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**DR. M. O. LANGO**

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# **PART A: THE PROTOCOL**

Word count: 2,078

## List of Abbreviations

DEBM	-	Donated Expressed Breast Milk
EBM	-	Expressed breast milk
ELBW	-	Extremely low birth weight
GV	-	Growth Velocity
HIV	-	Human Immunodeficiency Virus
IVF	-	Intravenous Fluids
NEC	-	Necrotising Enterocolitis
NVD	-	Normal Vaginal Delivery
PT	-	Preterm
PVL	-	Periventricular Leucomalacia
UAC	-	Umbilical Arterial Catheter
USA	-	United States of America
VLBW	-	Very Low Birth Weight

## **Purpose of the study**

### **Primary objective**

To describe the growth velocity of extremely low birth weight babies seen at Groote Schuur Hospital nursery and to compare this to growth velocities of similar babies in published literature.

### **Background**

Extremely low birth weight preterms are increasingly surviving in recent times due to advances in care and more availability and use of surfactant. These babies present the neonatologists with new feeding and growth challenges due to the extreme prematurity of their various body systems. In utero, the fetus gets its nutrition from the mother via the umbilical vessels. However, the fetus does swallow large amounts of amniotic fluid which is thought to provide proteins and hormones which stimulate gut growth. The intrauterine growth velocity decreases from approximately 21 g/kg/d between 23 and 27 weeks' gestation to 12 g/kg/d between 35 and 37 weeks' gestation. The average growth velocity for the entire period from 23 to 37 weeks' gestation is approximately 16 g/kg/d.[1] Our aim in feeding the preterm is to mimic these growth rates. This is a great challenge. The preterm fetus has diminished glycogen stores compared to its term counterpart due to the interruption in the laying down of these glycogen stores – a process that takes place in the third trimester. Similarly, the preterm has diminished fat stores with 2% of its body weight as fat compared to its term counterpart who has 15% of its body weight as fat.[2] With an increased metabolic rate, worsened by morbidities, and coupled with an immature gut – achieving intrauterine rates of nutrients accretion is almost impossible, despite use of parenteral

nutrition. Many researchers hold the opinion that faced with these challenges, growth restriction at 36 weeks post menstrual age is an inevitable consequence in these ELBW preterm babies.[3]

Growth can be monitored adequately in these babies by anthropometry - the measurement of body weight, length, head circumference, and, to a lesser extent, skin fold and arm circumference. Weight is a good indicator of total body composition. It however fluctuates in the short term with hydration status and contraction of the total water compartment postnatally. Due to its ease of measure, it still offers us the best tool to monitor growth in our babies. The initial weight loss reaches its nadir at around the fourth to the sixth day of life[4,5] Once birth weight is regained, subsequent weight gain of 10 to 20 g/d for infants less than 27 weeks GA and 20 to 30 g/d for infants older than 27 weeks GA is desired. Weight gain is evaluated weekly and expressed relative to current body weight (g/kg/d), with ideal relative weight gains ranging between 10 and 20 g/kg/d.

Length on the other hand is more reliable as it is seldom influenced by variations in hydration status. It represents an increase in the lean tissue mass. It is a better indicator of long term growth. However, it is more difficult to take as it requires two operators and is more prone to errors. Ideally, the length should be measured weekly to the nearest 0.1cm. The expected incremental gain in the crown – heel length is 0.9cm per week.[4]

Increase in the head circumference usually correlates well with the overall growth of the neonates and their long term neurodevelopmental outcomes.[6] There may be an initial reduction in the head circumference of the very preterm infants in the first week of life correlating with receding edema. Thereafter, a weekly increment of 0.9cm per week is considered adequate.[4]

Assessing the weight for length in a particular preterm helps in determining ideal weight for length and asymmetry in growth. It is known that infants with symmetrical intrauterine growth restriction will have increased morbidity compared to their asymmetrical counterparts.[6] Many postnatal growth charts have been developed to assess the growth trends of VLBW preterms.[3-5] With improvement in feeding strategies, the subsequent growth curves show less and less time to achieve birth weight after the initial fall in weight with a lesser percentage loss in weight in these preterms. It was previously thought to be acceptable and expected for extreme low birth weight preterms to lose up to 20% of their birth weight and to take up to 3 weeks to regain birth weight – a phenomenon less frequently seen in more recent growth charts.[5]

### **Study Justification**

The current published data on growth velocities from the developed world reflect the “ideal” growth in preterms in those particular populations. Growth is tightly linked to the feeding practices in our nurseries plus the obvious influences of genetics and the environment. Different nurseries have different feeding protocols. Unlike in the developed world where there is frequent use of parenteral nutrition, our feeding protocol places emphasis on early human breast milk feeding with supplemented intravenous fluids prior to achieving full enteral feeds. This study will enable us compare the growth velocity of our ELBW preterms in our resource constrained centre to those achieved in the first world.

## **Methodology**

### **Study setting**

The study will be conducted at Groote Schuur Hospital nursery. This is a tertiary neonatal unit with a 75 bed capacity – 20 ICU and high care beds, 25 medium care beds and 30 general ward beds. The unit admits around 2000 babies every year with slightly less than 200 of these babies weighing less than 1000g. Almost half of these babies are born with intrauterine growth restriction. This could be attributed to the fact that being a tertiary referral centre, the maternity unit receives a high number of pregnancies complicated with hypertension leading to majority of the preterm deliveries. We know from unpublished data that around 16% of the mothers delivering in our maternity are HIV positive and our current rate of mother to child transmission of HIV with our current preventative strategy is less than 1%. (Harisson MC, Department of Neonatal Medicine, University of Cape Town 2011)

### **Study design**

This will be a retrospective cohort study. Patients weighing less than 1000g will be identified from a prospectively collected database. Files of babies born during the 6 month study period, that is from 1<sup>st</sup> March 2010 to 31<sup>st</sup> August 2010, will be retrieved and relevant data extracted.

### **Characteristics of study population**

These are babies that were born with a birth weight of less than 1000g during the study period, who were admitted to the nursery at Groote Schuur Hospital and who survived to discharge.

## **Recruitment and Enrolment**

All files of babies born with a birth weight of less than 1000g during the study period will be retrieved and reviewed to assess if the baby met the study's eligibility criteria. All eligible babies will be enrolled into the study.

### **Eligibility Criteria**

- Birth weight of less than 1000g
- Survived to discharge

### **Exclusion Criteria**

- Major congenital malformations
- Grade 3 or 4 IVH, hydrocephalus or PVL
- NEC (Bell's grade II or worse)
- Babies who require withholding of enteral feeds for more than 3 days, whatever the reason.

## **Research procedures and Data collection methods**

### **Weight measurements**

Babies in our unit are weighed between 5am and 6am everyday when in the ICU, high care and medium care units, and three times weekly (on Mondays, Wednesdays and Fridays) in the general wards. All babies are weighed naked on digital weighing machines that are routinely calibrated by our full time technicians in the unit. Weighing is usually skipped for the very unstable patients, for example those undergoing mechanical ventilation and continued once they

are more stable. Any unusual discrepancies noted on the weight trend, for example unusual gains or losses are usually confirmed by a repeat weighing.

For our study, weekly weights will be retrieved from the weight charts in the folders and any missing weight will be gotten from the average of the immediate weight before and after the weight in question.

### **Head Circumference**

All newborns in our unit routinely have their birth and discharge head circumference plotted on the infant's growth chart. For our study, these figures will be retrieved from the growth chart in the infant folder.

### **Feeding practice**

Feeding of neonates in our unit follows a strict protocol as described in a copy attached hitherto (appendix 1).

