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Growth patterns in a cohort of very low birth weight infants in Johannesburg: a retrospective review

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1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Background

1.1.1 The Role of Growth Monitoring

Disease prevention and health promotion in infancy and childhood are global health priorities. This is particularly so in developing countries where the burden of disease is greatest.[1] The commitment of the United Nations (UN) and other international organizations such as the World Health Organisation (WHO) to improve the health and survival of the world's children is highlighted in programs such as the Millenium Development Goals (MDG)[2] and the Integrated Management of Childhood Illness (IMCI) program.[3] Primary healthcare is promoted for disease prevention and health promotion and the monitoring of growth in infancy and childhood forms an integral part of health care in this group regardless of birth weight.

Growth monitoring has been shown to be both useful and cost effective as a tool in primary health care.[4] The early identification of growth failure has important implications for appropriate referral, early diagnosis and timely management of illness and malnutrition in children. This is of particular importance in a developing country such as South Africa where there is a high low birth weight (LBW) rate and high levels of malnutrition.[1] The rates of underweight, wasting and stunting in under fives in South Africa have been reported as 12%, 3% and 25% respectively compared with

2%, 0% and 1% in the United States.[1] Accurate and careful measurement of growth parameters and the use of growth standards with which to compare these parameters can play a vital role in the healthcare of infants and children.

Unfortunately this is not always the case. In a study by Gerein et al[5] in Zaire it was found that, although growth measurements were accurately recorded, one third of infants with growth failure were not investigated further or referred appropriately. Furthermore, nutritional advice was found to be generally inadequate. These factors are of particular importance with regard to premature and LBW infants who may be assessed as having inadequate gains in weight or length when in fact their growth is appropriate for birth weight and gestational age. There have been anecdotal reports in our institution of VLBW infants being assessed as having growth failure at primary healthcare clinics. The infants' mothers have been strongly reprimanded by clinic staff for poor feeding practices when their growth is in fact appropriate for birth weight and gestational age.

Growth monitoring is an important tool in infant and child healthcare, particularly so in the preterm and VLBW infant. It does however require accurate assessment, insightful interpretation and appropriate further management.

1.1.2 LBW and VLBW Infants in Context

The problem of LBW and VLBW infants, with their attendant complications, is a significant one. The number of infants born with VLBW, defined as a birth weight less than 1500g, is reported as 1.43% in the USA.[6] Local statistics from South Africa are more than double with a VLBW rate of 3% being reported at Chris Hani Baragwanath Hospital for the years 2000-2002.[7] With the advent of modern neonatal intensive care and the advancement of pharmacological interventions, such as the use of surfactant therapy, the outcome of VLBW infants has improved steadily over the last 50 years.[8] This improvement in survival raises a number of management dilemmas. Amongst these is the role of growth monitoring which, although important, is complicated by differences in growth between VLBW infants and healthy term infants as well as high associated morbidity in VLBW infants.

1.2 Growth of the VLBW Infant

1.2.1. Pattern of Growth

Postnatal growth in preterm and VLBW infants is different to that of term infants and has a number of characteristic features. Growth failure is common in the early postnatal period and is followed by a period of catch up growth, defined as a growth velocity (centimeters per year) greater than the median for chronological age and gender.[9-14] This was demonstrated by Hack et al[10] in their cohort of 103 male and 92

female VLBW infants with a mean gestation of 29.8 weeks. They showed a decrease in mean Z scores for weight and length from birth to 40 weeks postmenstrual age followed by gradual catch up growth.

The period of initial growth failure may be more marked and of longer duration in preterm and VLBW infants than in term appropriate for gestational age infants (AGA). Gill, Yu, Bajuk and Astbury found that in their sample of 184 Australian infants born between 1977 and 1982 at 23 to 29 weeks gestation, the mean postnatal weight loss was 14% of birth weight at a mean of 6 days of life.[9] It took on average 18.6 days for the infants to regain their birth weight and there was a tendency in this sample to greater postnatal weight loss and longer duration to regain birth weight with increasing prematurity. This is in contrast to healthy term infants who have a median weight loss of 3.5% of their birth weight in formula fed infants and 6.6% in breastfed infants in the postnatal period. Birth weight is on average regained by 6.5 days of life in formula fed infants and by 8.3 days of life in breastfed infants.[15]

1.2.2 Factors affecting Growth

Growth of an infant, regardless of birth weight, comprises changes in weight, length, head circumference and body composition which are influenced by genetic, ethnic, hormonal (insulin-like growth factors I and II, insulin-like growth factor binding protein 3, insulin, thyroxin and the hypothalamo-pituitary-adrenal axis), nutritional and

environmental factors.[16-20] VLBW infants differ from term infants in that they are a heterogeneous group with varying birth weights and gestational ages, associated morbidities, and appropriateness for gestational age, all additional factors which affect growth and complicate our understanding of what can be regarded as normal growth in this group.

Early growth failure, especially in the first week of life, is predominantly due to loss of body water.[21] In preterm and VLBW infants growth failure is also due to inadequate nutritional intake. In a study by Embleton et al[17] approximately 45% of this variation in weight was attributed to nutrient deficiencies. Furthermore, delayed enteral feeding and delay in achieving full enteral feeds has been associated with a delay in catch up growth.[12]

Postnatal growth is also affected by ethnicity, complications during pregnancy (for example antepartum hemorrhage) and birth weight and gestational age *per se.*[9,11,12,22,23] The sex of the infant is also important in infant size with male infants being of greater weight and length from birth and throughout infancy, a phenomenon which is less marked in VLBW infants when compared with LBW infants.[23-25]

Illness in the neonatal period, including necrotizing enterocolitis (NEC), severe respiratory disease, bronchopulmonary dysplasia (BPD), severe intraventricular

hemorrhage (IVH) and late onset sepsis, are associated with failure of growth in weight, length and head circumference both in the early neonatal period and at follow up.[12,22] Prolonged use of systemic steroids (longer than 8 weeks) is another important and possibly confounding cause of impairment in postnatal growth, specifically in the subgroup of patients with BPD.[22] Factors which play a role after hospital discharge include feeding difficulties (swallowing difficulties, food refusal or both) and severe neurological disability which, once corrected for the confounding factor of feeding problems, has greatest association with impaired growth in head circumference.[22]

It is clear that the growth of VLBW infants differs significantly from that of healthy term neonates. The growth of VLBW infants is affected by a number of factors and associated morbidities making the monitoring and assessment of growth in this group difficult.

1.2.3 Catch up Growth

The initial period of growth restriction seen in VLBW infants is followed by a period of catch up growth. According to the American Academy of Pediatrics Committee on Nutrition, the rate of postnatal growth of preterm infants should approximate that of the fetus in the third trimester of intrauterine life.[26] This equates to a weight gain of approximately 15g/kg/day which is seen in preterm and VLBW infants once they have regained their birth weight.[12] The rate of catch up growth is most rapid in infancy but

extends up to 2 years of age corrected for prematurity and in some cases up to 7 years of age or longer.[9-11,27]

Even in children who do not attain complete catch up growth their rate of weight gain significantly exceeds that of term infants with an inverse relationship between birth weight and percentage weight gain by 12 months.[28] Monitoring of growth velocity and incremental changes in growth measurements of VLBW infants may be of greater value than the assessment of individual growth measurements alone as it allows a more accurate representation of the pattern of growth and the degree of catch up growth in VLBW infants.[25,28,29]

Patterns of catch up growth between infants who are born prematurely and appropriate size for gestational age (AGA) and those who are born small for gestational age (SGA) may differ. Some studies[11,12] show that catch up growth is slower in the AGA group with the majority of children catching up by school age while others show that catch up growth is slower in the SGA group.[23,30] Furthermore Radmacher,[31] in a study of 199 ELBW infants, found SGA to be the strongest predictor of extrauterine growth retardation in this group.

Strauss et al,[30] studied 818 preterm infants prospectively to assess the impact of intrauterine growth retardation and body proportionality on growth in infancy and early

childhood. They assessed growth in this cohort up to 36 months of age and found that infants born AGA showed more rapid catch up growth than infants who were growth retarded, both symmetrically and asymmetrically. Growth deficits in utero appeared to persist into early childhood and even, in some studies,[27] into adulthood.

In some cases of both SGA and AGA infants catch up growth is incomplete. Approximately 13% of VLBW infants and term SGA infants remain greater than 2 standard deviations below the mean throughout childhood.[13,32] These findings have been supported by other studies which have similarly shown failure of and delays in catch up growth in VLBW infants.[10,11,14,27,33]

The growth of VLBW infants is clearly different from that of healthy term neonates. The period of catch up growth described above is an attempt to accelerate growth in VLBW infants in order to approximate that of their term counterparts. These differences in patterns of growth again highlight the difficulties of growth monitoring and assessment in this group.

1.2.4 Growth of the South African VLBW Infant

The growth of VLBW infants in South Africa has not been extensively studied. Of note, however, is the study by Cooper and Sandler[34] on outcomes of a group of VLBW infants born in Soweto in 1990. Weight, length and head circumference were

monitored over a 12 month period and compared with a term infant growth reference. A degree of catch up growth occurred in weight, length and head circumference by 12 months CGA but was incomplete with respect to weight and length. By 12 months CGA, head circumference plotted close to the 50th percentile on average whereas weight and length had failed to catch up and were still plotting below the 25th percentile despite correcting for prematurity.

Based on limited evidence, it appears that the South African VLBW infant fails to show complete catch up growth in weight and length by 12 months CGA. This is in keeping with studies on VLBW infants elsewhere in the world. [9,11]

1.2.5 Association between LBW and the Metabolic Syndrome

Growth monitoring in VLBW infants is not only complicated by the differences in growth between VLBW infants and healthy term infants, but also by the number of complications associated with catch up growth. The association between LBW and cardiovascular and metabolic disease in adulthood was first put forward by Barker et al.[35,36] In 1989 they published a study of 5654 men born between 1911 and 1930 in England in which they found an increased risk of death from ischaemic heart disease associated with lower birth weight.[35] In 1993 they published the results of two follow up studies showing an association between lower birth weight and increased risk of developing syndrome X (defined as type II diabetes mellitus, hypertension and

hyperlipidaemia).[36] These findings have been replicated in other studies, for example those of Eriksson, Law and Ong.[37-39]

The increased risk of cardiovascular and metabolic disease in adulthood is not only due to low birth weight *per se* but also due to catch up growth in infancy and early childhood. Childhood obesity, with its associated complications, has been shown to be associated with the rate of weight gain in infancy.[40,41] Stettler et al,[41] in a cohort of 19 397 children, found that rapid weight gain in the first 4 months of life was associated with an increased risk of being overweight at 7 years of age. A similar association of rate of childhood increase in BMI with the metabolic syndrome in adulthood was found by Fall and colleagues in India.[42]

Catch up growth has both advantages and disadvantages. It is associated with improved neurodevelopmental outcomes, fewer psychosocial problems in later childhood, and lower risk of persistent short stature especially if complete by 12 months of age.[14,33,43,44] It does however increase the risk of cardiovascular and metabolic disease, including overweight and obesity, in later childhood and adulthood. Catch up growth may need to be modified to a more gradual process to avoid excess adiposity. It remains unanswered whether a slower rate of catch up growth would impair neurodevelopmental outcomes or attenuate the benefits in stature.

Growth monitoring in VLBW infants is complicated by characteristic growth patterns and high associated morbidity. The difficulties in growth monitoring are further compounded by controversies surrounding optimal catch up growth.

1.2.6 The Role of Adiposity

In addition to the pattern of growth described above, the growth of VLBW infants also differs from that of term infants in changes in body composition. An example is the degree and distribution of adiposity which is different in preterm and VLBW infants compared with larger term infants. Uthaya et al[45] studied 67 infants, 38 born preterm and 29 born at term. Growth parameters were measured and magnetic resonance imaging (MRI) was performed at 40 postmenstrual weeks to determine growth and fat distribution in both groups. The group of preterm infants showed increased abdominal fat content on MRI when compared with healthy term infants at a comparable postmenstrual age. In a second study by Ong et al,[39] the growth of 848 term infants with intrauterine growth restriction was assessed. They found an association between catch up growth in infancy with increased body mass index (BMI) and increased central fat distribution at 5 years, both known risk factors for metabolic and cardiovascular disease in later life.

The central adiposity and, in some cases, increased BMI that is characteristic of VLBW infants may be an adaptation to premature birth. Animal studies, for example

those of Vickers et al,[46] support this hypothesis and demonstrate well the association between fetal undernutrition and postnatal hyperphagia and adiposity. They suggest the process of fat and hence energy accumulation to be an adaptive response following intrauterine deprivation.

