Morbidity and Mortality in small for gestational age very low birth weight infants in a middle-income country.

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Declaration

I, Marcia Mangiza do hereby declare that the work on which this dissertation is based on is my original work (except where acknowledgements indicate otherwise) and neither the whole work nor any part of it has been or is being submitted for another degree to any other university.

Signature……. Signed by candidate

Date 13/03/2021……………………………………………

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Chapter 1:

1.1 INTRODUCTION

Small for gestational age (SGA) is defined as a birth weight that is below the 10th percentile for gestational age [1]. There is a high prevalence of SGA infants in low and middle-income countries (LMIC) with approximately 20% of infants having a birth weight which is less than the 10th centile[2].

SGA includes infants who are constitutionally small and those who have intrauterine growth restriction due to environmental or genetic factors. SGA is commonly used as a proxy for intrauterine growth restriction and in settings with a high prevalence of SGA it is more likely a result of fetal intrauterine growth restriction [3]. Intrauterine growth restriction occurs when gaseous exchange and nutrient delivery to the fetus are not sufficient to allow it to thrive in-utero. In LMIC factors like poor maternal nutrition [4], maternal infections plus other morbidities [5], young maternal age and short birth spacing [6, 7] contribute significantly to the increased prevalence of SGA.

Prematurity and its complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015[8]. The mortality risk associated with being premature and small for gestational age is substantially higher than for either alone [9]. In a pooled country analysis in low and middle-income countries infants who were preterm and small for gestational age were found to have a 10-40 times higher risk of mortality compared with term and appropriate for gestational age infants (AGA) [9].

Groote Schuur Hospital (GSH) is a public hospital, with a highly specialized neonatal unit. There are 75 neonatal beds of which 20 are for intensive care. The neonatal unit admits up to 2000 babies a year and approximately 500 very low birth weight (VLBW) infants. Since 2012 GSH NICU has been using the Vermont Oxford Network (VON) database for collecting data on neonatal morbidity and mortality of

VLBW infants. VON is a non-profit, voluntary worldwide collaboration dedicated to improving the quality, safety, and value of neonatal intensive care [10]. The GSH VON VLBW database enrolls neonates with birth weights between 401 and 1500g if they are born at GSH or transferred there within the first 28 days of life. Infants that are subsequently transferred from GSH to other hospitals are followed up to document morbidity and mortality prior to discharge in the GSH VON VLBW database. Using this database we sought to evaluate the impact of small for gestational age on outcomes of very low birth weight infants as this was unknown in our institution and has generally not been well described in low and middle-income countries.

It is crucial to have accurate information on the outcomes of small for gestational age infants as obstetric decision making on such issues as timing of delivery and mode of delivery are usually based on the likelihood of survival without major disabilities. Data on these outcomes is also important for parental counselling. Insight on the morbidities which are faced by small for gestational age infants can be used to guide prevention and management strategies.

In Taiwan Li-Yi Tsai et al found an increased risk of mortality among small for gestational age very low birth weight infants [11]. In contrast to these findings, Horbar et al. found that SGA status was associated with an increased likelihood of survival among VLBW infants in the first 28 days of life at participating VON member hospitals in the USA [12]. The analyses in this study, however, were based on birth weight rather than gestational age. The authors concluded that SGA had a lower risk of mortality than AGA at any given birth weight, recognizing that these infants were more mature, with older gestational ages at birth. This distinction in analyses is important as gestational dating of pregnancies in LMIC is improving [13] allowing for better characterization of preterm risks.

Respiratory distress syndrome is a significant cause of morbidity and mortality among very low birth weight infants. It is generally believed that in SGA infants the incidence of RDS is much lower because of increased corticosteroid production as a result of exposure to prenatal stress [14]. Some studies however have shown no difference in respiratory distress syndrome among SGA and appropriate for gestational age (AGA) very low birth weight infants [11, 15] with other studies quoting an increased incidence of respiratory distress syndrome among the SGA [16]. Fetal growth restriction is associated with acidosis and hypoxia, which may result in reduced surfactant production and decreased blood flow to the fetal lungs hence an increase in the incidence of respiratory distress syndrome [17].