### **Gestational Age estimation**

The gestational age will be extrapolated from an ultrasound report done at < 20 weeks gestation and where this is not available, the Ballard score from the infant records will be used.

### **Growth velocity calculation**

Growth velocity will be determined from the weekly weights starting from day seven (as at this point, weight loss usually has reached its nadir), using the two point system (6) as shown below:

$$GV = [1000 \times (W_n - W_1)] / \{(D_n - D_1) \times [(W_n + W_1)/2]\}$$

Where:

W – weight in grams, D – day, l –beginning of time interval, n – end of time interval in days.

The calculated weekly growth velocities for the first 8 weeks or to discharge (whichever comes first) will be averaged to give the mean growth velocity of the individual baby.

Increase in head circumference was determined by dividing the gain on the head circumference at discharge from that at birth by the duration of stay in weeks.

## **Data Collection**

Data will be collected by reviewing the babies' medical records and recorded onto a data sheet (see appendix 2).

The following information will be sought:

- Date of birth
- Birth weight
- Gestation at birth
- Head circumference at birth
- Whether antenatal steroids were given or not
- HIV exposure (mum's HIV status)
- Weekly weights for the first 8 weeks or till discharge (whichever comes first)
- Predominant feed for the first 4 weeks of life

- Number of days to achieving full feeds
- Number of days to regaining birth weight
- Discharge head circumference
- Weight at discharge
- Number of days admitted

## **Data Analysis**

The information will subsequently be transferred onto an excel spreadsheet, and then transferred to STATA for analysis. Data will be explored for distribution, baseline characteristics of the study population will be sought and measures of association between the different variables will be undertaken.

## **Study definitions**

- Full enteral feeds will be defined as total enteral feeds of 150ml/kg/day.
- Time to regain birth weight will be defined as the day birth weight is achieved and sustained (or exceeded) for two consecutive days.
- Predominant feed will be taken as the type of feed given more than half the times in the first four weeks of life.
- Where a particular weight to be recorded was missing, the average of the immediate weight before and after the sought weight will be taken as representative.
- Small for gestational age babies were babies that fell below the 10<sup>th</sup> percentile for birth weight on the Lubchenco growth charts.[7]

## **Biases and quality assurance**

- Weights are always taken at around the same time of the night
- Accuracy of the weighing scales in the unit is regularly checked and confirmed by the technicians
- Babies in the unit are routinely weighed without any clothes on

## **Study Limitations**

Use of retrospective data decreases certainty of our measurements

## **Data safety and Monitoring**

The data sheets will be maintained in a locked cabinet in the department of Neonatal Medicine offices. The data in the computer is anonymous keeping patient confidentiality and access will be password protected.

## **Description of Risks and Benefits**

There are no foreseeable risks to the patients in this study as there will be no contact with the patients given the retrospective nature of this folder review study. Results of this study may benefit our future patients as comparison of our data with the rest of the world may subsequently form a basis for change and improvement in our current practices.

### **Informed consent process**

This study will not require individual consents from the parents and guardians of the study infants given the nature of the study. The study has been approved by the University of Cape Town Human Research Ethics Committee.

### **Privacy and confidentiality**

Privacy and confidentiality shall be maintained throughout the study as there shall be no record of any identifiable information like name or folder numbers of the patients right from recruitment to analysis and results presentation.

### **Reimbursement for Participation**

There shall be no reimbursement to any of the study participants for taking part in this study.

### **Emergency care and insurance for research – related Injuries**

This is not applicable for this study.

### **What happens at the end of the study?**

Results of the study will be made available to faculty members and will be published in a peer reviewed medical journal.

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## Appendices

### Appendix 1:

#### Feeding Protocol For Extremely Low Birth Weight Infants At Groote Schuur Hospital

##### Nursery

Intravenous fluids are started on day 1 as shown below:

Category	Fluid type	Day 1 (ml/kg/day)	Glucose (mg/kg/min)
<800g	5% Dextrose	100	3.5
800 – 1200	10% Dextrose	90	6.25

Enteral feeds are usually started on day 2 of life unless the infant is very unstable. It usually takes about a day to get the mothers settled post caesarean section or just settled in the wards for those who delivered NVD and generally it's the kind of duration it will take to have the doctors counsel the mothers on breastfeeding and obtain consent for use of donated breast milk. Thus, enteral feeds usually are prescribed, available and running by the second day of life. The feeds are usually increased by 20mls-35mls/kg everyday. The corresponding intravenous fluids are decreased appropriately to fit into the prescribed total fluid intake for the day as shown below:

FEED/IVF	DAY						
	1	2	3	4	5	6	7
Total Fluid	90	100	130	150	150	150	150
IVF	2.6-3.7	2-3mls/hr	2.7-4.4	3.3-5.2	2.2-4.2	1.2-3.2	-
FEEDS	NIL/1mlx6	1mls/hr	2mls/h	3mls/hr	4mls/hr	5mls/hr	6mls/hr

Once the baby is off intravenous fluids, enteral feeds are increased at the same rate till a total volume of 200ml/kg for those on breast milk and 160 – 180mls/kg/day for those on formula

feeds. The fluid is switched to 10% Neonatalyte or 5% Paediatric infants maintenance solution (for hyperglycaemic infants) after 48 hours.

Total perenteral nutrition is initiated if there is a reason to keep baby nil by mouth for more than 3 days.

The contents of the fluids used as shown on the container are given below:

	SABAX® Neonatalyte Per 1000mls	SABAX® PMS Per 1000mls
Glucose monohydrate	110.00g	55.00g
Potassium Chloride	1.12g	0.89g
Calcium Chloride Dihydrate	376mg	
Magnesium Chloride Hexahydrate	102mg	
Sodium Lactate	2.24g	
Phosphoric Acid	376mg	
Sodium Chloride		2.05
Approximate millimoles		
Sodium	20	35
Potassium	15	12
Calcium	2.5	
Magnesium	0.5	
Chloride	21	47
Lactate	20	
Phosphate (as HPO <sub>4</sub> <sup>-</sup> )	3.75	
Hypertonic approximate milliosmoles	645	372
Approximate pH	4.2	4.0

### Enteral feeds

The enteral feeds used in order of preference are:

1. Mother's own breast milk (fresh or pasteurized as is the case with HIV positive mothers)
2. Donated breast milk (pasteurized breast milk from screened donor mothers)
3. Preterm formula feeds

Contents of the breast milk fortifier - FM85® and Kiddivit® multivitamin drops as given on the packet inserts are shown below:

	Contents per 7.5g of FM85	Contents per 0.6 mls of kiddivits multivitamin drops
Vit A (I.U)	750	3000
Vit D (I.U)	150	400
Vit E (I.U)	4.5	
Vit K (µg)	6	
Vit C (mg)	15	50
Thiamine (B1) (mg)	0.075	1.5
Riboflavin (B2) (mg)	0.15	1.2
Niacin (B3) (mg NE)	1.2	10
Folic acid (µg)	60	
Vit B6 (mg)	0.075	0.5
Fat (g)	0.3	
Protein (Whey) (g)	1.5	
Carbohydrate (g)	5.03	
Energy (kcal)	27	
Calcium (mg)	112.5	
Phosphorus (mg)	67.5	
Magnesium (mg)	3.6	
Sodium (mg)	30	
Potassium (mg)	63	
Chloride (mg)	25.5	
Iron (mg)	1.95	
Copper (µg)	60	

## Supplements

- On attainment of full feeds, those on breast milk feeds have their feeds fortified with FM85 (Nestlé Nutrition) and receive additional multivitamin drops.
- All infants less than 32 weeks corrected gestation receive additional oral supplementation of sodium chloride at 2 to 3 mmol per day for 4 – 6 weeks.