The prevention of adiposity in VLBW infants is therefore difficult. The use of calorie dense formulae in the immediate postnatal period improves catch up growth but this may be at the expense of cardiac and metabolic health in adulthood. Breastfeeding, on the other hand, has been shown to be protective against adiposity which could ameliorate this risk.[47] Lucas et al[48] studied 502 infants weighing less than 1850g and found that infants fed term donor breast milk had significantly better neurodevelopmental scores at 18 months of age than those fed term formula. Despite the relative nutrient deficiency of breast milk versus preterm formula, breast milk had a protective effect on neurodevelopmental outcomes comparable with that of preterm formula. The promotion of breastfeeding may be a solution to more regulated weight gain while optimizing neurodevelopmental outcome and cognitive performance.

The excess adiposity seen in VLBW infants relative to healthy term infants further complicates the monitoring and assessment of growth in this group.

1.3 Growth Monitoring in Preterm and VLBW Infants

1.3.1 Growth Monitoring in the Postnatal Period

The monitoring of growth (including weight for age, length for age, weight for length, head circumference for age and indicators of adiposity such as the BMI) is an essential component of the care of the VLBW infant. Growth of VLBW infants is, however, different from that of healthy term infants which complicates growth monitoring and assessment. Currently intrauterine growth charts are widely used for assessing growth up to term corrected for gestational age (CGA). Examples include the charts of Usher and McLean,[49] Gairdner and Pearson,[50] Babson and Benda,[51] Lubchenco[52] and Brandt.[53]

These charts have a number of limitations. The data is outdated, most of the sample sizes are small, male and female infants are not always charted separately, many of the samples are not representative with data collected only on infants of a specific race and from a specific geographical area and in some cases the infants' gestational ages are inaccurate as they are based on maternal menstrual history alone. One of the major limitations of all these references is that they are based on size at birth and have no reference to postnatal growth.

More recent references for the growth of VLBW infants up to term CGA have been developed, for example the references produced by Ehrenkranz et al and the National Institute of Child Health and Human Development (NICHD).[12] The data collected is more recent, the sample is large and representative of different ethnicities, estimation of gestational age is accurate, the data is collected prospectively and standardized measuring techniques by specially trained research nurses are used. However, measurements are only performed up to 120 postnatal days or a maximum of 2000g which is a significant limitation in terms of ongoing growth monitoring. In addition, infants with major congenital anomalies are excluded but those with major morbidities (such as IVH, NEC, late onset sepsis and BPD) are not. The curves therefore do not reflect optimal growth of healthy VLBW infants and cannot be used as a growth standard. Despite this, the inclusion of major morbidities, which are common in this group, may provide a more realistic growth reference than one in which they are excluded.

Another example of more recent growth references are those produced by Fenton.[54] These references are based on the earlier charts by Babson and Benda[51] with additional information obtained by meta-analysis of more recent growth data in the literature. Although an improvement on earlier references, the curves generated still have limitations. The measurements before term are obtained cross-sectionally, those beyond 40 postmenstrual weeks are derived from healthy term infants, the individual studies forming part of the meta-analysis are heterogeneous in both methodology and results which affects the validity of the meta-analysis and curve smoothing was

required which may or may not reflect actual growth accurately. The data only extend to 50 postmenstrual weeks which is a limitation to ongoing growth monitoring.

An ideal growth chart for early postnatal growth monitoring of VLBW infants is not currently available. This complicates the monitoring and assessment of growth in VLBW infants.

1.3.2 Growth Monitoring after Term CGA

The monitoring of growth in the VLBW infant after term CGA remains controversial. There are two broad categories of references, namely growth charts based on well term infants, for example those published by the World Health Organisation (WHO)[55] and the National Centre for Health Statistics and the Centre for Chronic Disease Prevention and Health Promotion (CDC),[56] and charts based on preterm or LBW and VLBW infants. An example of the latter is the charts produced by Casey et al and the Infant Health and Development Program (IHDP).[57,58]

There are several advantages of the charts produced by Casey et al[58] including a large sample size (n=212 – 219 at each measurement), a representative sample of varied ethnicities, longitudinal data collection from 40 weeks postmenstrual age, specified exclusion criteria (including supplemental oxygen for more than 90 days, extended hospitalization, presence of a neural tube defect, severe neurological

abnormality, severe sensory defect and presence of a chromosomal or multiple anomaly syndrome), standardized appropriate measurement techniques, gender specific data collection and data available up to 36 months CGA.

There are also, however, disadvantages of these charts including that they were developed in 1985 before many developments in medical technology, data is cross sectional up to term CGA, gestational age is adjusted by Ballard score which has been shown to overestimate gestational age by approximately 2 weeks,[59,60] measurements were performed at 4 monthly intervals in the first year which may not accurately reflect growth patterns and length measurements are only available after term CGA. The sample is divided into birth weight groups 1 (≤1250g), 2 (1251g - 2000g) and 3 (2001g - 2500g) which don't correspond with the commonly used birth weight groups of extremely LBW (<1000g), VLBW (1000g - 1499g) and LBW (1500g - 2499g). This makes direct comparison with other samples difficult.

The same data from the IHDP were used by Guo et al[24,25] in 1996. They developed growth references for actual growth measurements in weight, length and head circumference as well incremental changes in these parameters giving an indication of growth velocity. The data is organized into weight categories for LBW (1501g - 2500g) and VLBW (≤1500g) infants and allows useful comparison between VLBW infants and other VLBW infants. The charts, however, have similar limitations to those produced by Casey et al.[58]

Standard growth charts, for example those published by the WHO,[55] or the charts developed by the CDC[56] are commonly used after infants have reached term CGA. These charts are based on large samples of healthy term infants which, in the case of the WHO charts, are representative of infants from varied ethnic, national and environmental backgrounds. The disadvantage of using these charts is that they reflect growth patterns of healthy term infants which, as described above, are not the same as those of preterm and VLBW infants. The VLBW infant will almost invariably plot on or below the lower percentiles of these charts in the first few months of life, even if they are growing appropriately for their birth weight and degree of prematurity.

Currently available charts for monitoring the growth of VLBW infants after term CGA all have limitations. Much controversy surrounds which growth chart is ideal. This complicates the monitoring and assessment of growth in this group.

1.3.3 The "Ideal" Growth Reference for VLBW Infants

It is difficult to determine the ideal growth reference for VLBW infants. Sherry et al[61] evaluated available growth references for VLBW infants in a critical analysis of references produced by Casey et al,[58] Brandt,[53] Gairdner and Pearson,[50] Babson and Benda,[51] Lubchenco[52] and Ehrenkranz et al.[12] The best available reference, that of Casey et al,[58] was selected from these using preformed criteria.

The reference by Casey at al[58] was then compared with the CDC growth charts.[56] The 5th and 50th percentiles for weight for age, length for age and head circumference for age were initially below those of the CDC charts with catch up shown by 36 months for length for age and head circumference for age but not for weight for age.

In addition to this comparison, two external data sets of growth measurements for VLBW infants were compared with both the CDC references[56] and the references produced by Casey et al.[58] The external data sets more closely resembled the latter for length for age and weight for age but more closely resembled the former for weight for length. Head circumference for age was not compared.

From this study it is not possible to recommend a single growth reference for monitoring the growth of VLBW infants. The limitations of current references are clear and much research is required in this area. The monitoring of growth in VLBW infants is complicated by the lack of an ideal growth reference.

1.4 Conclusion

It is clear that the monitoring of growth in VLBW infants is associated with a number of difficulties. The growth of VLBW infants differs from that of healthy term infants and is complicated by high associated morbidity. There is no clear consensus at present

as to the most suitable growth charts for infants of VLBW. Furthermore, it is difficult to adopt a single reference as a global standard as several factors affect the development of a reliable, standardized growth chart. Many of the growth references available, including those of Casey et al,[58] are outdated and flawed in methodology. It is particularly difficult to collect a large sample of "healthy" VLBW infants in order to produce an ideal growth reference as this group has a high rate of associated morbidity and mortality.

There is a paucity of information on growth patterns in VLBW infants after the introduction of medical advances known to improve their survival such as the use of maternal steroids, surfactant therapy, newer modes of ventilation and advances in nutritional therapy. There is even less known about the growth of VLBW infants in the South African setting. This study attempts to address this issue by comparing the growth of South African VLBW infants with references from healthy term infants as well with available references for both international and South African VLBW infants.

2.0 AIM OF THE STUDY:

VLBW infants in Johannesburg appear to grow below that expected for CGA. The aim of the current study was to assess the growth of a group of VLBW infants at a public hospital in Johannesburg.

The primary objectives of the study were to:

1. Assess the pattern of growth (weight, length and head circumference) in a cohort of VLBW infants at a public hospital in Johannesburg
2. Compare the growth parameters of a cohort of VLBW infants with healthy term infants (WHO-CGS), international VLBW infants (IHDP and Casey references) and other South African VLBW infants (Cooper and Sandler[34])
3. Assess the extent of catch up growth of this cohort of VLBW infants by 20 months CGA

A secondary objective of the study was to assess factors in the neonatal period contributing to growth failure in the current cohort.

3.0 METHODS:

3.1 Subjects:

A prospective study, the "Outcome review of very low birth weight infants in Johannesburg" study (submitted for publication), was commenced in July 2006 and data collection completed in December 2008. The purpose of the study was to assess neurodevelopmental outcomes in a cohort of VLBW infants in Johannesburg. VLBW infants, defined as a birth weight less than or equal to 1500g, born at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) or surrounding hospitals and clinics between 1 July 2006 and 28 February 2007 were eligible for the study.

The “Outcome review of very low birth weight infants in Johannesburg” study comprised a convenience sample of VLBW infants selected over this eight month period. Patients who were transferred away from CMJAH were excluded from the study as follow up was deemed to be difficult in this group. Patients who died as inpatients were also excluded. All other patients with a birth weight ≤1500g were included in the study, including those with major morbidities (ventilated infants, BPD, early and late onset sepsis, IVH and NEC). Informed consent was obtained from each patient prior to enrolment. The sample of the “Outcome review of very low birth weight infants in Johannesburg” study was selected for retrospective analysis as the growth data and information available from patient files was accurately measured and recorded and considered to be reliable.

In the current study the patient files of the cohort of VLBW infants forming part of the “Outcome review of very low birth weight infants in Johannesburg” study were reviewed retrospectively and growth measurements obtained. One hundred and seventy four infants were initially enrolled as part of the initial “Outcome review of very low birth weight infants in Johannesburg” study. Of these infants, 139 (49 male and 90 female) attended at least one follow up visit and were included in the current review. All patients forming part of the study attended their first follow up clinic at a minimum of term CGA. Of the 139 infants forming part of the study, 96 (69%) attended follow up to at least 12 months CGA and only 53 (38%) attended follow up to at least 18 months CGA. Several measures were put in place to facilitate follow up attendance. Funds for transport were paid to mothers attending each follow up clinic

and all defaulters were contacted telephonically and by mail at the time of non-attendance as well as several times thereafter. Despite these measures loss to follow up was high.

The infants enrolled in the study received standard nutritional support in the early neonatal period as per unit protocol. Trophic feeds were commenced at 24 – 48 hours of life. Feeds were increased gradually by 20ml/kg/day to a maximum of 160ml/kg/day. Parenteral nutrition was commenced in patients who did not tolerate enteral feeds or in whom enteral feeds were contraindicated (for example patients with congenital abnormalities of the gastrointestinal tract or NEC). The majority of infants were fed preterm formula until they were ≥1500g at which time they were changed to term infant formula. VLBW Infants were fed maternal breast milk where possible. Unfortunately breastfeeding rates in our unit are low due to the high prevalence of HIV exposure, abandonment, severe maternal illness and maternal absenteeism from the unit.

Infants forming part of the study were followed up at a neonatal follow up clinic at CMJAH at 3 monthly intervals. They were seen by a nursing sister and a pediatrician at each visit. Intercurrent history, physical examination findings and growth parameters (including weight, length and head circumference) were documented at each visit.

Ethics approval for this study was granted by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand.

3.2 Data Collection:

Growth parameters (weight, length and head circumference) were measured by the same nursing sister at each visit. Weight was measured on a “Seca” electronic scale, length on a standard length board and head circumference with a non-deformable measuring tape. Hospital files for the patients forming part of the cohort were drawn and reviewed retrospectively. Data was collected on a data collection sheet (see appendix C). Data obtained from the patient files included:

1. Gestational age at birth (determined by Ballard score[60])
2. Birth weight, length and head circumference (birth weight was recorded for all patients but length and head circumference measurements were not always available)
3. Illness in the neonatal period including IVH, NEC, BPD and sepsis
4. Admission to ICU
5. Modes of ventilation
6. Growth parameters (weight, length and head circumference) at each follow up visit
7. HIV exposure and HIV PCR results where available

8. Feeding history post discharge (breast milk only, formula only or mixed feeding)
9. History of intercurrent illnesses and admissions post discharge

The data obtained were recorded in Excel spread sheet format (using Microsoft Excel 2007) and further analyzed.