GSH has reported low prevalence of bronchopulmonary dysplasia (BPD) [18], a serious pulmonary morbidity in premature infants with lifelong complications. The incidence of BPD has been shown to be two to six fold higher among SGA infants compared to their AGA counterparts [19, 20]. Proposed mechanisms for the increased risk include increased exposure to pro-inflammatory cytokines both prenatally and immediately postnatally in addition to malnutrition [21]. Zaw et al found no difference in the risk of BPD in preterm SGA compared to AGA infants [22].

Necrotizing enterocolitis is the most serious gastro-intestinal complication affecting very low birth weight infants. The incidence of NEC is 5% for VLBW infants and 10% for ELBW infants [23]. Intrauterine growth restriction is one of the documented risk factors for NEC. [24]IUGR is associated with hypoxia and ischemia, redistribution of blood flow occurs with a resultant reduction of blood flow to the splanchnic circulation. Ischemic injury to the bowel and reperfusion injury with an increased formation of oxygen free radicals are thought to be some of the mechanisms that increase the risk of NEC in growth retarded infants. [25]Boghossian et al in a VON study done in the United states of America found that the risk of NEC was significantly higher among SGA infants starting from week 27 and increasing to 29 weeks[26] . Li-Yi-Tsai et al did not find any difference between the incidences of NEC in SGA versus AGA infants [11].

Retinopathy of prematurity is one of the most common preventable causes of blindness in the premature infant. As more premature infants survive due to improved neonatal care the incidence of

ROP has been increasing and South Africa has become part of the so called 'third epidemic of ROP' [27] .Among infants < 32 weeks the incidence of ROP is approximately 20% in countries with very low neonatal mortality rates (<5 per thousand births) to nearly 40% in countries with greater mortality rates. [28].There is conflicting evidence when it comes to the association of intrauterine growth restriction with ROP , with some studies showing a four-fold increase in risk of severe forms ROP [26,11] .Other studies have failed to find a difference between the development of severe forms of ROP in growth restricted very low birth weight infants as opposed to those who are well grown[29].

Early onset neonatal sepsis is defined as bacteremia or bacterial meningitis occurring at $\leq$ 72 hours in infants hospitalized in the NICU [30]. Up to 20% of all very low birth weight deaths are related to sepsis, and infants with sepsis are 3 times more likely to die than those without[31]).Boghossian et al found a protective effect of SGA against Early onset sepsis from GA 24-29 weeks. This protective effect was thought to be as a result of the lower chorioamnionitis rate in SGA infants [26].

Late onset neonatal sepsis is defined as sepsis occurring after 72 hours in infants admitted to the neonatal intensive care unit [32]. In contrast to their findings for early onset sepsis, Boghossian and colleagues found a higher risk of late onset sepsis among SGA infants [26]. Troger et al found an increased risk of neonatal sepsis in very low birth weight small for gestational age infants. This finding was elucidated to the different treatment modalities required by SGA infants such as increased rate for central venous catheters, longer time to reach full enteral feedings and frequent use of third-line antibiotics compared with non-SGA infants [33]. Little is known to what extent differences in humoral and adaptive immune responses in SGA infants contribute to sepsis pathophysiology. Previous studies have noted thymic atrophy as well as lymphopenia and deficiencies in humoral responses in SGA infants [34].

1.2 ETHICAL CONSIDERATIONS

The study was done using the GSH VON database which has ethical approval R117/2020. It posed no risks to patients. Informed consent to collect data for the VON database was waived for the following reasons;

- GSH is a teaching hospital and it is understood that data is collected-there are notices stating this at the hospital
- Many preterm infants die in the first 24 hours of life. It would be inappropriate to ask parents for consent for the database in these situations.
- All identifying information is removed.
- A dataset that did not capture all admissions would not be worthwhile.

A separate ethics approval was also granted for using the dataset for the present study reference 102/2019.

1.3 AUTHOR GUIDELINES OF THE JOURNAL WHICH PAPER HAS BEEN FORMATTED.

This study has a manuscript that has been formatted for submission to the journal of perinatology. The journal of perinatology is an American based journal which publishes articles that include perinatal topics aimed at improving neonatal outcomes. Our study was on outcomes of small for gestational age infants involves infants who are a product of high risk pregnancies which is of special interest in perinatology. The results of our study are important for obstetric decision making and the counselling of parents who have small for gestational age infants which is highly relevant to the readers of the journal of perinatology. There are very few studies done on outcomes of small for gestational age very low birth weight infants in low and middle-income countries which I think would entice the readers.