- Iron is given to all infants as from 2 weeks at 2-4mg/kg/day to discharge.
- Oral phosphate at 0.5 to 1 mmol is added from 4 to 6 weeks depending on serum calcium, phosphate and alkaline phosphate levels.

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## Appendix 2 - Sample Data Capture Sheet

ID	DOB	SEX	GEST	GR	HIV	HC1	HC2	BWT	WT1	WT2	WT3	WT4	WT5	WT6	WT7	WT8	DA	DWT	DBW	DFF

### KEY

ID Study identification number

DOB Date of birth

SEX Gender

GEST Gestation at birth

GR Growth restriction

HIV HIV exposure status

HC1 Head circumference at birth

HC 2 Head Circumference at discharge

BWT Birth weight

WT1 – WT8 Weight at end of week 1, week2, week3 , etc

DA Age at discharge in days

DW Weight at discharge

DBW Days to regaining birth weight

DFF Days to establishing full enteral feeds

# **PART B: LITERATURE REVIEW**

Word count: 3,512

## **OBJECTIVES OF THE LITERATURE SEARCH AND REVIEW**

The objective of the literature search and review in this study was to

- Summarize published literature on growth monitoring strategies, growth patterns and growth velocity of extremely low birth weight preterm babies
- Summarize literature on current feeding practices and controversies surrounding the extremely low birth weight preterm baby
- Summarize the current recommendations on feeding and growth of the extremely low birth weight preterm baby

## **LITERATURE SEARCH STRATEGY**

A comprehensive literature search was undertaken by searching MEDLINE through PUBMED (1975 – Feb 2011) and the Cochrane library. The key words used were: growth velocity; growth patterns; enteral nutrition and parenteral nutrition. The search was limited to infants of 0 to 24 months and articles in the English language.

Standard text books of Neonatology and Gastroenterology were also referred to. Relevant references quoted in these text books and the already accessed journal articles were also referred to for additional information. The articles finally quoted in this review are those found to be most recent and relevant to the topic in discussion.

## LITERATURE REVIEW

### Introduction

It has been observed the world over that extremely low birth weight (ELBW) preterm babies are increasingly surviving thanks to advances in perinatal and neonatal care.[1,2] The growing challenge has been to ensure optimal growth by implementing feeding strategies that address delivery of optimal calories and proteins at the same time keeping feeding associated morbidities to the minimum. The trend in practice is to aim for early and aggressive use of parenteral nutrition with early introduction of proteins, and early initiation of enteral feeds. Our practice involves early initiation of enteral feeds with expressed breast milk where feasible, and concomitant use of intravenous dextrose enriched with electrolytes in place of parenteral nutrition in most cases. Parenteral nutrition is reserved to neonates who have been kept off enteral feeds for more than three days for one reason or the other. Our judicious use of parenteral nutrition is guided by resource constraints and fear of infection given the relative overcrowding in our unit.

It is now well established that early nutrition has a great influence on long term neurocognitive outcomes.[3-9] Ehrenkranz and colleagues recently demonstrated the dangers of poor growth in their study which clearly demonstrated the association between growth velocity and neurodevelopmental outcomes at 18 – 22 months corrected age for these ELBW preterm babies.[9] In their cohort of 490 ELBW infants, they found that as the rate of weight gain increased, the incidence of cerebral palsy (CP), mental developmental index (MDI) and psychomotor developmental index (PDI) scores <70, abnormal neurologic examination, and neurodevelopmental impairment (NDI) and the need for rehospitalization fell significantly.

Similar findings were observed as the rate of head circumference growth increased. Latal-Hajnal and coworkers[7] also demonstrated the importance of postnatal growth in their study in which small for gestational age (SGA) children who showed substantial catch-up growth with weight above the 10th percentile at 2 years of age, had neurodevelopmental outcomes comparable to appropriate for gestational age (AGA) children whose weight remained appropriate for age, whereas SGA children who remained below the 10th percentile by age 2 were impaired in their motor development. In this study of VLBW children, postnatal growth pattern rather than SGA status, was found to be significantly associated with adverse neurodevelopmental outcome at 2 years of age.

Following previous feeding strategies, extra uterine growth restriction was a common phenomenon in many of these published works.[3-9] This primarily arose from an accumulating protein and calorie deficit from the first weeks of life as demonstrated by Embleton et al.[10]The greatest influences on the growth velocity of these babies as shown by Olsen et al[11] has been the protein and caloric intakes. Stephens and colleagues went further to demonstrate that what we feed these babies as early as the first week of life influences the neurodevelopmental outcomes at 18 months corrected age.[12]

## **Monitoring Growth**

Growth can be monitored adequately in these babies by anthropometry - the measurement of body weight, length, head circumference, and, to a lesser extent, skin fold and arm circumference. Weight is a good indicator of total body composition. It however fluctuates in the short term with hydration status and contraction of the total water compartment postnatally. Due to its ease of measure, it still offers us the best tool to monitor growth in our babies. The initial

weight loss reaches its nadir at around the fourth to the sixth day of life.[3,13] Once birth weight is regained, subsequent weight gain of 10 to 20 g/d for infants less than 27 weeks GA and 20 to 30 g/d for infants older than 27 weeks GA is desired. Weight gain is evaluated weekly and expressed relative to current body weight (g/kg/d), with ideal relative weight gains ranging between 10 and 20 g/kg/d to mimic intrauterine growth rates.[14,15]

Length on the other hand is more reliable as it is seldom influenced by variations in hydration status. It represents an increase in the lean tissue mass. It is a better indicator of long term growth. However, it is more difficult to take as it requires two operators and is more prone to errors. Ideally, the length should be measured weekly to the nearest 0.1cm. The expected incremental gain in the crown – heel length is around 0.9cm per week. Increase in the head circumference usually correlates well with the overall growth of the neonates and their long term neurodevelopmental outcomes.[9] There may be an initial reduction in the head circumference of the very preterm infants in the first week of life correlating with receding edema. Thereafter, a weekly increment of around 0.9cm per week is considered adequate.[3]

Assessing the weight for length in a particular preterm helps in determining ideal weight for length and asymmetry in growth. It is known that infants with symmetrical intrauterine growth restriction will suffer more morbidity compared to their asymmetrical counterparts. Many postnatal growth charts have been developed to assess the growth trends of VLBW preterms.[3,13,16] With improvement in feeding strategies, the subsequent growth curves show less and less time to achieve birth weight after the initial fall in weight with a lesser percentage loss in weight in these preterms. It was previously thought to be acceptable and expected for extreme low birth weight preterms to lose up to 20% of their birth weight and to take up to 3

weeks to regain birth weight – a phenomenon less commonly seen in more recent growth charts.[13]

Nutritional assessment can also be made by doing whole body composition analysis. This can be done using Dual-energy x-ray absorptiometry (DXA) which measures lean and fat mass and bone mineral content. The other methods that can be used to assess body composition include air displacement plethysmography (ADP), total body electrical conductivity (TOBEC), and bioelectrical impedance (BIA).