3.3 Data Analysis

3.3.1 General

The sample size was 139 patients. Data were analyzed at age corrected for gestational age rounded to the nearest month. Statistical analysis was performed using *Statistica* version 8, series 0608, for Windows. Term pregnancy was defined as 37 completed weeks to 42 completed weeks of gestation and term gestation was corrected to 38 postmenstrual weeks. Determination of gestation is an estimate based on maternal menstrual history, sonographic findings and obstetric and neonatal assessment. In this study accurate maternal history and sonographic findings were not available and gestational age was estimated postnatally using the Ballard score.[60] The use of 38 weeks as a cut off for term is within the normal range of this estimate of term gestation and would correct for the overestimation of gestational age by the Ballard score.[59,60]

3.3.2 Comparison with the WHO-CGS

For comparison with WHO-CGS, growth parameters were entered into the WHO Anthropometry statistical package version 2.0.4[62] at age corrected for prematurity. Sex and age appropriate standard deviation (*Z*) scores were derived for each measurement. The *Z* score indicates the number of standard deviations an individual value is above or below the population mean adjusted for age and sex. A positive *Z* score indicates a value above the mean, a negative *Z* score indicates a value below the mean and a value of 0 is equal to the population mean. The calculation requires that the population parameters (mean and standard deviation) be known. The *Z* score can be calculated as follows:

$$Z = \frac{x - \mu}{\sigma}$$

where Z = the Z score

x = the individual or sample value

μ = the mean of the population

σ = the standard deviation of the population

The WHO-CGS was chosen for comparison for two reasons. Firstly, growth references for term infants are the references used by healthcare workers for monitoring growth in both normal and LBW infants in healthcare clinics and on the South African “Road-to-Health” card. Secondly, the references are based on a large,

representative sample of predominantly breastfed children from various cultural and ethnic backgrounds which is a more accurate reflection of South African infants than for example the CDC growth charts which are based on American infants only.

Data relating to *Z* scores is presented graphically below (figures 4.5 – 4.8) showing mean and 95% confidence interval of the mean.

3.3.3 Comparison with International VLBW infants

3.3.3.1 Comparison with IHDP growth references

For comparison with the IHDP growth references,[24] the measurements for weight, length and head circumference were grouped by sex and represented graphically using Microsoft Excel 2007. The mean, 5th percentile and 95th percentile for each growth parameter were plotted and a trend line was inserted for each to reflect the trend of measurements over time. The graphs thus developed were superimposed on the IHDP growth charts (distributed by Ross Products Division of Abbot Laboratories inc. and shown in Appendix B) for comparison. The data are presented up to 20 months CGA for female infants but only up to 12 months CGA in male infants. The sample sizes were too small in the male subgroup beyond 12 months CGA for accurate analysis and the impact of outliers beyond this point was significant. The results are presented below (see tables 4.4 – 4.5 and figures 4.9 – 4.14).

3.3.3.2 Comparison with Casey references

The presentation of the curves described above gives a visual description of the growth of the study sample compared with that of international VLBW infants but doesn't give a reflection of the statistical significance of the differences noted. Actual growth references after term CGA, including means and standard deviations, for VLBW infants are hard to find. The IHDP references do not supply this information. The references produced by Casey et al[58] do supply this information but infants are grouped into ≤1250g, 1251g - 2000g and 2001g - 2500g categories. These groups do not correspond with the study sample which is ≤1500g. If the study sample is analyzed using only infants in the current sample with a birth weight less than 1250g the sample sizes in each age category are too small for accurate analysis.

The assessment of statistical significance has therefore been performed in two ways. Firstly, the study sample has been compared with reference data by Casey et al[58] for reference group 1 (birth weight ≤1250g) and reference group 2 (birth weight 1251g - 2000g) separately for which mean and standard deviation values are available. The data in both the study sample and the reference data are normally distributed with similar standard deviation values. Statistical significance has therefore been assessed using the unpaired *t* test and a *p* value of <0.05 is considered significant.

The Casey references are not ideal as the weight subgroups used differ from those of the study sample. They were, however, used in the analysis as they are the only available references which include data on VLBW infants with documented mean and standard deviation values. Since birth weight affects post neonatal growth the comparison is likely to underestimate differences between the study sample and reference group 1 (smaller birth weight) and overestimate differences between the study sample and reference group 2 (larger birth weight).

The second method of assessment of statistical significance has been performed as follows. The 50th percentile has been determined from the IHDP growth reference charts and compared with the mean of the study sample at CGA of 0, 4, 8, 12 and 18 months with the 95% confidence limits of the study sample shown. If the 95% confidence limits for the mean of the study sample did not incorporate the 50th percentile value of the IHDP reference the difference between the two was considered significant. The limitation of this approach is that the reading of a continuous variable off a chart is prone to inaccuracies and may affect the results obtained.

3.3.4 Comparison with South African VLBW infants

Growth data for a cohort of South African VLBW infants have been collected previously (1990 – 1991) in Soweto.[34] The original database from this study was reviewed and weight and length parameters compared with those of the current

cohort at age groups 0-2 months, 6-8 months and 11-13 months for male and female infants separately. Head circumference measurements were not available for comparison. The data in both groups were normally distributed and presented as mean and standard deviations. The unpaired *t* test was used to assess the statistical significance of differences between the two samples.

3.3.5 Factors contributing to Growth Failure

The sample was further analyzed to determine whether the following factors affect growth attainment at 12 months CGA in the current sample:

1. Size with respect to gestational age (SGA defined as a birth weight less than the 10th percentile for age and sex using the references by Fenton[54])
2. Severe illness in the neonatal period (NEC grade 2 and 3, IVH grade 3 and 4, BPD and early or late onset sepsis)
3. The need for ventilation (both invasive and non-invasive forms of ventilation)
4. HIV exposure: Only patients of known HIV status were included in the analysis; those who refused testing or were of unknown status were excluded as it has been shown that there is a higher prevalence of HIV positivity in women who refuse HIV testing than in the general population.[63]

Severe illness in the neonatal period was defined as follows:

1. NEC grade 2 and 3 graded using the modified Bell staging system[64]

2. IVH grade 3 and 4 using the modified Papile classification system[65,66]

3. Bronchopulmonary dysplasia (BPD) defined as:[67]

- Infants born < 32 weeks gestation who are oxygen dependent at 36 weeks postmenstrual age

- Infants born ≥ 32 weeks gestation who require supplemental oxygen ≥ 28 days

4. Early and / or late onset sepsis manifest by clinical signs and supporting laboratory investigations (elevated C-reactive protein, elevated or decreased white cell count, decreased platelet count and positive culture from a normally sterile site).

The sample sizes were too small to analyze the effects of breastfeeding relative to mixed or formula feeding. The data pertaining to hyperalimentation in the sample were not sufficiently reliable for analysis. These possible contributing factors towards growth failure have therefore been omitted from the analysis.

The data relating to growth parameters in infants with and without severe illness as well as those ventilated and not ventilated in the neonatal period were non parametric and were analyzed using the median and range. The Mann Whitney U test was used to assess statistical significance. The data relating to growth parameters in infants born SGA and those born AGA as well as data relating to HIV exposure follow a normal distribution and have been analyzed using the mean and standard deviation. The unpaired *t* test was used to test statistical significance.

4.0 RESULTS

4.1 Descriptive Data

4.1.1 Clinical and Demographic Data

Table 4.1: Clinical and Demographic Features of the Study Sample (n=139)

Variable		Number (%)
Birth weight:	Mean	1199.6 ± 200.2g[1] (1166.0; 1233.2)[2]
	<1000g	21 (15%)
	1000 - 1500g	118 (85%)
Gestational Age:	Mean	31 ± 2.7 weeks (30.5; 31.5)[2]
Sex:	Male	49 (35.3%)
	Female	90 (64.7%)
Race:	African	129 (92.8%)
	Mixed	7 (5%)
	Asiatic	2 (1.5%)
	White	1 (0.7%)
No. of babies:	Singleton	119 (85.6%)
	Twins	18 (12.9%)
	Triplets	2 (1.5%)
Size for gestation:	AGA[3]	71 (51.1%)
	SGA[4]	68 (48.9%)
ICU admission:	Yes	30 (21.6%)
	No	109 (78.4%)
Ventilation:	Nasal CPAP[5]	10 (7.2%)
	IPPV[6]	30 (21.6%)
	Total	40 (28.8%)
Feeding[7]:	Breastfed only	7 (5%)
	Formula fed only	109 (78.4%)
	Mixed feeding	23 (16.6%)

[1]Standard deviation; [2]95% confidence interval; [3]Appropriate for gestational age; [4]Small for gestational age; [5]Continuous positive airway pressure (patients were not admitted to ICU); [6]Intermittent positive airway pressure (patients admitted to ICU); [7]Feeding post discharge.

Detailed descriptive and demographic data are presented in table 4.1 above. The cohort consisted of 139 infants, 49 (35.3%) males and 90 (64.7%) females. The mean gestational age was 31 weeks with a standard deviation of 2.7 weeks and a 95% confidence interval of 30.5 to 31.5 weeks. The mean birth weight was 1199.6g with a standard deviation of 200.2g and a 95% confidence interval of 1166.0g to 1233.2g.

4.1.2 Comorbid Conditions

Data relating to severe disease in the neonatal period are presented in table 4.2 below. The data relating to HIV testing in the sample are presented in figures 4.1 and 4.2 below.

Table 4.2: Comorbid conditions in the study sample (n=139) in the neonatal period

CONDITION	NUMBER (%)
NEC (Grade 2 and 3)	5 (3.6%)
IVH (Grade 3 and 4)	5 (3.6%)
BPD	10 (7.2%)
Proven sepsis	13 (9.4%)

Figure 4.1: Pie chart showing maternal HIV results for the sample (n=139)

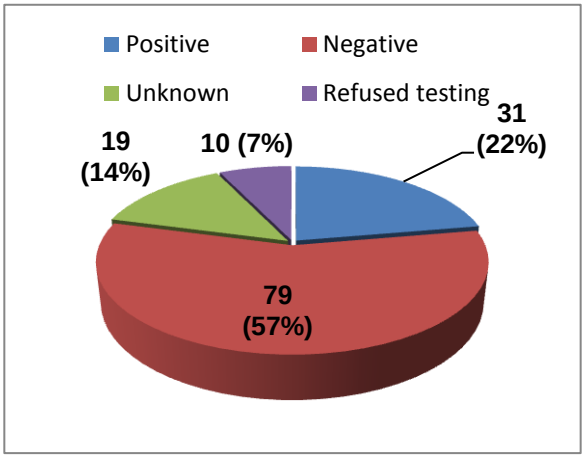
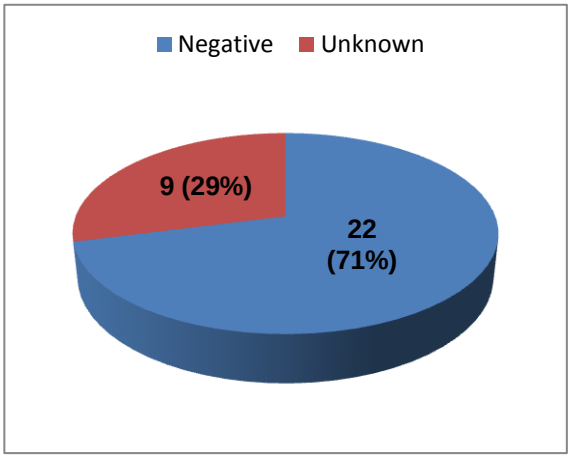


Figure 4.2: Pie chart showing HIV PCR results of HIV exposed infants in the sample (n=31)



In addition to illness in the neonatal period, a number of patients in the study sample became ill after discharge. Twenty six of the 139 patients in the cohort (18.7%) required readmission after discharge from the neonatal unit with a total of 30 admissions post discharge. Two of the patients were admitted more than once (3 admissions each) and some patients had more than one diagnosis on admission. The reasons for readmission were lower respiratory tract infections including pneumonia and bronchiolitis (14 cases), gastroenteritis (7 cases), apneas (4 cases) and other (4 cases with surgical diagnoses, 1 case of febrile convulsions, 1 case of urinary tract infection and 1 case of persistent tachycardia of unknown etiology). Two of the 139 patients (1.4%) developed cerebral palsy and 2 patients (1.4%) were diagnosed with patent ductus arteriosus at follow up.