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CHAPTER 2

MORBIDITY AND MORTALITY IN SMALL FOR GESTATIONAL AGE VERY LOW BIRTH WEIGHT INFANTS IN A MIDDLE-INCOME COUNTRY

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ABSTRACT

Objective: To evaluate the impact of small for gestational age on outcomes of very low birth weight infants at Groote Schuur Hospital, Cape Town, South Africa.

Study design: Data was obtained from Vermont Oxford Network Groote Schuur Hospital database from 2012 to 2018. Fenton growth charts were used to define small for gestational age as birth weight < 10^{th} centile for gestational age.

Results: Mortality (28.9% vs 18.5%, adjusted risk ratio (aRR) 2.1, 95% confidence interval (CI) 1.6-2.7), bronchopulmonary dysplasia (14% vs 4.5%, aRR 3.7, 95% CI 2.3-6.1) and late onset sepsis (16.7% vs 9.6%, aRR 2.3, 95% CI 1.6-3.3) were higher in the small for gestational age than in the non-small for gestational age group.

Conclusion: Small for gestational age infants have a higher risk of mortality and morbidity among very low birth weight infants at Groote Schuur Hospital. This may be useful for counselling and perinatal management.

INTRODUCTION

Small for gestational age (SGA) is defined as a birth weight that is below the 10th percentile for gestational age [(1)]. SGA includes infants who are constitutionally small and those who have intrauterine growth restriction due to environmental or genetic factors [(2)].

SGA is commonly used as a proxy for intrauterine growth restriction and, in settings with a high prevalence of SGA, it is more likely to be as a result of intrauterine growth restriction rather than being constitutionally small [(3)]. Intrauterine growth restriction is more prevalent in low- and middle -income countries (LMIC) [(4)], due to contributing factors like poor maternal nutrition, young maternal age, maternal infections and short birth spacing [(5, 6, 7, 8)]. Approximately one in five infants born in LMIC is small for gestational age [(4)]. Despite this high prevalence of SGA, the outcomes of preterm babies have not been well described in these settings.

In LMIC, mortality risk associated with being premature and SGA is substantially higher than for either alone, with these infants having a 10-40 times higher risk of mortality in the first month of life compared with term and appropriate for gestational age infants [(9)]. We sought to evaluate the impact of SGA on outcomes of very low birth weight (VLBW) infants at the Groote Schuur Hospital neonatal unit in Cape Town, South Africa. Our objectives were to compare rates of in-hospital mortality and neonatal morbidities of SGA preterm infants with non-SGA preterm infants and to compare outcomes of symmetrical versus asymmetrical SGA infants.

MATERIALS AND METHODS

Groote Schuur Hospital (GSH) is a public hospital with a highly specialized public neonatal unit. There are 75 neonatal beds of which 20 are for intensive care. The neonatal unit admits up to 2000 babies a year and approximately 500 VLBW infants. We obtained data from the Vermont Oxford Network (VON) GSH database from 2012 to 2018. VON is a non-profit, voluntary worldwide collaboration dedicated to improving the quality, safety, and value of neonatal intensive care [10]. The GSH VON VLBW database enrols neonates with birth weights between 401 and 1500g if they are born at GSH or transferred there within the first 28 days of life. Infants that are subsequently transferred from GSH to other hospitals are followed up to document morbidity and mortality prior to discharge in the GSH VON VLBW database. Our study included infants born at 27 weeks 0 days - 30 weeks 6 days gestational age in order to capture both SGA and AGA for the weight category 501 - 1500g. We excluded neonates with major congenital or chromosomal anomalies. The study was approved by the Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town (R117/2020).

Study Variables

SGA was defined as a birth weight below the 10^{th} centile and non-SGA as birth weight $\geq 10^{th}$ centile using sex-specific Fenton growth charts (Figure 1) [11]. Non-SGA comprised of appropriate for gestational age (AGA), defined as between the 10^{th}-90^{th} centile and large for gestational age (LGA), defined as >90^{th} centile on the sex-specific Fenton growth charts. Gestational age was estimated using early ultrasound (<20 weeks) as the gold standard. Ballard score or postnatal foot length [12] were used when early ultrasound was not available. Symmetric SGA was defined as both birth weight and head circumference below the 10th centile on the Fenton growth chart and asymmetric SGA when birth weight was below the 10th centile and head circumference was above the 10th centile for gestational age on the Fenton growth chart.