### **Laboratory measurements**

Many markers have been identified and used to monitor infants as indicators of nutritional status, but none is without problems as they are all affected by other factors like disease status, infection, intake, hydration status etc. Blood urea Nitrogen (BUN), a byproduct of protein degradation has been used to monitor adequacy of protein intake in the past. Its level however is influenced by hydration status. Prealbumin and retinol-binding protein (RBP) concentrations appear to correlate better with nitrogen balance during nutrition therapy and have been shown to be a more sensitive measure of protein and calorie intake in small premature infants.[17]

### **Calculating growth velocity**

Actual growth velocity is calculated by the formula

$$GV = \frac{[(W_{n+1} - W_n) \times 1000]}{[(W_n + W_{n+1})/2]}$$

Where  $W_n$  = weight in grams on day “n” and  $W_{n+1}$  = weight in grams on the following day. Daily changes in the growth velocity are calculated and the average growth velocity for the duration in question is then reported in g/kg/day. This is a laborious endeavor, which has led to simpler mathematical methods for estimating growth velocity to be developed. These are 2-point models using the difference between weights at 2 time points divided by time and weight (either birth weight or average weight), linear regression models that are normalized for either birth weight or average weight, and an exponential model.

The two point average weight model’s formula:

$$GV = \frac{1000 \times (W_n - W_l)}{\{(D_n - D_l) \times [(W_n + W_l)/2]\}}$$

Where W=weight in grams, D= day, l=beginning of time interval and n=end of time interval in days.

The Exponential Model’s formula:

$$GV = [1000 \times \ln(W_n/W_l)]/(D_n-D_l)$$

The linear regression model formula:

Linear birth weight (BW) model: linear regression of weight (in grams) versus time (in days),

where

$$GV = [1000 \times (\text{slope of regression line})/BW]$$

Or

Linear average weight model:

Linear regression of weight (in grams) versus time (in days), where estimated

$$GV = [1000 \times (\text{slope of regression line})] / [(W1 - Wn)/2]$$

These formulas have been compared to the actual growth velocity and their accuracy tested.[18,19] In these comparisons, it was noted that the exponential method was most accurate, being influenced minimally by increase in the duration of stay or by decrease in birth weight, having mean absolute errors of 0.02% to 0.10% in comparison to the true growth velocity. The 2-point and linear models were highly inaccurate when birth weight was used in the denominator, with mean absolute errors of 50.3% to 96.4%. The 2-point and linear models were fairly accurate when average weight was used in the denominator, with mean absolute errors of 0.1% to 8.97% . These two latter methods were however highly influenced by increasing duration of stay and birth weight.

### **Feeding the ELBW preterm baby**

As eluded to earlier, studies have well established the fact that the greatest influence on the growth velocity of these ELBW preterm babies is their protein and caloric intake.[11] Because of their gut immaturity and associated enzyme and hormone inactivity, these babies are never put on full enteral feeds from the first day of life. In fact, until recently, neonatologists have been extremely cautious in initiating and advancing enteral feeds taking up to 21 days to the establishment of full enteral feeds.[3-9] Inevitably, growth charts from these old studies show a longer duration to achieving birth weight after the initial drop with a corresponding greater percentage loss of birth weight. It is well established that ELBW infants who receive glucose alone lose approximately 1.2 g/kg per day of protein, corresponding to a daily loss of 1% to 2% of their total endogenous body protein stores. It is also well established that what we feed these

babies as early as the first week of life influences their neurodevelopmental outcomes at 18 months corrected age.[12] This information has triggered increased interest in the administration of proteins (amino acids) early after delivery as studies have shown that administration at rates of 3g – 3.5g/kg/day is both safe and associated with better postnatal weight gain and head circumference growth. Supplementation at these rates lead to intrauterine protein accretion and plasma amino acid levels close to those achieved in intrauterine life.[20]

In the recent past, there has been more and more interest in early initiation of breast milk feeds to preterm babies. Excitement reigns as to the protective effects of breast milk and its short and long term benefit to the preterms – including, but not limited to gut priming, promotion of physiological and endocrine functions of the gut, better long term neurodevelopment, better visual development, protection against late onset sepsis, and a reduction in the incidence of NEC. There is now a general consensus that for stable preterm infants, oral feeds should be started on day 1.[21] Similar recommendations are being made for the sick preterm, though understandably, there is still a cautious approach among the neonatologists with concerns of Necrotising Enterocolitis (NEC).

It has been shown in RCTs that advancing feeds at the higher rate of 30 - 35ml/kg/day as compared to the traditional lower rate of 15-20mls/kg/day is safe and has the added benefit of earlier attainment of birth weight with no increase in the incidence of NEC.[22,23] NEC is the main reason for the cautious approach taken to feeding the sick and less stable preterms and the reason for the cautious approach in feed advancement as captured in a recent survey of NICU feeding practices in the USA.[24] In this survey, despite data showing that more rapid feeding

advancement is safe, more than 80% of respondents increased feedings at rates of 10 to 20 mL/kg per day across all weight categories. It is known that the infants at highest risk of developing necrotising enterocolitis (NEC) are those born preterm, those with growth retardation, those with poor blood flow in utero and unstable infants on ionotropes.

In a recent Cochrane review,[25] the trials analysed provided no evidence that delayed introduction of progressive enteral feeds affected the incidence of necrotising enterocolitis, mortality or other neonatal morbidities. In view of the small number of participants, important beneficial or harmful effects could not be excluded. Furthermore, the total number of 115 (very few of whom were ELBW) in this trial was small and cannot be used to guide clinical practice. It was the authors' conclusion that further large pragmatic randomised controlled trials are needed to determine how the timing of the introduction of progressive enteral feeds affects important clinical outcomes. Unfortunately, this lack of properly designed and executed randomized control trials still prevents us from making firm recommendations on the feeding dilemmas in the high risk preterms. Retrospective studies, however, have raised concerns that early enteral nutrition of preterm infants may lead to an increased risk of NEC.[26] Most prospective, randomized trials show that initiating enteral nutrition within the first 3 days of life compared with a more delayed introduction improves time to reaching full enteral nutrition and improves weight gain.[27-29] Other potential benefits include decreased incidence of osteopenia, decreased need for central venous catheters, decreased cholestasis, and decreased incidence of sepsis.[30-32] None of these studies showed an increased risk of NEC. Delays in the introduction of enteral nutrition often are intertwined with the controversy regarding the safety of enteral nutrition when an umbilical artery catheter (UAC) is in place. The presence of a catheter in the aorta may alter intestinal blood flow and increase risk of ischemia. Intestinal blood flow does not

seem to be affected by the presence of a UAC. Several studies show no association between the incidence of NEC and early feedings with a UAC in place.[27, 33]

A recently concluded large multicentre study in Britain looking at early versus late initiation of enteral feeds to growth restricted babies born after abnormal antenatal Doppler is yet to have its results published. The Abnormal Doppler Enteral Prescription Trial (ADEPT) is likely to shed light as to how to optimally feed the high risk preterm.[34] There is consensus however, that implementing a standard feeding protocol in the unit will in itself help in optimizing growth and minimizing incidences of NEC.[35]

### **Benefits of early enteral feeds and use of breast milk**

After birth there is rapid colonization of the baby's gut with a variety of microbial species setting up the beginning of a cross talk between the gut and its microflora with implications for immune, inflammatory and allergic responses. Babies born vaginally tend to have their guts colonized earlier than those born via cesarean section as they are exposed to maternal vaginal and colonic flora during delivery. Some bacteria are almost always pathogenic, such as clostridia, pseudomonas, staphylococcus and proteus. Others can be either pathogenic or beneficial, such as Escherichia coli, Bacteroides and Enterobacteriae. Others are thought to be primarily beneficial, most commonly Lactobacillus and Bifidobacterium species.[36]

With the increasing population of the facultative anaerobes in the gut such as Enterobacteriae, Enterococci, and Staphylococci, oxygen is consumed allowing for colonization by anaerobic bacteria. Thereafter colonization is influenced by feeding, with bacteria introduced via breast milk or formula feeds along with factors, particularly in breast milk, which influence colonization.[37] Introduction of solid foods and the environment further affect the intestinal

flora. This ultimately leads to the complete adult colonization by 2 years of age with 400-1000 different species and a stable pattern that is unique to each individual.