4.1.3 Data on Loss to Follow Up

Data on loss to follow up are presented in figures 4.3 and 4.4 below.

Figure 4.3: Pie chart showing percentages of patients who were lost to follow up before 12 months CGA (n=139)

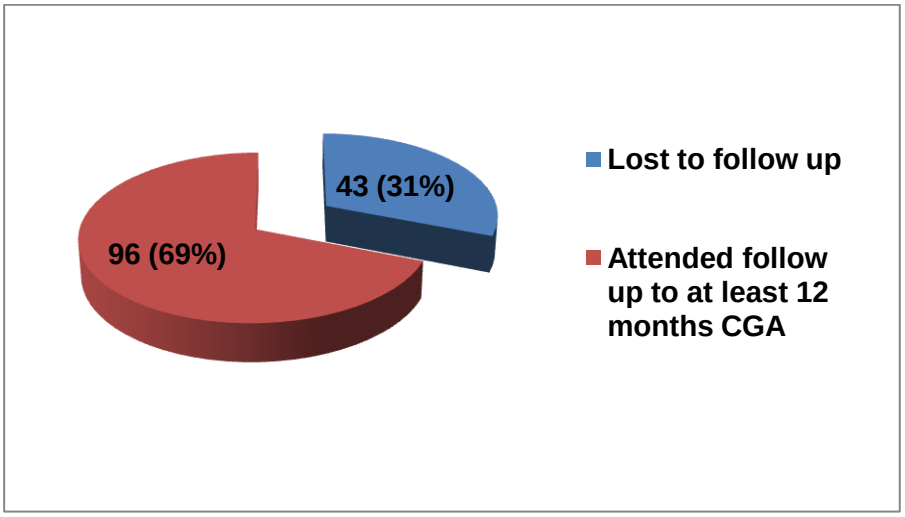
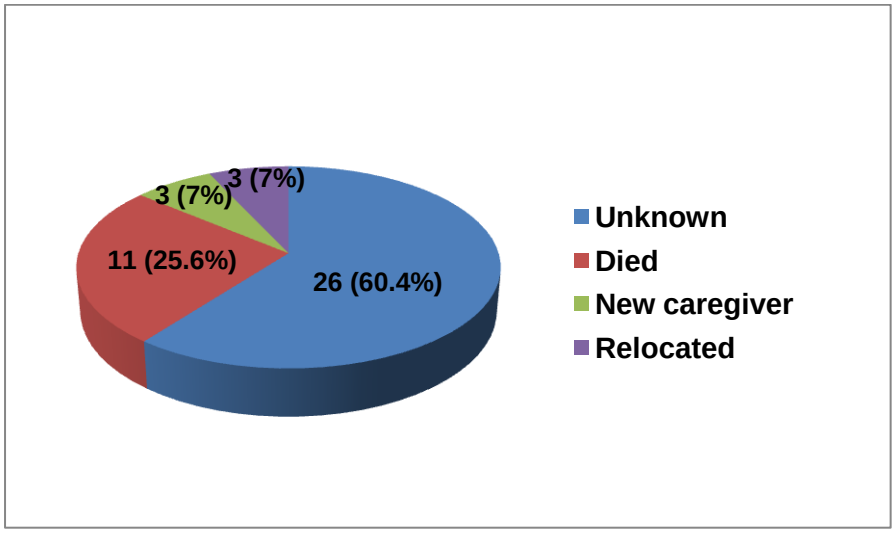


Figure 4.4: Pie chart showing reasons for loss to follow up before 12 months CGA (n=43)



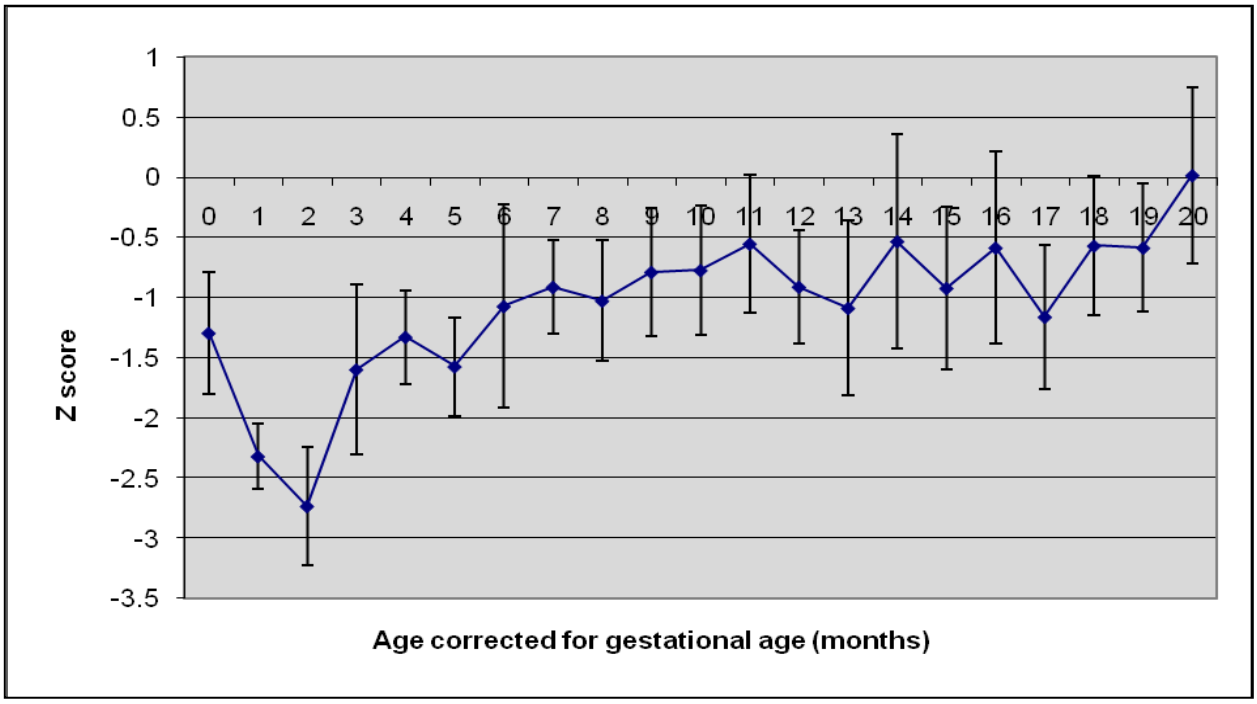
4.2 Growth Measurements and Analysis

4.2.1 Comparison with healthy term infants

4.2.1.1 Weight for Age

The mean and 95% confidence intervals of the weight for age *Z* scores determined for the study sample from the WHO-CGS are shown in figure 4.5 below. Error bars signify the 95% confidence intervals.

Figure 4.5: Line graph representing weight for age *Z* scores for male and female infants combined

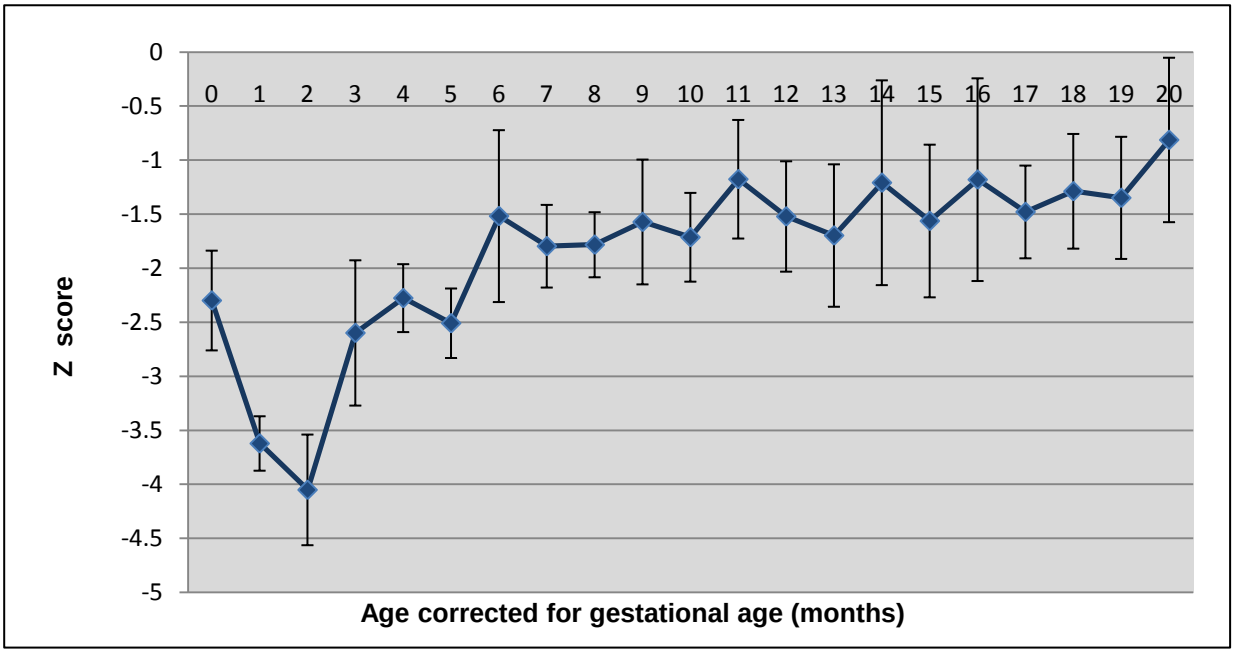


The mean *Z* score for weight for age was less than 0 for most of the study period. At term CGA the mean was -1.3 with a 95% confidence interval of -1.8 to -0.8. There was an initial decrease in *Z* score to a minimum of -2.7 (-3.2;-2.2) at 2 months CGA followed by a gradual increase in *Z* score to -1.1 (-1.9;-0.3) at 6 months, -0.9 (-1.4;-0.4) at 12 months and -0.6 (-1.2;0) at 18 months. By 20 months the mean *Z* score was 0 with a 95% confidence interval of -0.7 to 0.7. This is in keeping with catch up growth by 20 months CGA.

4.2.1.2 Length for Age

The mean and 95% confidence intervals of the length for age *Z* scores determined for the study sample from the WHO-CGS are shown in figure 4.6 below. Error bars signify the 95% confidence intervals. The mean length for age *Z* scores remained below 0 for the entire study period. At term CGA the mean was -2.3 with a 95% confidence interval of -2.8 to -1.8. Similar to the weight for age *Z* scores, the length for age *Z* scores showed an initial decline to a minimum of -4.1 (-4.6;-3.6) at 2 months CGA followed by a gradual increase to -1.5 (-2.3;-0.7) at 6 months, -1.5 (-2.0;-1.0) at 12 months and to -1.3 (-1.8;-0.8) at 18 months. Length for age *Z* scores did not catch up to the WHO standard by 20 months CGA and the mean *Z* score remained -0.8 with a 95 % confidence interval of -1.6 to 0 at this point.

Figure 4.6: Line graph representing length for age *Z* scores for male and female infants combined



4.2.1.3 Weight for Length

The mean and 95% confidence intervals of the weight for length *Z* scores determined for the study sample from the WHO-CGS are shown in figure 4.7 below. Error bars signify the 95% confidence intervals. The weight for length *Z* scores differed from those of weight for age and length for age. They showed an initial increase in *Z* score from 0.6 with a 95% confidence interval of 0.2 to 1.0 at term CGA to a maximum of 1.3 (0.9 - 1.7) at 2 months CGA. This suggests that the infants in this sample had weight in excess of length compared with the WHO standard. After 2 months of age, the weight for length *Z* score decreased to 0 (-0.6;0.6) by 6 months CGA where it

remained until 18 months CGA. At 20 months the weight for length *Z* score increased to 0.5 (-0.2;1.2).