Infants were considered to have exposure to antenatal corticosteroids if betamethasone, dexamethasone or hydrocortisone was administered intramuscularly or intravenously to the mother during pregnancy at any time prior to delivery. Mothers were reported to have received prenatal care if any obstetric care was provided prior to the admission during which the birth occurred. Maternal hypertension was defined as chronic or pregnancy induced hypertension (above 140 systolic or 90 diastolic), with or without edema or proteinuria. Eclampsia or pre-eclampsia were considered forms of pregnancy induced hypertension.

Mortality was defined as death before discharge home. Respiratory distress syndrome (RDS) was defined as respiratory distress from birth with need for >35% Fio2 in the first 48 hours of life despite CPAP or invasive mechanical ventilation. Papille's criteria [(13)] was used to define intraventricular haemorrhage (IVH) noted on cranial ultrasound scan and severe IVH was defined as grades 3 and 4. Bronchopulmonary dysplasia (BPD) was defined as the requirement of oxygen and or respiratory support at 36 weeks postmenstrual age or, if discharged at 34 or 35 weeks, oxygen requirement at discharge [(14)]. Severe retinopathy of prematurity (ROP) was defined as grades 3-5[(15)] documented by an ophthalmologist's examination, with the worst stage examination in the eye with the most advanced stage recorded. Early onset sepsis was defined as recovery of a bacterial organism on a specified list from a blood or cerebrospinal fluid culture within three days of birth. Late onset sepsis was defined as recovery of a bacterial organism on a specified list from blood or cerebrospinal fluid culture, coagulase negative staphylococcal infection or fungal organism after day 3 from birth; coagulase negative staphylococcus also required signs and symptoms of infection and at least 5 days of antibiotic therapy

[16]. Necrotizing enterocolitis (NEC) was diagnosed by the clinical team at surgery, post-mortem or clinically and radiographically using standard criteria from the VON Manual of operations definitions [16].

Analyses

All analyses were conducted in statistical analysis system 9.4. Logistic regression with a Poisson distribution and log link were used to produce risk ratios for each outcome adjusted for sex, antenatal steroid exposure, inborn/ outborn status, and gestational age in weeks [17].

RESULTS

Characteristics of the study population

A total of 1879 VLBW infants between the gestational ages of 27 weeks 0 days - 30 weeks 6 days were admitted at GSH NICU between 2012 and 2018. The prevalence of SGA among the study population was 12.7%. The mean gestational age for both SGA and non-SGA infants was 29 weeks. The mean birth weight in the SGA group was 799 grams and 1083 grams in the non-SGA group. The majority (99%) of the non-SGA group were AGA with only 20 infants being LGA. The mothers of SGA infants were more likely to have received antenatal steroids (73.6% vs 66.4%) and to have hypertension (60.1% vs 40.4%). Table 1 depicts demographic features of the study population based on SGA status. Figure 2 shows the proportion of SGA infants at each gestational age.

Neonatal Morbidity and Mortality

During the study period 372 of the infants demised before discharge home with an overall mortality rate of 19.7%. Mortality rate was significantly higher in the SGA group at 28.9% vs 18.5% (adjusted risk ratio (aRR) 2.1, 95% confidence interval (CI) 1.6-2.7) compared to the non-SGA group. Bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and late onset sepsis (LOS) were significantly higher in the SGA group. Table 2 shows the incidence of neonatal morbidity and mortality in SGA vs non-SGA VLBW neonates.

Table 3 shows the incidence of neonatal morbidities among survivors in the study population. Among survivors only BPD and late onset sepsis remained statistically significant, with both morbidities occurring more frequently in the SGA group. Total length of stay among survivors was a median of 42 days (IQR 28, 56) for SGA infants and a median of 41 days (IQR 25, 56) for non-SGA infants.

Among the SGA infants, 217 were categorized into symmetrical /asymmetrical SGA (22 infants were missing birth head circumference). There were no statistically significant differences in mortality or morbidities when these two groups were compared.