The gut has an elaborate defense system designed to limit the bacteria to the intestinal lumen. This includes peristalsis, gastric acid, proteolytic enzymes, intestinal mucus, cell surface glycoconjugates, and tight junctions between intestinal epithelial cells. There is in addition, intestinal T and B lymphocytes, sIgA, human defensins secreted by the Paneth cells, and intestinal trefoil factor secreted by the intestinal epithelium itself. These will limit the growth of bacteria that managed to breach the physical barrier.

Three cell types – the M cells, the surface enterocytes and the dendritic cells – interact with the intestinal microflora tolerating commensal bacteria, while triggering inflammatory responses for pathogenic bacteria.

M cells are found throughout the digestive tract in the specialized follicle associated epithelium of mucosal lymphoid follicles or Peyer's patches. They transport bacteria to the subepithelial dendritic cells via endocytosis, pinocytosis or phagocytosis.

Surface enterocytes recognize bacteria via Toll-like receptor (TLR). Bacterial attachment to the TLR leads to activation of nuclear factor kappaB (NF- $\kappa$ B), which in turn activates transcription of genes including cytokines such as IL-6 and TNF $\alpha$ , chemokines such as IL-8, adhesion molecules, and regulators of apoptosis.

Antigens from either food or bacteria that come into contact with the intestinal epithelium are presented by dendritic cells in the context of MHC class II molecules to naïve T lymphocytes in the Peyer's patches, with resultant either T helper type 1 (Th1) or T helper type 2 (Th2) responses. Inappropriate Th1 responses are associated with autoimmune disease while

inappropriate Th2 responses are associated with allergy, thus the association of early feeds with autoimmune disease and allergy later in life.

Healthy term infants staying with their mothers and breastfeeding will acquire genetically compatible microbiota which improves nutrition and fortifies gut's epithelial barrier.[38] On the other hand, abnormal gut flora will increase the incidence of late onset sepsis and NEC. Factors which lead to abnormal gut colonization include birth by cesarean section, hygiene practices, prolonged antibiotic administration, reduced bowel motility, immature epithelial host defenses, type or mode of nutrition, and parenteral nutrition. Needless to say, our very low birth weight and ELBW preterms, the bulk of whom are born via emergency cesarean section for maternal reasons like elampsia and pre-eclampsia, snugly fit into this risk category for abnormal gut colonization.

Studies have demonstrated many beneficial effects of the intestinal flora. Bacteria are responsible for the provision of essential nutrients such as vitamin k, vitamin B12, and short chained fatty acids such as butyrate. Bacteria are important for the metabolism of polysaccharides saving the host from expending energy for this process. Through competitive colonization, nonpathogenic bacteria reduce colonization of the gut by the pathogenic bacteria. Certain bacteria such as E. Coli, Streptococcus thermophilus, Lactobacillus, and Bifidobacterium protect against cell death associated with pathogenic bacteria. Commensal bacteria interact with the paneth cells promoting the development, maintenance and repair of the intestinal villus. The intestinal flora is also responsible for the maturation of the gut with improvement of its absorptive function. It has been demonstrated that the intestinal barrier function is compromised when the gut is colonized by pathogenic bacteria such as Salmonella but improves with

colonization with commensal bacteria such as E. Coli, Streptococcus thermophilus, Lactobacillus and Bifidobacterium.[39]

In the recent past, there has been increasing excitement with the discovery of more and more beneficial and bioactive components in breast milk.[40] Many benefits of breast milk to the preterm have been elucidated including improved defense against infection, better nutrient absorption, reduction in the incidences of NEC and sepsis, gut priming, promotion of physiological and endocrine functions of the gut, gut growth and better long term immunity and neurodevelopment.[41-45] It is known that human breast milk contains prebiotics and probiotics and promotes appropriate initial gut colonization with beneficial bacteria at the expense of pathogenic bacteria. Breast milk also selectively nourishes the beneficial intestinal microbiota at the expense of the pathogenic bacteria with its many prebiotics. It is speculated that proper gut colonization and establishment of a balanced microbiome in the preterms' gut is associated with the many beneficial effects observed in the breast milk fed babies.

## **SUMMARY**

1. The recommendations on feeding the ELBW preterm may be summarized as initiation of parenteral nutrition on day 1 of life, optimizing caloric and protein intake with concomitant early initiation of enteral feeds.
2. The target growth velocity for the ELBW preterm is 15g/kg/day, which aims at mimicking the third trimester intrauterine growth rate.

3. Post natal growth velocity is an important and independent risk factor for later neurodevelopmental outcomes in ELBW preterm babies.
4. Protein and caloric intakes have the greatest influence on the growth velocity in this group of babies. The benefits and safety of early enteral feeds and of breast milk are now well established.

### **GAPS FOR RESEARCH**

Due to resource constraints, our feeding practice deviates from current recommendations. There is a need to document how ELBW preterm babies in our unit grow given our feeding practice which encourages early enteral feeds with breast milk with supplemental intravenous dextrose water in comparison to other babies in the developed world who receive parenteral nutrition.

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# **PART C: THE ARTICLE**

Written as per the instructions from “Archives of Diseases in Childhood – Fetal and Neonatal Edition.

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11<sup>th</sup> August 2011

The Editor,

Archives of Diseases in Childhood,

Fetal and Neonatal Edition

Dear Sir/Madam,

RE: SUBMISSION OF ORIGINAL ARTICLE FOR PUBLICATION

I hereby submit our original research report titled "Growth velocity in extremely low birth weight preterms in a tertiary neonatal unit in South Africa" for consideration for publication. None of the authors have any conflict of interests to declare.

Thank you.

Yours faithfully,

Dr. M. O. Lango

**GROWTH VELOCITY OF EXTREMELY LOW BIRTH  
WEIGHT PRETERMS AT A TERTIARY NEONATAL UNIT IN  
SOUTH AFRICA**

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KEY WORDS: Growth velocity. Growth rate. Growth curves. Extremely low birth weight. Early enteral nutrition.

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## **ABSTRACT**

**Introduction:** There is wide variation in the feeding practices of extreme low birth weight (ELBW) preterms often guided by tradition and resources. The feeding regimen at Groote Schuur Hospital (GSH) nursery, a tertiary neonatal unit, follows a restricted use of parenteral nutrition and concentrates on early introduction of breast milk. There is a need to determine if this approach achieves acceptable growth velocity.

**Objectives:** This study aims to describe the growth velocity of ELBW babies at GSH.

**Design:** This was a retrospective cohort study.

**Methodology:** Infant hospital records of all ELBW born at GSH from 1<sup>st</sup> March to 31<sup>st</sup> August 2010 were accessed from a previously collected database and relevant data extracted. Growth data was collected from birth to 8 weeks post natal age or discharge, whichever came first.

**Results:** Ninety one ELBW babies were born during the study period. Forty were excluded from the study. Thirty died before discharge and 10 were excluded for other reasons. The mean (SD) gestation of the cohort was 28.5 (1.6) weeks and the median (range) birth weight was 875(640 to 995)g. The overall mean (SD) growth velocity was 14 (2.9) g/kg/day. There was no statistically significant association between the growth velocity and the type of feed given, days to establishing full enteral feeds, time to regaining birth weight, HIV exposure status, intra-uterine growth restriction or exposure to antenatal steroids.