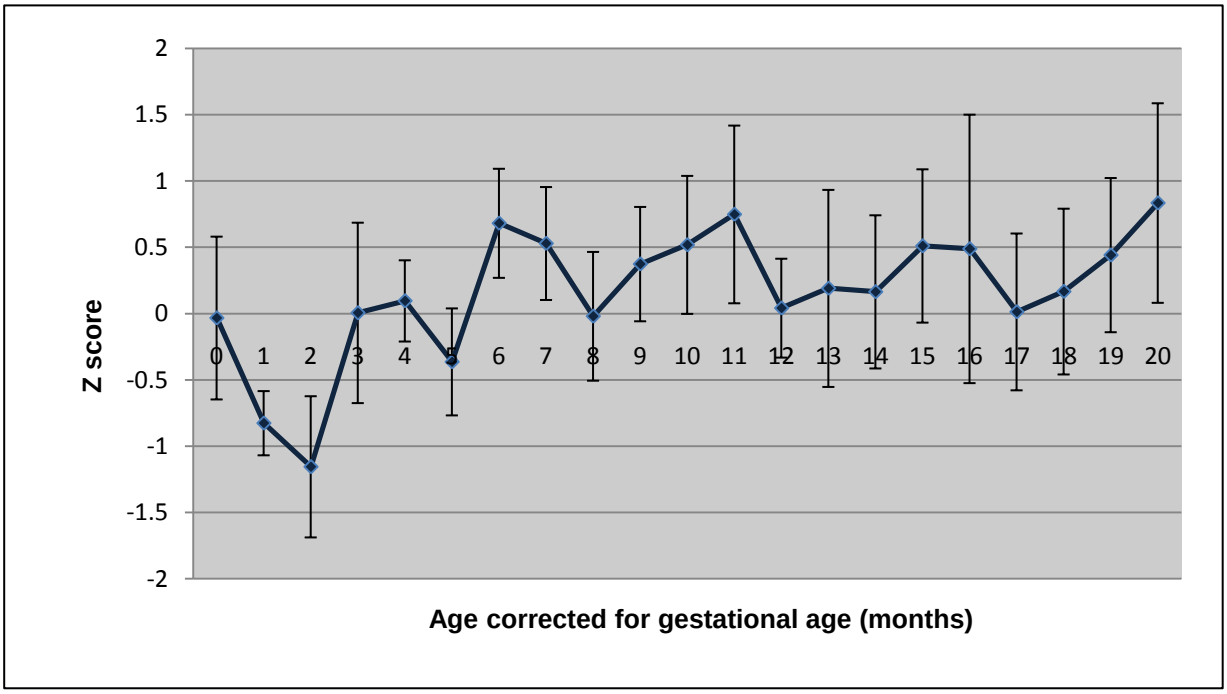
Figure 4.7: Line graph representing weight for length *Z* scores for male and female infants combined



4.2.1.4 Head Circumference for age

The mean and 95% confidence intervals of the head circumference for age *Z* scores determined for the study sample from the WHO-CGS are shown in figure 4.8 below. Error bars signify the 95% confidence intervals.

Figure 4.8: Line graph representing head circumference for age *Z* scores for male and female infants combined



The mean head circumference for age *Z* score at term CGA was 0 with a 95% confidence interval of -0.6 to 0.6. This decreased to -1.2 (-1.7;-0.7) at 2 months corrected for prematurity followed by an increase to 0.7 (0.2;1.0) at 6 months, 0 (-0.4;0.4) at 12 months, 0.2 (-0.4;0.8) at 18 months and 0.8 (0;1.6) at 20 months. This is in keeping with catch up in head circumference growth.

4.2.1.5 Extent of Growth Failure relative to Term Infants

It is generally accepted that normal variation in growth falls within 2 standard deviations (SD) above or below the mean. Growth parameters that fall more than 2 SD below the mean are regarded as suboptimal. The proportion of the current sample

that was greater than or equal to 2 SD below the mean for weight, length and head circumference at 0, 6, 12 and 18 months CGA are presented in table 4.3.

Table 4.3: Proportion of the sample greater than or equal to 2 SD below the mean for weight, length and head circumference

CGA[α] (months)	Wt[β]-for-age ≥-2SD	Lt[δ]-for-age ≥-2SD	HC[ε]-for-age ≥-2SD
0	23.5%	82.4%	5.9%
6	36.8%	36.8%	0%
12	18.9%	32.4%	3.0%
18	13.3%	17.4%	5.0%

[α]CGA = Age corrected for gestational age; [β]Wt = Weight; [δ]Lt = Length; [ε]HC = Head circumference

4.2.2 Comparison with international VLBW infants

4.2.2.1 Overview of Data Collected

The mean, 5th and 95th percentiles for the growth parameters (weight, length and head circumference) grouped according to sex are shown in tables 4.4 and 4.5 below. Growth data for the study sample, represented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP growth references for VLBW infants are presented in figures 4.9 – 4.14. The original data points with the relevant trend lines are presented in appendix D and actual reference data for reference groups 1 and 2 as per Casey et al[58] are shown in appendix E.

Table 4.4: Growth parameters (weight, length and head circumference) according to age for male infants

	CGA	n	Mean ± SD	95% CI of the Mean	Reference 1[1] (Mean ± SD)	Reference 2[2] (Mean ± SD)	*p* (1)[3]	*p* (2)[4]
Weight (kg):	0	7	3.08 ± 0.32	± 0.3	2.68 ± 0.6	3.13 ± 0.5	0.0418	0.39740
	4	18	5.88 ± 1.11	± 0.55	5.77 ± 0.9	6.50 ± 0.9	0.3300	0.00298
	8	7	7.57 ± 1.56	± 1.44	7.51 ± 1.1	8.13 ± 1.0	0.4483	0.07640
	12	13	8.74 ± 1.39	± 0.84	8.91 ± 1.1	9.41 ± 1.1	0.3156	0.01786
Length (cm):	0	7	47.57 ± 1.77	± 1.63	46.4 ± 2.8	48.8 ± 2.5	0.1357	0.0409
	4	18	58.55 ± 1.99	± 0.99	59.8 ± 2.9	62.0 ± 2.6	0.0427	<0.001
	8	7	66.56 ± 1.56	± 1.44	67.7 ± 3.4	69.2 ± 2.7	0.1922	0.0051
	12	13	72.71 ± 4.6	± 2.77	73.6 ± 3.2	74.7 ± 2.8	0.1977	0.0087
HC[5] (cm):	0	7	34.86 ± 1.18	± 1.09	34.2 ± 2.1	35.2 ± 1.5	0.2061	0.2119
	4	17	41.62 ± 0.95	± 0.49	41.3 ± 1.6	42.1 ± 1.2	0.3897	0.2981
	8	7	44.51 ± 1.65	± 1.53	44.1 ± 1.6	44.9 ± 1.4	0.2611	0.2358
	12	12	45.55 ± 1.08	± 0.69	45.9 ± 1.6	46.6 ± 1.4	0.2327	0.0055

[1]Reference group 1 (Casey et al)[58]: infants with birth weight ≤1250g; [2] Reference group 2 (Casey et al)[58]: infants with birth weight 1251g - ≤2000g; [3]*p* (1) = *p* value for reference group 1; [4]*p* (2) = *p* value for reference group 2; [5]HC = Head circumference

Table 4.5. Growth parameters (weight, length and head circumference) according to age for female infants

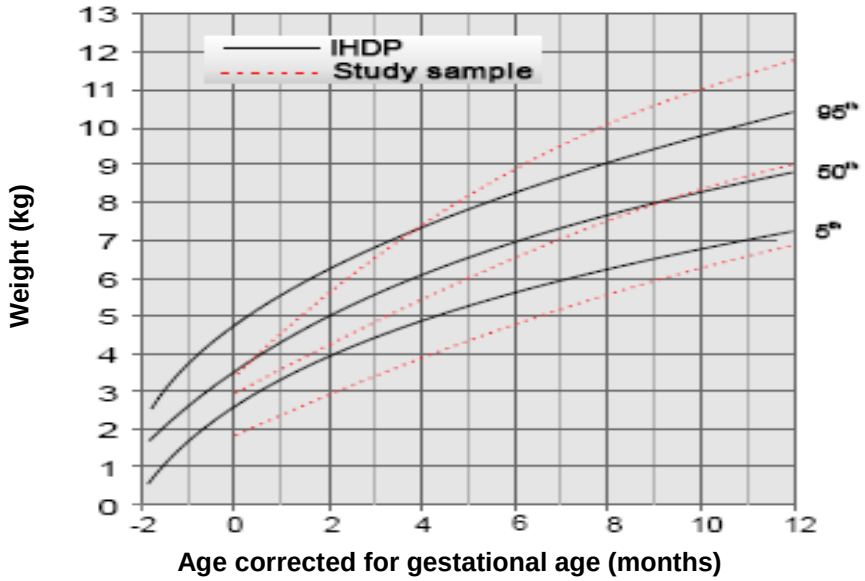
	CGA[1]	N	Mean ± SD	95% CI of the Mean	Reference 1[1] (Mean ± SD)	Reference 2[2] (Mean ± SD)	*p* (1)[3]	*p* (2)[4]
Weight (kg):	0	10	2.93 ± 0.36	± 0.26	2.72 ± 0.6	3.10 ± 0.6	0.1423	0.18670
	4	27	5.71 ± 0.71	± 0.28	5.70 ± 0.9	6.12 ± 0.9	0.4801	0.01101
	8	21	7.15 ± 0.95	± 0.43	7.42 ± 0.9	7.74 ± 1.0	0.1292	0.00523
	12	24	8.18 ± 1.44	± 0.61	8.58 ± 1.1	8.97 ± 1.1	0.0793	0.1423
	18	16	9.63 ± 1.51	± 1.01	9.93 ± 1.3	10.32 ± 1.3	0.2119	0.02118
Length (cm):	0	10	46.72 ± 1.43	± 1.02	46.0 ± 3.0	48.8 ± 2.6	0.2296	0.00604
	4	27	57.93 ± 2.20	± 0.87	59.1 ± 2.9	61.0 ± 2.7	0.0287	<0.001
	8	21	64.50 ± 1.82	± 0.83	66.6 ± 2.8	67.9 ± 3.0	0.0062	<0.001
	12	24	69.69 ± 3.62	± 1.53	72.3 ± 3.1	73.7 ± 3.1	<0.001	<0.001
	18	16	76.89 ± 3.45	± 1.84	79.1 ± 3.7	80.4 ± 3.6	0.0150	<0.001
HC[5] (cm):	0	10	35.5 ± 1.55	± 1.11	34.1 ± 2.0	34.8 ± 1.5	0.0170	0.07
	4	27	41.0 ± 1.43	± 0.57	40.7 ± 1.5	41.0 ± 1.3	0.2206	0.17
	8	21	43.31 ± 1.64	± 0.75	43.4 ± 1.5	43.8 ± 1.4	0.4052	0.07
	12	21	45.3 ± 1.54	± 0.7	45.1 ± 1.5	45.4 ± 1.3	0.2981	0.37
	18	13	46.6 ± 1.84	± 1.2	46.4 ± 1.5	46.8 ± 1.4	0.4013	0.25

[1]Reference group 1 (Casey et al)[58]: infants with birth weight ≤1250g; [2] Reference group 2 (Casey et al)[58]: infants with birth weight 1251g - ≤2000g; [3]*p* (1) = *p* value for reference group 1; [4]*p* (2) = *p* value for reference group 2; [5]HC = Head circumference

4.2.2.2 Weight for Age

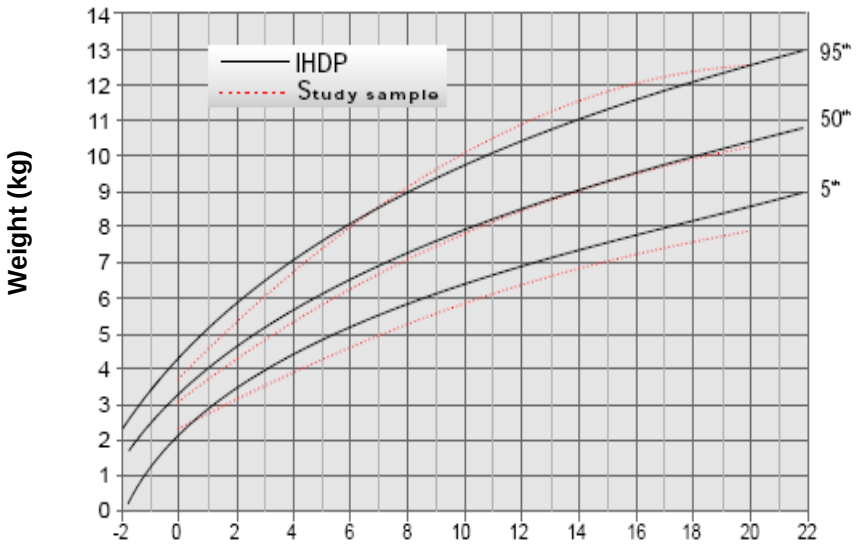
As can be seen in table 4.4, the sample mean was significantly greater than that of reference group 1 at term CGA (p=0.0418) but was significantly less than that of reference group 2 at 4 and 12 months CGA (p=0.00298 and p=0.01786 respectively). Weight for age data for male infants in the sample, represented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP growth references are presented in figure 4.9 below. In male infants the 5th percentile of the weight for age curve fell below that of the IHDP reference for the study period. The 50th and 95th percentiles fell below the IHDP reference at term CGA but caught up to the reference and, in the case of the 95th percentile, surpassed it at 4 months CGA. The 95% confidence limits of the sample mean incorporated the 50th percentile of the IHDP reference after term CGA. The difference in mean weight for age for male infants in the sample showed some variability over time but was similar to that of the IHDP reference.