DISCUSSION

In our study population, 12.7% of the infants were SGA as defined as weight less than the 10th centile at birth by the Fenton growth charts [(11)]. This is higher than the prevalence in two studies done in high income countries which found a SGA prevalence of 9% among infants 501-1500g [(18)] and 10% in infants 22-29 weeks.[(19)] Our finding is in support of studies that have documented SGA to be more prevalent in resource limited countries[(4)]. Poor maternal nutrition [(5)], maternal infections plus other morbidities [(6)], young maternal and age and short birth spacing contribute significantly to this increased prevalence [(7,8)].

We found the mortality rate to be significantly higher among the SGA infants compared to non-SGA infants. The increased risk of mortality is similar to the mortality that Li-Yi Tsai et al. found in Taiwan which was a middle-income country at that time.[20] Several studies in high income countries have evaluated the association of SGA status on the outcomes of VLBW infants. These analyses have differing conclusions depending on the basis of the comparison groups, by gestational age at birth or by birth weight. In a study including VON member hospitals in the United States of America (USA), Boghossian et al. found an increased risk of mortality among SGA infants born at 22-29 weeks' gestational age and they noted that mortality was however not homogenous across gestational ages. [19] In contrast to our findings, Horbar et al. found that SGA status was associated with an increased likelihood of survival among VLBW infants in the first 28 days at participating VON member hospitals in the USA [21]. The analyses in this study, however, were based on birth weight rather than gestational age. The authors concluded that SGA had a lower risk of mortality than AGA at any given birth weight, recognizing that these infants were more mature, with older gestational ages at birth. This distinction in analyses is important as gestational dating of pregnancies in LMIC is improving, [22] allowing for better characterization of preterm risks. Our study, therefore, compared infants based on gestational age using a hierarchy of early ultrasound, followed by postnatal examination with Ballard score or foot length. In extremely low birth weight (ELBW) infants in the United Kingdom, Charles et al. found no difference in mortality between SGA and AGA even after correcting for gestational age [23]. Their study population was more premature than ours with a generally higher mortality. Although the ELBW population is a high-risk group globally, they do not represent the focus for neonatal improvement efforts in LMIC, hence the VLBW inclusion in our study.

Levels of BPD are very low at GSH [24] but we found an increased risk of BPD among SGA infants, 14% vs 4.5% in the non-SGA group. This finding is in keeping with other studies which have found the risks of BPD being two to six fold higher among SGA infants.[23,25,26] Proposed mechanisms for the increased risk of BPD include exposure to pro-inflammatory cytokines both prenatally and immediately postnatally in addition to malnutrition [(27)]. Despite having an increased risk of BPD there was no statistically significant difference in RDS between the SGA and non-SGA infants. It is postulated that in SGA infants the incidence of RDS is much lower because of increased corticosteroid production as a result of exposure to prenatal stress. [(28)] Despite a higher percentage of antenatal steroids in the SGA group as compared to the AGA group, the incidence of RDS was not lower in the SGA infants. Our clinical definition of RDS could have captured additional respiratory pathology unrelated to surfactant deficiency, such as congenital pneumonia and respiratory distress due to sepsis and therefore masked a true difference in RDS. However in a study including US member hospitals of VON, Boghossian et al. found no difference in the incidence of RDS between SGA and non-SGA infants who had not received antenatal steroids, and for those who received antenatal steroids the incidence of RDS was higher among the SGA group. [(19)]

NEC is the most serious gastrointestinal complication affecting VLBW infants. The risk of NEC was higher in the SGA group when looking at the entire study population but when we analysed the risk among survivors the difference between the groups did not reach statistical significance. This finding suggests a high mortality for SGA babies who develop NEC. Bhoghossian et al also found an increased risk of NEC among SGA infants.[(19)] Redistribution of blood flow with a resultant reduction of blood flow to the splanchnic arteries are thought to be some of the mechanisms that increase the risk of NEC in growth restricted infants. [(29)]

SGA infants in our study were more prone to developing late onset neonatal sepsis. Troger et al. had similar findings and this was elucidated by an increased use of central venous catheters and a longer time to reach enteral feeds in the SGA population [(30)]. Previous studies have noted thymic atrophy as well as lymphopenia and deficiencies in humoral responses in SGA infants as additional potential mechanisms related to late onset sepsis. [(31)]

As more premature infants survive due to improved neonatal care the incidence of ROP has been increasing and South Africa has become part of the third epidemic of ROP. [32] Bhoghossian [19] et al in VON USA study and Li-Yi-Tsai [20] in Taiwan found an increased risk of ROP among SGA infants. We did not find a statistically significant risk of ROP in our SGA babies. This may be explained by the small numbers of infants who were screened as the screening program for ROP only started in 2015 at GSH.