**Conclusion:** In our cohort of ELBW infants, growth velocity was within the range currently deemed acceptable by international consensus.

## **INTRODUCTION**

There has been improved survival of extremely low birth weight (ELBW) infants in recent times.[1] With this came the challenge of supplying nutrients to these infants to match their in utero accretion rates. There is a wide variation in feeding practices across nurseries primarily guided by tradition and available resources.[2,3] In utero, the fetus grows at approximately 16g/kg/day as from 23 to 37 weeks gestation.[4] This forms the basis for the current American Academy of Pediatrics (AAP) recommended target growth rate of 15g/kg/day for the ELBW preterm.[5]

The low protein and caloric content of breast milk leading to the need for unfeasibly large enteral volumes together with gut immaturity prevalent in ELBW infants in the first days of life forms the rationale for early parenteral nutrition. However, early establishment of full enteral feeds has been associated with better postnatal growth.[6-8] Due to limited resources and capacity, our practice involves early initiation of enteral feeds with expressed breast milk where feasible, with progressive advancement of these feeds and concomitant use of intravenous dextrose enriched with electrolytes. Parenteral nutrition is reserved for the infants unable to tolerate enteral feeds.

This study aims to describe the growth velocity of our cohort of ELBW infants and to compare this with internationally acceptable benchmarks.

## **SUBJECTS AND METHODS**

### **Setting**

The study was carried out in the tertiary neonatal unit at Groote Schuur Hospital in Cape Town South Africa. This 75-bed unit admits approximately 2000 babies every year, 10% of whom are ELBW.

### **Study population**

This was a retrospective cohort study. Patients were identified from a previously collected database of ELBW preterms. All ELBW babies born and admitted into Groote Schuur Hospital's neonatal intensive care (NICU) from 1<sup>st</sup> March to 31<sup>st</sup> Aug 2010 who met the eligibility criteria and survived to discharge were included into the study.

We excluded babies with the following abnormalities: major congenital malformations, necrotizing enterocolitis Bell stage II or greater, grade 3 or 4 intraventricular haemorrhages or periventricular leucomalacia (PVL).

The following data were collected by chart review: Demographic data, weekly weights, head circumference, type of feed, days to full feeds, days to regaining birth weight, exposure to HIV and antenatal exposure to steroids. Data were recorded for the period from birth to day 56 of life or discharge, whichever came first.

### **Statistics**

Data were analyzed using Stata software version 11 (Statacorp, College Station, Texas, USA). Parametric data were expressed as mean (standard deviation) while non-parametric data were expressed as median (range). The two-tailed student t-test and analysis of variance (ANOVA) were used to compare means while a logistic regression analysis was used to assess risks.

Categorical data were analyzed with the Chi-square test. Statistical significance was assumed at  $p < 0.05$ .

### **Weight measurements**

Babies were weighed between 5am and 6am everyday when in the intensive, high care and medium care areas, and three times a week when in the general wards. Unstable patients were weighed less frequently. Babies were weighed on digital weighing machines (Seca, Hamburg, Germany) that are routinely calibrated. Weekly weights from day 7 to day 56 were retrieved from the weight charts in the patient folders and any missing weights were calculated from the average of the immediate weight before and after the weight in question.

### **Gestational Age estimation**

The gestational age was extrapolated from the antenatal ultrasound report if it was done at less than 20 weeks gestation and where this was not available or was uncertain, the Ballard score[9] from the infant records was used.

### **Growth Velocity Calculations**

Growth velocity (GV) was determined from weekly weights starting from day seven (as at this point, weight loss usually has reached its nadir) using the two point system[10] as shown below:

$$GV = \frac{[1000 \times (W_n - W_1)]}{\{(D_n - D_1) \times [(W_n + W_1)/2]\}}$$

Where:

W – weight in grams, D – day, 1 –beginning of time interval, n – end of time interval in days.

The calculated weekly growth velocities for the first 8 weeks or to discharge (whichever came first) were averaged to give the mean growth velocity of the individual baby.

Increase in head circumference was determined by dividing the gain on the head circumference at discharge from that at birth by the duration of stay in weeks.

### **Study definitions**

Full enteral feeds was defined as total enteral feeds of 150ml/kg/day which gives a total calorie of 100kcal/kg/day estimated from breast milk intake which gives 67 kcal/100mls.

Time to regain birth weight was defined as the day birth weight was regained and sustained (or exceeded) for two consecutive days. The type of feed was defined as the predominant feed received in the first 4 weeks. Small for gestational age babies were defined as babies that fell below the 10<sup>th</sup> percentile for birth weight on the Lubchenco growth charts.[11]

### **Nutritional Practices**

Intravenous fluids were commenced on day 1 at 80-100mls/kg/day with an electrolyte enriched 5% or 10% dextrose solution depending on blood glucose levels. Enteral feeds were usually started on day 2 of life at 10-20mls/kg/day. The feeds were increased by 20mls-35mls/kg every day. Intravenous fluids were decreased appropriately to achieve the prescribed total fluid intake which increased by 10 to 20mls/kg/day until a total fluid intake of 150mls/kg/day was achieved. After attainment of full enteral feeds at 150ml/kg/day, feeds were increased further by 20-

35mls/kg/day to a maximum of 200mls/kg for breast milk and 160-180mls/kg/day for formula feeds.

The enteral feeds of choice in order of preference were mother's own breast milk (pasteurized for HIV positive mothers), donated breast milk (pasteurized breast milk from screened donor mothers) or preterm formula.

On attainment of full feeds, those on breast milk feeds had their feeds fortified with a breast milk fortifier - FM85<sup>®</sup> (Nestlé Nutrition) at 1g per 20mls and received additional multivitamin drops at 0.3mls daily to discharge. All infants less than 32 weeks corrected gestation received additional oral supplementation of sodium chloride at 2 to 3 mmol per day till 32 weeks corrected gestational age. Iron supplements were given to all infants as from 2 weeks of age at 2-4mg/ kg /day to discharge. Oral phosphate at 0.5 to 1 mmol was added from 4 to 6 weeks and the dose titrated according to the serum calcium, phosphate and alkaline phosphate levels.

## **RESULTS**

Figure 1 shows how the study population was derived. Ninety one babies weighing less than 1000g were born and admitted to the GSH nursery during the 6 month study period (from 1<sup>st</sup> March to 31<sup>st</sup> Aug 2010). Forty were excluded from the study – 30 died before discharge, two were transferred out before regaining birth weight, two had hydrocephalus, one had congenital cytomegalovirus (CMV) infection and one had PVL. Four files were not available for analysis, leaving a total study population of 51.

Table 1 shows the baseline characteristics of our study population.

The median birth weight of the cohort was 875(640g-995)g. The mean gestation of the cohort was 28.5 (1.6) weeks. The overall mean growth velocity for the entire cohort was 14.0 (2.9) g/kg/day, while the mean increase in head circumference was 0.73 (0.37)cm per week.

The median duration of admission was 55 (36-93) days while the median discharge weight was 1620 (1540-2080) g. The median duration to achieving full feeds was 7 (6-12) days, while the median number of days to regaining birth weight was 15 (1-28).

Table 2 shows the relationship between growth velocity and other variables.

There was no statistically significant variation in the mean growth velocity with respect to the presence of growth restriction, type of feed, sex, HIV exposure or exposure to antenatal steroids.