Figure 4.9: Comparison of weight for age between the IHDP sample and the study sample for male Infants



As can be seen in table 4.5, there was no significant difference between the mean of the study sample and the mean of reference group 1(birth weight ≤1250g) for female infants. The study sample was significantly lighter than reference group 2 (birth weight 1251g - 2000g) at CGA 4 months (p=0.01101), 8 months (p=0.00523) and 18 months (p=0.02118). The difference between the sample mean and reference group 2 is to be expected as group 2 has a larger representation of infants with greater birth weight. Weight for age data for female infants in the study sample, presented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP references are presented in figure 4.10 below. The 5th percentile of weight for age for female infants was consistently below that of the IHDP reference but the mean and 95th percentiles closely resembled the IHDP reference. The 95% confidence limits of the sample mean incorporated the 50th percentile of the IHDP reference after term CGA. The study sample of female infants appears to grow similarly to infants with a birth weight ≤1250g (reference group 1) and to the IHDP VLBW reference with respect to weight for age.

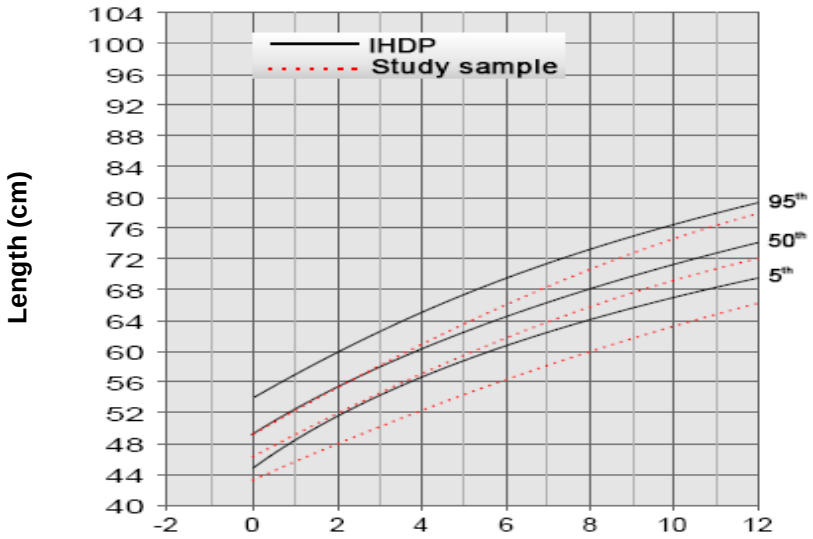
Figure 4.10: Comparison of weight for age between the IHDP sample and the study sample for female infants



4.2.2.3 Length for Age

As can be seen from table 4.4, the difference in mean values for length for age in male infants was statistically significant at 4 months CGA relative to reference group 1 (p = 0.0427) and at term, 4 months, 8 months and 12 months CGA relative to reference group 2 (p values 0.0409, <0.01, 0.0051 and 0.0087 respectively). Length for age data for male infants in the study sample, presented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP growth references for VLBW infants are presented in figure 4.11 below. The 5th, 50th and 95th percentile curves for length for age in male infants fell below those of the IHDP reference from term CGA to 12 months CGA. The 95% confidence limits of the sample mean were less than the 50th percentile of the IHDP reference for male infants at 4 and 8 months CGA but not at term or 12 months CGA. Mean length for age of male infants in the study sample was significantly less than that of reference group 2 throughout the study period but only significantly less than reference group 1 at 4 months CGA and less than the 50th percentile of the IHDP reference at 4 and 8 months CGA.

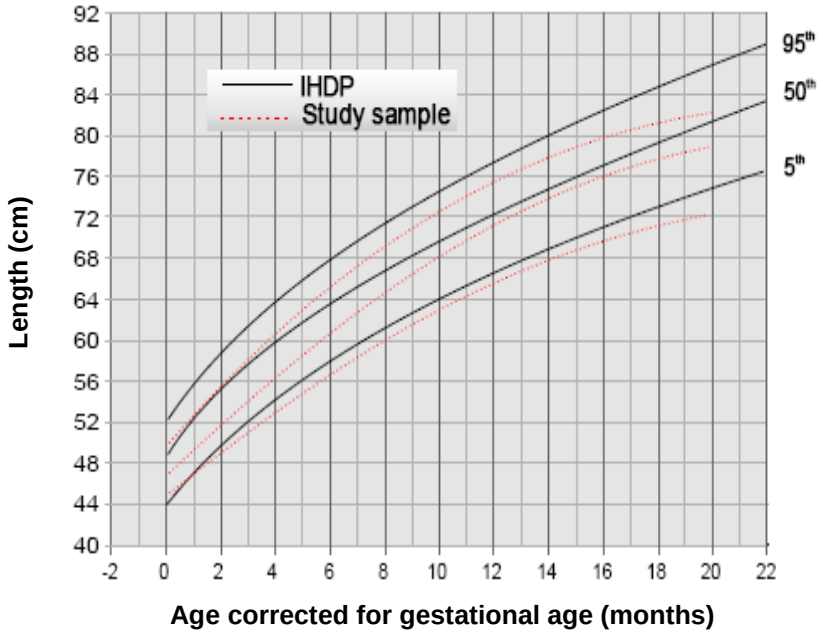
Figure 4.11: Comparison of length for age between the IHDP sample and the study sample for male infants



As can be seen in table 4.5, the difference in mean values between the study sample and reference group 1 were statistically significant for female infants at 4, 8, 12 and 18 months CGA (*p* values 0.0287, 0.0062, <0.001 and 0.015 respectively). The difference between the study sample and reference group 2 was statistically significant for female infants at term, 4 months, 8 months, 12 months and 18 months CGA (*p* = 0.00604 at term and <0.001 thereafter). Length for age data for female infants in the study sample, presented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP growth references for VLBW infants are presented in figure 4.12 below. The 5th, 50th and 95th percentile curves for length for age in female infants remained below those of the IHDP reference from term CGA to 20 months CGA. The 95% confidence limits of the sample mean were less than the 50th percentile of the IHDP reference at 4, 8, 12 and 18 months CGA for female infants. Length for age of female infants in the study

sample was significantly less than that of reference group 1, reference group 2 and the 50th percentile of the IHDP reference chart for VLBW infants.

Figure 4.12: Comparison of length for age between the IHDP sample and the study sample for female infants

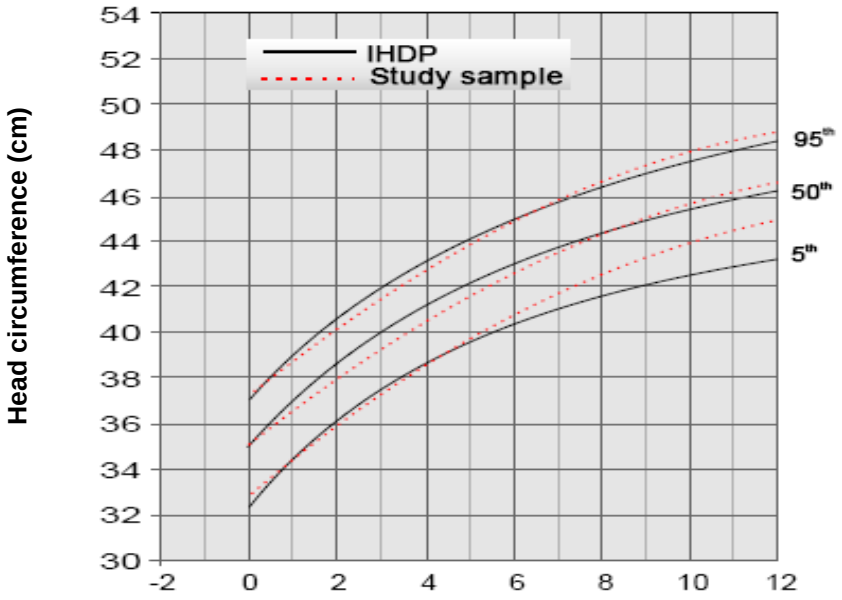


4.2.2.4 Head Circumference for Age

As can be seen in table 4.4, the difference between the mean values of the study sample compared with that of reference group 2 for male infants reached statistical significance at 12 months CGA (p = 0.0055). There were no other statistically significant differences between the head circumferences of the male subgroup of the study sample and either reference group 1 or 2.Head circumference for age data for male infants in the study sample, presented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP growth references for VLBW infants are presented in figure

4.13 below. The 95% confidence limits of the mean for the study sample incorporated the 50th percentile of the IHDP reference from term to 12 months CGA. Growth in head circumference in male infants of the study sample was similar to that of other male VLBW infants.

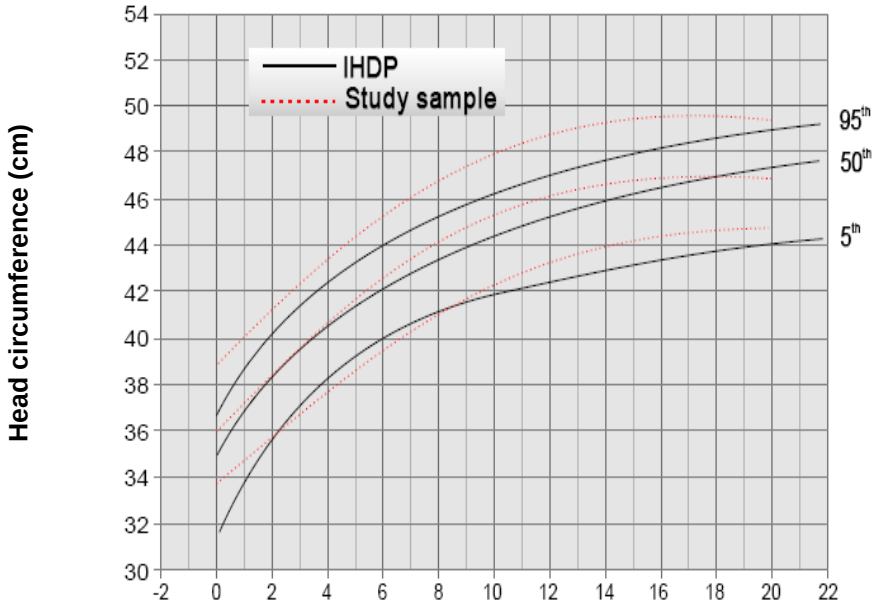
Figure 4.13: Comparison of head circumference for age between the IHDP sample and the study sample for male infants



As can be seen in table 4.5, the mean values for the study sample compared with that of reference group 1 for female infants was only statistically significant at term CGA (p = 0.017) when the mean head circumference for the study sample was greater than that of the reference group. There were no other statistically significant differences between the study sample and reference group 1 or 2 for female infants. Head circumference for age data for female infants in the study sample, represented as trend lines of the mean, 5th and 95th percentiles, compared with the IHDP growth references for VLBW infants

are presented in figure 4.14 below. The 95th percentile of head circumference for age for female infants was above that of the IHDP reference. The 5th and 50th percentiles showed some variation with crossing of percentiles between 2 – 8 months CGA but largely resembled those of the IHDP reference. The 95% confidence limit of the mean for the study sample was greater than the 50th percentile of the IHDP reference at term CGA. The 95% confidence interval of the mean incorporated the 50th percentile of the IHDP reference for the remainder of the study period. Growth in head circumference in the female group of the study sample was similar to that of other female VLBW infants.

Figure 4.14: Comparison of head circumference for age between the IHDP sample and the study sample for female infants



4.2.3 Comparison with South African VLBW infants

Weight and length parameters for the current study sample and the previous South African sample studied by Cooper and Sandler[34] are presented in tables 4.6 and 4.7 below for male and female infants respectively. Both male and female infants in the study sample were significantly shorter in the 0 – 2 month age group than those in the study by Cooper and Sandler.[34] There were no other statistically significant differences between the 2 samples for weight or length parameters. Head circumference data was not available for comparison.