Table 3 shows the results of a logistic regression analysis corrected for sex, looking at predictors of a higher growth velocity in our cohort. That is, a growth velocity greater than the cohort's mean growth of 14g/kg/day. None of the factors analyzed were statistically significant predictors.

## DISCUSSION

The growth velocity of our study population of 14g/kg/day approximates the target growth as recommended by the AAP of 15g/kg/day.[5] Despite lack of parenteral nutrition in the first days of life in our cohort, the overall GV is similar to those reported in current literature.[2,12-14]

This could be attributed to the rapid achievement of full enteral feeds in our cohort - median of day 7(6-12), indicating that half of our cohort received a total caloric intake from breast milk of 50kcal/kg by day 3 and 100kcal/kg by day 7. In comparison, Diekman et al [13] reported the mean (SD) duration to achieving at least 100kcal/kg/day as day 10.4(4.9) while Donovan[8] reported the mean time to full feeds as day of life 12.7(8.6). Olsen and colleagues[2]

investigating the possible contributors to the differences in growth velocities seen in 6 different level 3 neonatal intensive care units reported that none of the 6 NICUs had achieved a mean caloric intake of 100kcal/kg/day by day 7 and only two had achieved or surpassed this target by the 14<sup>th</sup> day of life. This study also identified caloric and protein intake as the most significant contributors to the differences in growth velocities. Benefits to our cohort may have resulted from early maturation and adaptation of the gut by the early introduction of enteral feeds. It has previously been shown that early enteral feeds promote intestinal villi growth, development, and improve their absorptive and endocrine function.[15]

Olsen et al[2] calculated growth velocity of their cohort by subtracting the weight on day 3 from that of day 28 and dividing this by the number of days (25) and the birth weight. The mean growth velocities of the six NICUs they studied were 14.7, 12.5, 12.0, 9.4, 11.2 and 8.6 /kg/day. Early parenteral nutrition was used in all the six nurseries. Diekman et al[13] reported a mean growth velocity of 15g/kg/day in a cohort of 163 ELBW infants. Their feeding protocol involved initiation of enteral feeds together with parenteral nutrition on day 1 of life with gradual

advancement of the enteral feeds. This was a cohort similar to ours in terms of the weight distribution and enteral feeding practice other than for the early use of parenteral nutrition. Caution is however advised in comparing the growth velocities because of the different methods of calculation in use.[16] For instance, Martin et al[17] reporting on the growth velocity of a recent large cohort of ELBW preterms with early initiation of enteral feeds reported a mean growth velocity of 18.3g/kg/day when the two point method was used with the day 7 weight as the denominator, and 11g/kg/day when birth weight was used as the denominator. The exponential equation, which has been shown to be the most accurate[16] gave a mean growth velocity of 15.5g/kg/day for the same cohort.

Our cohort's mean growth in head circumference of 0.7cm per week is comparable to that reported by Ehrenkranz and colleagues.[12] This is assuring given the established strong association between postnatal head growth and later neurodevelopmental outcomes.[18-19]

A logistic regression analysis exploring the risk factors for a growth rate higher than 14g/kg/day did not identify any statistically significant risks in our cohort. Time to establishing full feeds and state of being small for gestational age have both been repeatedly shown in previous studies to be positive influences on the growth velocity.[7,12,13] It is likely that our small sample size lacked the power to show these differences.

## **CONCLUSION**

In our resource constrained setting, early enteral feeding of extremely low birth weight preterms with breast milk with concomitant administration of intravenous dextrose enriched with electrolytes until the establishment of full enteral feeds is associated with a mean growth velocity comparable to that achieved by neonates who received aggressive early parenteral nutrition with

early establishment of enteral feeds. There is need for studies to assess the possibility and benefits of more rapid advancement of enteral feeds in ELBW preterms. This may further cut down on the early nutrient deficit and improve growth velocity in this group of neonates.

### **WHAT IS ALREADY KNOWN ON THIS TOPIC**

Initiation of parenteral nutrition on day 1 of life, optimizing caloric and protein intake with concomitant early initiation of enteral feeds forms the current recommendation in feeding the ELBW preterm.

The current recommended target growth velocity for the ELBW preterm is 15g/kg/day.

Post natal growth velocity is an important and independent risk factor for later neurodevelopmental outcomes in ELBW preterm babies.

### **WHAT THIS STUDY ADDS**

This study shows how the growth velocity of ELBW preterms in a resource constrained setting receiving early enteral feeds without parenteral nutrition is similar to that of their counterparts in developed countries receiving early parenteral nutrition.

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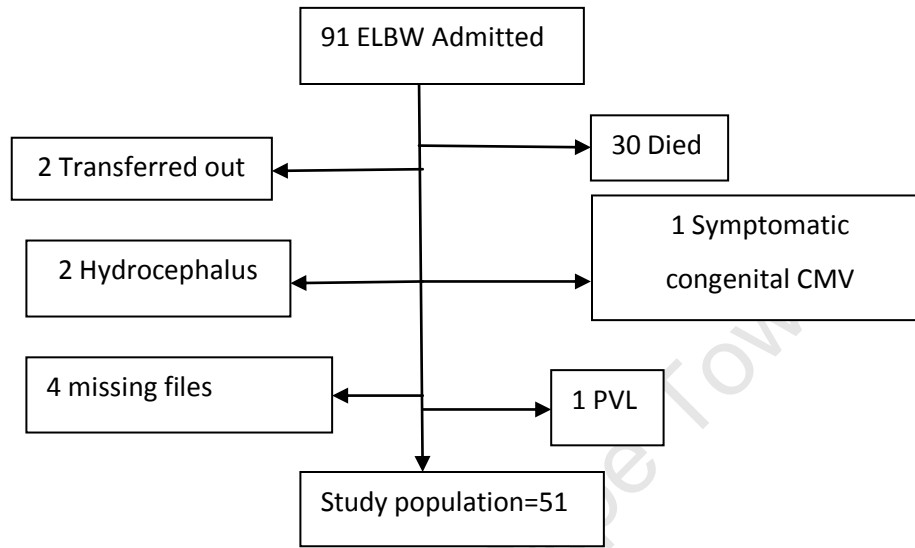
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## FIGURES AND TABLES

**Figure 1: The study population**



ELBW – Extremely Low Birth Weight; CMV – cytomegalovirus; PVL – Periventricular Leukomalacia

**Table 1: Baseline characteristics**

<b>Characteristics</b>	<b>Number (%)</b>
Male Sex	22 (43)
Small for Gestational Age	23 (45)
HIV Exposed	19 (37)
Antenatal steroids received	37 (72)
Surfactant given	21 (41)
Normal Vaginal Delivery	9 (18)
Cesarean Section	42 (82)
Antenatal pre-eclamptic toxemia	36 (70)
Unexplained preterm labor	10 (20)
Infants on expressed breast milk	30 (59)
Infants on DEBM	12 (23)
Infants on PEBM	8 (16)
Infants on formula feeds	1 (2)

DEBM – Donated expressed breast milk; PEBM – Pasteurized expressed breast milk

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**Table 2: Relationship between growth velocity and other variables**

<b>Factor</b>		<b>No.</b>	<b>Mean GV</b>	<b>Test</b>	<b>P- value</b>
Type of feed	EBM	30	14.3	ANOVA	0.09
	DEBM	12	13.8		
	PEBM	8	12.9		
HIV exposure	Exposed	19	13.6	T Test	0.46
	Not exposed	32	14.2		
Antenatal Steroids	Received	37	14.6	T Test	0.30
	Not received	14	13.7		
Appropriateness of weight for age	SGA	23	14.3	T Test	0.52
	AGA	28	13.7		
Gender	Male	22	13.1	T Test	0.05
	Female	29	14.7		

EBM – expressed breast milk; DEBM – Donated expressed breast milk; PEBM – Pasteurized expressed breast milk; HIV – Human immunodeficiency virus; SGA – Small for gestational age

**Table 3: logistic regression analysis examining the predictors of appropriate growth velocity**

Factor		Total	GV > 14		O.R.	95% C.I.
			No	%		
Type of feed	EBM	30	18	60.0	1	Ref
	DEBM	12	6	50.0	0.7	0.2 – 2.7
	PEBM	8	3	37.5	0.4	0.1 – 2.0
Appropriateness for GA	SGA	23	13	56.5	1.3	0.4 – 4.1
HIV Exposure	Exposed	19	10	52.6	1.0	0.3 – 3.3
Antenatal Steroids	Received	37	19	51.4	0.9	0.3 – 3.4
Days to achieving full feeds	Less than 8 days	31	19	61.3	2.2	0.7 – 7.2
Days to regaining birth weight	Less than 15 days	28	15	50	0.8	0.3 – 2.5

EBM – expressed breast milk; DEBM – Donated expressed breast milk; PEBM – Pasteurized expressed breast milk; SGA – Small for gestational age; GA – Gestational age

**PART D: OTHER  
SUPPORTING  
DOCUMENTS**

# ETHICS APPROVAL LETTER



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences  
Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6626 • Facsimile [021] 406 6411  
e-mail: shuretta.thomas@uct.ac.za

15 June 2011

Sent via Internal mail & Email

HREC REF: 278/2011

Dr M Lango,  
Department of Neonatal Medicine  
H-46 Rm:63  
OMB

Dear Dr Lango,

**PROTOCOL NUMBER 278/2011**

**PROJECT TITLE: GROWTH VELOCITY OF EXTREMELY LOW BIRTH WEIGHT PRETERMS AT GROOTE SCHUUR HOSPITAL NURSERY**

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

**Approval is granted until 15 June 2012**

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

**PROF MRC BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

## STATISTICS

### Exploration of variables:

Variable	Obs	Mean	Std. Dev	Min	Max	median
Duration of adm	51	57.60	13.247	36	93	54
Gestation	51	28.60	1.6257	26	33	28
Head growth	48	0.72	0.3679	0.3	2.9	0.7
Birth weight	51	858.21	100.70	640	995	870
Weight gain/kg/d	51	13.98	2.9282	6.16	19.73	14.1
Discharge weight	50	1675.8	138.07	1540	2080	1630
Days to full feeds	51	7.33	1.2596	6	12	7
Days to Bwt	51	14.11	5.7189	1	28	15

### Shapiro-Wilk W test for normal data

Variable	Obs	W	V	z	Prob>z
Duration of admission	51	0.94	2.414	1.882	0.029
Gestation	51	0.95	2.204	1.688	0.045
Head growth	48	0.58	18.761	6.237	0.000
Birth weight	51	0.94	2.446	1.909	0.028
Weight gain (wt/kg/d)	51	0.98	0.611	-1.050	0.853
Discharge weight	50	0.79	9.446	4.789	0.000
Days to full feeds	51	0.90	4.410	3.168	0.000
Days to birth weight	51	0.98	0.558	-1.248	0.893

Only the “average weight gain per kg per day” and “days to achieving full feeds” are normally distributed.

## **INSTRUCTION TO AUTHORS – ARCHIVES OF DISEASES IN CHILDHOOD, FETAL & NEONATAL EDITION**

### **Original reports**

These should report original research. (max 2500 words, excluding abstract, tables and figures, and references). The body of the report should be double spaced. The tables should be single spaced and the tables and figures should be at the end of the submission after the references.

Please note that all RCT must be appropriately registered and this should be noted on the cover page.

### **Title**

The title should have no more than 10 words. If relevant the title should include the information as to whether the paper is a randomised control trial, meta-analysis, audit, observational study, etc.

### **Abstract**

The abstract of an experimental or observational study must clearly state in sequence and in not more than 250 words (i) the main purpose of the study, (ii) the essential elements of the design of the study, (iii) the most important results illustrated by numerical data but not p values, and (iv) the implications and relevance of the results.

We require a structured abstract of up to 250 words for reports of randomised controlled trials and meta-analyses, and we encourage it for other studies, where appropriate. The following headings should be used for original research:

- Objective
- Design
- Setting
- Patients
- Interventions
- Main outcome measures
- Results: give numerical data rather than vague statements that drug x produced a better response than drug y. Favour confidence intervals over p values, and give the numerical data on which any p value is based.
- Conclusions: do not make any claims that are not supported by data in the paper in the abstract.

### **Important considerations**

- All research reports involving human subjects must contain a statement about ethics committee approval (or equivalent) at the end of the methods section.
- On a separate page (before the references) all original papers should include:
  1. "What is already known on this topic" - followed by a maximum of 3 brief statements (no more than 25 words per statement);
  2. "What this study adds" - followed by a maximum of 3 brief statements (no more than 25 words per statement).
- Illustrations should be used only when data cannot be expressed clearly in any other way. When graphs are submitted the numerical data on which they are based should be uploaded to ScholarOne as a supplementary file.

[Further details of RCTs and systematic reviews.](#)

Word count: up to 2500 words (excluding title page, abstract, tables, figures, and references)

Structured abstract: up to 250 words

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References: up to 40

Additional material may be considered as data supplements.

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6. **Reference list.**

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[Guidelines on presenting statistics.](#)

[Guidelines on RCTs: CONSORT, QUORUM, MOOSE, STARD, and Economic submissions.](#)

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Abbreviations and symbols must be standard and SI units used throughout except for blood pressure values which are reported in mm Hg.

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12 Surname AB, Surname CD. Article title. Journal abbreviation Year; **Vol**:Start page–End page.

Use one space only between words up to the year and then no spaces. The journal title should be in italic and abbreviated according to the style of Medline. If the journal is not listed in Medline then it should be written out in full.

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List the names and initials of all authors if there are 3 or fewer; otherwise list the first 3 and add et al. (The exception is the Journal of Medical Genetics, which lists all authors.)

Example references:

**Journal article**

13 Koziol-Mclain J, Brand D, Morgan D, et al. Measuring injury risk factors: question reliability in a statewide sample. *Inj Prev* 2000;**6**:148–50.

**Chapter in book**

14 Nagin D. General deterrence: a review of the empirical evidence. In: Blumstein A, Cohen J, Nagin D, eds. *Deterrence and Incapacitation: Estimating the Effects of Criminal Sanctions on Crime Rates*. Washington, DC: National Academy of Sciences 1978:95–139.

### **Book**

15 Howland J. *Preventing Automobile Injury: New Findings From Evaluative Research*. Dover, MA: Auburn House Publishing Company 1988:163–96.

### **Abstract/supplement**

16 Roxburgh J, Cooke RA, Deverall P, et al. Haemodynamic function of the carbomedics bileaflet prosthesis [abstract]. *Br Heart J* 1995;73(Suppl 2):P37.

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1. Vole P, Smith H, Brown N, et al. Treatments for malaria: randomised controlled trial. Ann Rheum Dis 2003;**327**:765–8 doi:10.1136/ard.2003.001234 [published Online First: 5 February 2002].

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Additional figures and tables, methodology, references, raw data, etc may be published online only to link with the printed article. If your paper exceeds the word count you should consider if any of the article could be published online only as a "data supplement". These files will not be copyedited or typeset.

All Appendices should be considered Online only material.

All data supplement files should be uploaded using the File Designation: Web Only files.

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