Table 4.6: Weight and length parameters of male infants according to age for the current sample compared with a previous cohort of SA VLBW infants

	CGA (months)	n(1)[1]	Mean ± SD(1)[1]	n(2)[2]	Mean ± SD(2)[2]	*p*[3]
Weight (kg):	0-2	39	3.23 ± 0.58	42	3.20 ± 0.54	0.83
	6-8	38	7.54 ± 1.09	30	7.17 ± 1.38	0.22
	11-13	23	8.69 ± 1.56	29	8.69 ± 0.98	0.99
Length (cm):	0-2	39	49.76 ± 2.57	42	47.57 ± 2.18	<0.01
	6-8	38	65.56±2.90	30	64.49 ± 3.29	0.16
	11-13	23	72.0 ± 4.02	29	71.93 ± 1.96	0.94

[1]Sample 1: Data from Cooper and Sandler[34]; [2]Sample 2: Data from the current study; [3]p value calculated using the unpaired *t* test

Table 4.7: Weight and length parameters of female infants according to age for the current sample compared with a previous cohort of SA VLBW infants

	CGA (months)	n(1)[1]	Mean ± SD(1)[1]	n(2)[2]	Mean ± SD(2)[2]	*p*[3]
Weight (kg):	0-2	39	3.23 ± 0.79	81	3.36 ± 0.61	0.76
	6-8	36	7.19 ± 0.96	52	7.10 ± 0.98	0.66
	11-13	26	8.28 ± 1.26	50	8.35 ± 1.02	0.8
Length (cm):	0-2	38	49.91 ± 2.88	81	47.99 ± 2.27	<0.01
	6-8	35	64.86 ± 2.48	52	64.13 ± 2.43	0.18
	11-13	26	70.24 ± 3.26	50	70.92 ± 3.03	0.38

[1]Sample 1: Data from Cooper and Sandler[34]; [2]Sample 2: Data from the current study; [3]p value calculated using the unpaired *t* test

4.2.4 Variables Affecting Growth

Results of the analysis to determine whether size with respect to gestational age (SGA vs AGA), severe illness in the neonatal period (including IVH grade 3 and 4, NEC grade 2 and 3, BPD and proven sepsis) the need for ventilation (both invasive and non-invasive forms of ventilation) or exposure to HIV affected growth attainment at 12 months CGA in the current sample are presented in tables 4.8 – 4.11 below. Of the 139 infants forming part of the study sample, only 37 were seen at 12 months CGA and form part of this analysis. Furthermore, only patients of known HIV status (n=33) were included in the comparison of HIV exposed with HIV unexposed infants. There were also cases of missing data, for example head circumference measurements, resulting in the sample size being inconsistent between analyses. The data for severe illness in the neonatal period are presented as a composite of grade 3 and 4 IVH, grade 2 and 3 NEC

and proven sepsis as the numbers for each variable individually were too small for accurate analysis. The limitation of this approach is that one is unable to assess the impact of each variable individually.

Table 4.8: Growth parameters at 12 months CGA in infants born SGA and those born AGA

	AGA[1] (Mean ± SD)	SGA[2] (Mean ± SD)	p value[3]
Weight (kg)	9.01 ± 1.31 (n=19)	7.71 ± 1.26 (n=18)	0.004
Length (cm)	72.51 ± 3.39 (n=19)	68.9 ± 4.23 (n=18)	0.007
HC[4] (cm)	45.71 ± 1.16 (n=16)	45.08 ± 1.54 (n=17)	0.19

[1]AGA = Appropriate for gestational age; [2]SGA = Small for gestational age; [3]p value determined using the unpaired *t* test; [4]HC = Head circumference

Table 4.9: Growth parameters at 12 months CGA in infants with and without severe illness in the neonatal period

	Illness[1] Median (Range)	No Illness Median (Range)	p value[2]
Weight (kg)	8.7 (6.45 – 11.2) (n=7)	8.43 (5.8 – 11.4) (n=30)	0.38
Length (cm)	73.0 (66.5 – 79.0) (n=7)	70.75 (62.5 – 79.0) (n=30)	0.25
HC[3] (cm)	46.0 (45.0 – 47.0) (n=7)	45.0 (41.6 – 48.0) (n=26)	0.08

[1]Illness includes IVH grade 3 and 4, NEC grade 2 and 3, BPD and proven sepsis; [2]p value determined using the Mann Whitney U test for non parametric data; [3]HC = Head circumference

Table 4.10: Growth parameters at 12 months CGA in infants ventilated in the neonatal period and those not ventilated

	Ventilated[1] Median (Range)	**Not Ventilated** Median (Range)	**p value**[2]
Weight (kg)	8.66 (7.25 – 11.2) (n=6)	8.45 (5.8 – 11.4) (n=31)	0.55
Length (cm)	71.25 (67.0 – 78.5) (n=6)	71.0 (62.5 – 79) (n=31)	0.59
HC[3] **(cm)**	45.0 (45.0 - 46.0) (n=6)	45.5 (41.6 – 48.0) (n=27)	0.80

[1]Ventilated patients included both invasive (IPPV) and non-invasive (CPAP) forms of ventilation; [2]p value determined using the Mann Whitney U test for non parametric data; [3]HC = Head circumference

Table 4.11: Growth parameters at 12 months CGA in infants who were HIV exposed and those who were not exposed

	HIV Exposed (Mean ± SD)	**HIV Unexposed**[1] (Mean ± SD)	**p value**[2]
Weight (kg)	8.34 ± 1.8 (n=10)	8.47 ± 1.38 (n=23)	0.82
Length (cm)	70.92 ± 5.06 (n=10)	70.89 ± 4.21 (n=23)	0.96
HC[3] **(cm)**	45.15 ± 1.91 (n=8)	45.58 ± 1.21 (n=21)	0.48

[1]HIV Unexposed group includes only mothers who tested HIV negative; [2]p value determined using the unpaired *t* test; [3]HC = Head circumference

Infants born SGA were significantly lighter and shorter at 12 months CGA than those born AGA. There was, however, no statistically significant difference in head circumference between the SGA group and the AGA group at 12 months CGA. There was also no statistically significant difference in the current sample for weight, length or head circumference at 12 months CGA in infants with or without severe illness in the neonatal period, in infants who required assisted ventilation compared with those who did not or in infants exposed to HIV and those not exposed. Of importance is that there was no statistically significant difference in the proportion of male : female infants in each set of analyses described above as determined by the Chi square and Fisher's exact tests.

5.0 DISCUSSION

5.1 Introduction

Monitoring and assessment of growth in VLBW infants is complicated by the heterogeneity of VLBW infants as a group, their high associated morbidity and the lack of an ideal growth reference. Studies of growth in VLBW infants are therefore difficult. The current study demonstrates well the limitations of growth monitoring in VLBW infants related to these issues.

As evident in the current study, VLBW infants are heterogeneous with respect to sex, gestational age, birth weight, associated morbidity and feeding practices. These factors

all impact on growth. The study sample shows a pattern of initial growth failure followed by gradual catch up growth relative to healthy term infants which is characteristic of VLBW infants. Growth is comparable with that of international VLBW infants with the exception of length for age and resembles the growth of a previous cohort of South African VLBW infants in all parameters.

Detailed discussion of the growth parameters of the current study sample relative to term infants (the WHO-CGS[55]), international VLBW infants (IHDP references[24] and references produced by Casey et al[58]) and a group of South African VLBW infants (data by Cooper and Sandler[34]) is presented below. In addition, various factors impacting on growth are discussed.

5.2. Initial Growth Failure

Monitoring and assessment of growth in VLBW infants is difficult as their growth differs from that of healthy term infants on which a large number of growth references are based. The study sample was initially compared with the WHO-CGS[55] as a comparison with healthy term neonates. The weight for age, length for age and head circumference for age *Z* scores generated from the WHO-CGS showed an initial decline from 0 to 2 months CGA in keeping with growth failure in the first few months of life.

A similar pattern of growth has been found in other studies of VLBW infants, for example those of Hack[10] and Niklasson.[11] In the study by Niklasson mean *Z* scores decreased from 40 weeks to 6 months CGA followed by a period of catch up growth. The minimum *Z* score for weight for age after term CGA in our sample was earlier, at 2 months CGA, with earlier commencement of catch up growth. We did not have growth data on the current sample before term CGA.

Several factors may explain the differences noted between the current study and that of Niklasson et al.[11] In the study by Niklasson et al[11] the sample comprised more than 30% ELBW infants and all infants in the sample were less than 29 weeks gestation. In the current study only 15% of the sample was ELBW and the mean gestational age of the sample as a whole was 31 weeks. It has been shown that greater degrees of prematurity and smaller size at birth are associated with more significant growth failure and greater delay in catch up growth.[9,11,23]

In addition to birth weight and gestational age characteristics, the *Z* scores were also calculated from different references in the two studies which may affect the results obtained. In the study by Niklasson[11] *Z* scores were calculated from a population specific Swedish growth reference whereas the *Z* scores in the current study were calculated from the WHO-CGS. There may also have been differences in nutritional practices and environmental factors between the two samples which could account for

the differences seen. These are not, however, described in detail in either of the studies.

The period of growth failure relative to term infants is characteristic of VLBW infants. This is important in the interpretation of growth of VLBW infants and complicates growth monitoring in this group.

5.3 Catch up Growth

The presence of catch up growth is one of the factors differentiating the growth of VLBW infants from that of term infants. The current study showed variations in the timing and rate of catch up growth in weight, length and head circumference with catch up being most rapid with respect to head circumference and slowest with respect to length.

5.3.1 Weight

Growth in weight of the study sample was comparable with that of international VLBW infants and with other South African VLBW infants. The study showed catch up growth by 20 months CGA relative to term infants.

Catch up in weight was more rapid in the current study than has been reported previously.[10,11,29] It is usually most rapid in the first six months of life[29,43] but the extent and duration of catch up growth varies. Bertino et al[29] studied 262 VLBW infants from 1994 – 1999. They found the greatest rate of catch up growth in the first 5 postnatal months but with catch up growth remaining on average incomplete by the end of the second year of life. Similarly, studies have shown that catch up growth may extend into childhood and in some cases into adulthood.[10,11,23,27,29]

Infants in the current study were born between 2006 and 2007. They therefore had the advantage of improvements in nutritional and medical practices relative to infants in the study by Hack et al[10] who were born between 1977 and 1979. In addition, nutritional practices may play a role in the rapid catch up in weight seen in the current study. Information regarding feeding post discharge was available up to 4 – 6 months CGA in the current study but was not sufficiently detailed beyond this point for discussion.

A large proportion of the sample was either formula (78.4%) or mixed (16.6%) fed post discharge, with only 5% of the sample being exclusively breastfed, relative to the WHO-CGS which is based on predominantly breastfed infants. Formula fed infants are known to lose a smaller percentage of their birth weight, regain their birth weight more rapidly and then continue to gain weight in the early neonatal period when compared with breastfed infants.[15]

Mixed feeding is the norm in the South African setting.[68] In a study by Bland et al[68] in rural Kwazulu Natal it was found that approximately 50% of infants were exclusively breastfed in the first 48 hours of life. This number rapidly declined, especially in the first 2 weeks of life, and by 6 weeks approximately 7% of infants were exclusively breastfed and by 16 weeks as few as 3% were exclusively breastfed.

A number of factors have been shown to affect infant feeding practices including inadequate counseling and support, breast pain, the notion of “insufficient milk” and the failure to commence breastfeeding in the first hour of birth.[68] Specific to our neonatal unit is a high prevalence of HIV exposure, abandonment, maternal absenteeism from the unit, severe maternal disease, mothers returning to work who are unwilling or unable to express and store breast milk and insufficient breastfeeding support during and after the neonatal period. The low rate of breastfeeding in our unit is a weakness in current management and should be the focus for future intervention in the form of improved breastfeeding counseling, maternal support, breast milk pasteurization and the use of donor breast milk.

5.3.2 Length

Length for age parameters were similar between the study sample and a previous cohort of South African VLBW infants. There were, however, significant deficits in length for age relative to international VLBW infants and healthy term infants.

Catch up in length for age was incomplete by 18 months CGA relative to the WHO-CGS with 17.4% of the sample remaining more than 2 SD below the mean. Other studies show a similar pattern of incomplete catch up in length.[10,11,13] However, these studies show greater catch up in length than in weight when corrected for gestational age, the opposite of what is seen in the current study.

Comparison of the study sample with the IHDP references[24] and the references produced by Casey et al[58] also revealed significant deficits in length for age. These were most marked in the group of female infants. They were also statistically significant in male infants relative to Casey reference group 2 (birth weight 1251g - 2000g) and at variable points relative to Casey reference group 1(birth weight ≤1250g) and the IHDP reference chart. The lack of statistical significance of length for age deficits in male infants, especially at 12 months CGA, may have been due to small sample sizes with large variances and hence wide 95% confidence intervals at these points.

The deficits in length for age described above were confined to the comparison with healthy term infants and international VLBW infants. They were not borne out in the comparative analysis between the study sample and previous data on South African VLBW infants by Cooper and Sandler.[34] This suggests that the length for age deficits observed most likely reflect a broader issue of stunting in South African children and are not specific to the group of VLBW infants being studied.

The rate of stunting in South African children is high, regardless of birth weight.[1,34,69] Deficits in length for age have been found in previous studies of South African children[69] and in studies specific to VLBW South African infants.[34] The cause for relative growth failure with respect to length for age in the current sample is most likely multifactorial. It is important to note that factors which are known to be associated with stunting in children include poor socioeconomic circumstances, poor maternal education, large family size, higher birth order, shorter birth interval, chronic illness, anemia, and nutritional deficiencies.[19,70-78] Many of these factors are present in our community and predispose South African children to stunting.

An interesting association has been found between recurrent in addition to chronic illness in the etiology of stunting in children. Checkley et al,[71] in a study involving 5 countries over a period of 20 years, found that the cumulative burden of diarrheal episodes significantly increases the risk of stunting. In the current study 18.7% of patients required hospital readmission and of those readmitted 26.9% were due to gastroenteritis. The effect of recurrent illness is important in a country such as South Africa where 15% of under-5 deaths are attributed to diarrheal disease.[79]

The role of genetics and ethnicity remains an important one. It has been shown that, in addition to the factors mentioned above, final height also has a genetic determination.[80] Parental height needs to be taken into consideration when evaluating a child's growth potential. Unfortunately this information was not available in the current study.

The high proportion of infants in the current sample born SGA may also have contributed towards the observed deficits in length for age. The current sample comprised 48% SGA infants which is significantly greater than that reported in studies elsewhere in the world[12,31,81] and may be an important contributor towards growth failure.[23,27,30,31]

Evidence regarding the effect of SGA on growth is conflicting.[12,23,27,30,31] Ehrenkranz[12] reports that in infants of equivalent weight, those who are born SGA show more rapid catch up growth prior to discharge than those born AGA. Bertino,[23] on the other hand, reports that growth in infants born SGA is impaired relative to those born AGA.

It should be noted that growth failure is exaggerated and catch up growth is slower with greater degrees of prematurity.[9,23] It is therefore important to adjust for gestational age as a confounding factor in the assessment of growth failure. Bertino et al[23] do adjust for gestational age and, by doing so, are able to show impairment in growth in the AGA group prior to discharge. More rapid catch up growth, divergent from that of SGA infants, occurs after discharge. A similar pattern of more marked early growth failure in infants born AGA relative to those born SGA has also been reported by Diekmann.[81] Early growth failure in infants born AGA is most likely a function of lower gestational age and associated morbidities and is followed by more rapid catch up growth than that seen in infants born SGA.

A high proportion of infants born SGA has been shown in other studies of VLBW infants in South Africa.[34,82] Possible contributing factors include the high prevalence of HIV infection, maternal under nutrition and severe maternal disease such as hypertension, pre-eclampsia, eclampsia and maternal diabetes. Because CMJAH is a referral centre for complicated pregnancies and deliveries, a large number of cases of severe maternal illness are seen.

5.3.3 Weight relative to Length

VLBW infants differ from term infants in their pattern of excess weight relative to length. The difference was most marked in the current study between term and 4 months CGA and only disappeared between 5 to 6 months CGA. This excess in weight relative to length in preterm and VLBW infants has been reported previously.[9,11]

As discussed in 1.1 above, the VLBW infant has a propensity for excess abdominal fat deposition in the neonatal period.[39,45] In addition, emphasis on rapid catch up growth leads to the use of calorie dense formulae, breast milk supplementation and possible overfeeding. Increased caloric intake increases fat deposition and weight gain but doesn't necessarily increase length. These factors may contribute to the excess weight relative to length seen during catch up growth in VLBW infants.

5.3.4 Head Circumference

Growth in head circumference in the study sample was similar to that of both international and South African VLBW infants and showed early catch up by 3 months CGA relative to term infants. Only 5% of the sample remained more than 2SD below the mean at 18 months CGA. This is in contrast to studies by Cooke et al[33] and the EPICure study[22] which show marked deficits in head growth and an absence of catch up in head circumference by 7 years of age and by 30 months of age respectively. Important to note is that the subjects in the EPICure study were extremely premature (all ≤ 25 weeks gestation) which has been shown to be associated with impaired catch up growth in weight, length and head circumference.[9,11,12,22]

Rapid catch up in head circumference has similarly been reported by Cooper and Sandler[34] in their study of a group of South African VLBW infants in Soweto. They showed that catch up in head circumference occurred more quickly than catch up in weight and length. By 12 months CGA head circumference plotted on average on the 45^{th} – 46^{th} percentile of a term growth reference.

The process of catch up growth discussed above is characteristic of VLBW infants. The rate and extent of catch up growth complicates the interpretation of growth monitoring in this group. The excess weight relative to length in preterm and VLBW infants relative to

healthy term infants is also characteristic and is an additional factor complicating the monitoring and interpretation of growth based on term infant growth charts.

5.4 The Dilemma of Growth Monitoring

The growth of the current cohort of VLBW infants more closely resembled that of other VLBW infants than that of healthy term infants. When VLBW infants in the study were monitored using growth standards based on healthy term neonates (the WHO-CGS[55]) they invariably plotted on or below the lower percentiles, even when age was adjusted for prematurity. When the infants were assessed using a reference specific to VLBW infants (the IHDP reference[24]), growth deficits were largely confined to deficits in length for age. It is clear that the choice of growth reference has a significant effect on whether an infant is assessed as having optimal or suboptimal growth. This raises the dilemma of optimal growth and growth monitoring in the VLBW infant.

Rapid catch up growth, although beneficial for neurodevelopmental outcomes and final stature,[14,33,43,44] is associated with adverse metabolic and cardiovascular outcomes.[35-39,83] The allowance for more gradual catch up growth, for example by using a VLBW reference for growth monitoring, may ameliorate the associated long term adverse consequences. A second approach to avoid the need for rapid catch up growth would be to limit the extent of initial growth failure by optimizing nutritional management and decreasing morbidity in the early neonatal period where possible. In addition, the

promotion of breastfeeding may be protective against adiposity and rapid weight gain whilst maintaining positive neurodevelopmental outcomes.[15,47,48] These factors do, however, require further research.

The development of a growth reference specific for preterm and VLBW infants is difficult as many of these infants have significant morbidity in the neonatal period and infancy making it difficult to accumulate a large, representative sample of healthy VLBW infants. An ideal growth reference for monitoring the growth of VLBW infants is not currently available. This is an important factor complicating growth assessment and monitoring in this group.

5.5 Factors Contributing towards Growth Failure

As outlined above, the growth of VLBW infants is characterized by early growth failure followed by gradual catch up growth. The study sample was analyzed to determine if specific factors affect growth attainment at 12 months CGA. These factors included size relative to gestational age, severe illness in the neonatal period, the need for assisted ventilation and HIV exposure at birth. Of these factors only size relative to gestational age affected growth attainment at 12 months CGA in the current sample. Infants born SGA were significantly lighter and shorter at 12 months CGA than those born AGA. Head circumference was not significantly different between the 2 groups. Of importance is that the proportion of male and female infants was equal in the AGA and SGA groups.

The difference in weight and length at 12 months CGA therefore cannot be ascribed to differences in sex. Growth failure in infants born SGA has been demonstrated previously.[23,27,30]

The lack of a statistically significant difference in growth attainment at 12 months CGA in the analysis of need for ventilation and severe illness in the neonatal period may have been due to small sample sizes in these groups. For example, the number of infants admitted to ICU in the current study (21.6%) was less than would be expected. This occurred for two reasons; firstly, the neonatal unit's policy at Johannesburg Hospital is not to ventilate infants with a birth weight <900g due to limited resources. Secondly, neonates with HMD are given surfactant therapy and placed on nasal CPAP in the high care area as a first line of management. Only those patients who fail nasal CPAP are admitted to ICU for invasive forms of ventilation. These factors, in addition to loss to follow up, lead to small sample sizes at 12 months CGA in the relevant groups.

Previous studies have shown deficits in weight, length and head circumference associated with both illness in the neonatal period and severe respiratory disease.[12,22] The results from the current study should therefore be interpreted with caution.

The lack of a statistically significant difference in growth attainment at 12 months CGA in HIV exposed relative to HIV unexposed infants is to be expected as none of the HIV

exposed infants in the sample who were tested for HIV in infancy were HIV infected. This is important as HIV exposure, although known to cause LBW,[84-86] is associated with catch up growth in infancy and childhood.[84] Growth thereafter resembles that of HIV unexposed infants and exceeds that of HIV infected infants and children.[87-89]

The high associated morbidity seen in VLBW infants as a group can be appreciated from the findings in the current study. The impact of associated morbidity on growth attainment at 12 months CGA is not as well illustrated in the current study as in previous studies,[12,22] most likely due to the small sample sizes available for analysis. Despite this the impact of comorbid conditions in the neonatal period, which complicate growth in VLBW infants, should be acknowledged.

6.0 CONCLUSION

Growth monitoring and assessment is an important tool in the care of infants and children, particularly VLBW infants. As demonstrated in the current study, the assessment and monitoring of growth in VLBW infants is complicated by high associated morbidity and unique growth patterns relative to healthy term infants. Initial growth failure followed by gradual catch up growth is characteristic. Particular to South African VLBW infants is persistent length for age deficits. These deficits may be related to the large proportion of infants in the sample being born SGA but also likely reflect the high prevalence of stunting in South African children as a whole.

Difficulties in growth monitoring are compounded by controversies surrounding the optimal rate and extent of catch up growth. Rapid catch up growth, although advantageous in certain respects, is also detrimental to cardiovascular and metabolic health in later childhood and adulthood. More gradual catch up growth may be more appropriate in order to avoid adverse long term health outcomes while maintaining the advantages of catch up growth with respect to neurodevelopment and stature.

In addition to differences in growth patterns, the absence of an ideal growth reference for VLBW infants makes the interpretation of growth parameters difficult. Specific recommendations for growth monitoring in South African VLBW infants are put forward in section 7.0 below. However, ongoing research in the area of growth in VLBW infants is required, ideally with multicentre collaboration nationally and internationally, in order to develop a growth standard based on a large, representative sample of “healthy” VLBW infants.

7.0 RECOMMENDATIONS

Current recommendations for growth monitoring of VLBW infants in South Africa should include:

1. The use of growth references specific to VLBW infants (such as the IHDP growth references) until 2 years CGA

2. The use of growth references derived from healthy term infants (such as the WHO-CGS) after 2 years CGA
3. Promotion of breastfeeding, especially in the first 6 months of life
4. Education of caregivers and primary healthcare providers on expectations of growth in premature and VLBW infants

Adherence to the above recommendations will adjust current expectations of growth in the VLBW infant to a more realistic growth trajectory with a goal of healthy catch up growth in mind. The risks and benefits of this should be the focus of future research.

8.0 LIMITATIONS OF THE STUDY

8.1 Study design

A major limitation of this study is that it was a retrospective chart review. The original "Outcome review of very low birth weight infants in Johannesburg" study was designed and conducted prospectively to assess, amongst other things, neurodevelopmental outcomes of VLBW infants in this group. Growth was not a key feature of the original study and certain important information was therefore not sufficiently detailed, for example feeding history and parental anthropometry. The results obtained from the analysis were limited by what was available in patient files. In addition measurement techniques could not be adequately standardized before commencement of the study.

Due to the retrospective nature of the study we were also not able to follow patients up and measure growth parameters at specific ages. The result of this is that, even though the initial cohort consisted of 139 infants, the sample size for any given age group was relatively small. This was particularly so after 12 months CGA and was further compounded when the sample was differentiated into male and female subgroups making the interpretation of the data less reliable at these points.

8.2 Gestational Age Determination

A second limitation is that gestational age was determined by Ballard score. Ballard score is known to overestimate gestational age by approximately 2 weeks and is not as reliable as early ultrasound for the accurate assessment of gestational age.[59] In addition to this, the Ballard score was performed by junior attending staff which, especially in the case of a subjective assessment, leads to inaccuracies. The Ballard score should ideally have been performed by a single trained observer. This is, however, difficult to apply in our setting.

8.3 Loss to Follow Up

Loss to follow up is common. This is particularly so in the South African setting and has been found in previous studies.[34,82] In the current study 30.9% (43 infants) of the initial cohort was lost to follow up by 12 months CGA. Three of the 43 patients lost to follow up had demised, 3 had new caregivers (due to maternal death or adoption) and 11 had

relocated. In the remainder the cause for lack of attendance was not known as contact was unable to be made with the caregiver due to incorrect contact details or cell phones being switched off.

It is not surprising that the above factors contributed to loss to follow up in the current study given that the community that CMJAH serves is a high density urban and periurban population with high levels of poverty, unemployment and poor socioeconomic circumstances. In addition, the population is a very mobile one with many patients moving between provinces and travelling long distances to attend follow up clinics.

Despite these limitations, the current study provides valuable information regarding the growth of VLBW infants in Johannesburg and highlights many of the difficulties surrounding growth assessment and monitoring in this group.