About 30-40% of infants in our institution have an early ultrasound scan (<20 weeks gestation), when an early ultrasound was not available Ballard score or postnatal foot length were used to estimate gestational age which may be less accurate [33]. Our study was a single site hospital study hence it may not be generalized to all resource limited settings. We only looked at in-hospital mortality and yet the associations of SGA may be long-term. This study is one of very few studies to report on outcomes of SGA VLBW outcomes in a middle-income country. The study was done in a tertiary setting with high volumes of VLBW. We used the VON database with standard data definitions adapted to harmonize with institutional guidelines in management.

CONCLUSION

GSH, a public academic hospital in a middle-income country, had a 12.7% rate of SGA VLBW infants, higher than often reported from high-income countries. SGA VLBW infants at GSH had approximately twice the risk of mortality compared to their AGA counterparts, and increased morbidities. These findings are useful for perinatal decision making and counselling of parents. Further research should explore whether the use of guidelines in SGA VLBW infants may impact the development of neonatal morbidities such as NEC, late onset sepsis and BPD, and mitigate the increased mortality rates we found in the SGA VLBW infants at GSH in South Africa.

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

1. MM was responsible for designing the study proposal, writing the protocol and report, interpreting results and looking up references.
2. DE was responsible for designing the study proposal, editing the protocol and report, interpreting results and updating references list.
3. EE was responsible for designing the study proposal, analysing the data, designing tables and figures plus editing the report and references.
4. NR was responsible for designing study proposal and editing the report.
5. LT was responsible for designing the study proposal, editing the protocol and report, interpreting results, designing figure 1 and updating references.

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Anterior Lens, Last Menstrual Period and Also a Clinician's Non-Structured Assessment. *J Trop Pediatr*. 2021;67(1):fmaa113. doi:10.1093/tropej/fmaa113.

FIGURES

Figure 1: Fenton growth illustrating SGA (blue) and non-SGA (green) between 501-1500g.

Figure 2: Percent of total infants by SGA (blue) and non-SGA (red)

TABLE 1: Demographic features of study population of infants who were born 27-30weeks + 6days gestational age and 501-1500g from 2012-2018

	SGA (N=239)	**Non -SGA (N=1640)**
Gestational age (weeks), mean (SD)	29 (1)	29 (1)
Birth weight (grams), mean (SD)	799 (119)	1083 (182)
Head circumference at birth(cm), mean (standard deviation)	24 (2)	26 (2)
Maternal hypertension (%)	60.1	40.4
Antenatal steroids (%)	73.6	66.4
Female (%)	52.7	48.4
Prenatal care (%)	87.5	82.4
Inborn (%)	91.2	85.4

SD (standard deviation)

TABLE 2: Incidence of neonatal morbidity and mortality in very low birth weight infants classified as SGA or AGA. Risk ratios for association between SGA and Non-SGA (reference group) adjusted for sex, antenatal steroids, and gestational age at birth.

	SGA (N=239)	**Non-SGA (N=1640)**	**aRR (95% CI)**
	n/N (%)	n/N (%)	
MORTALITY	69/239 (28.9)	303/1640 (18.5)	2.1 (1.6, 2.7)
RDS	103/238 (43.3)	764/1632 (46.8)	1.0 (0.8, 1.3)
BPD	24 /171(14.0)	61/1343 (4.5)	3.7 (2.3, 6.1)
IVH (Grades III,IV)	10/211 (4.7)	116/1512 (7.7)	0.8 (0.4, 1.6)
NEC	24/238 (10.1)	107/1632 (6.6)	1.7 (1.1, 2.7)
ROP (Stages III-V)	4/78 (5.1)	15/579 (2.6)	3.2 (1.0, 10.2)
Early onset sepsis	2/238 (0.8)	30/1632 (1.8)	0.5 (0.1, 2.1)
Late onset sepsis	36/216 (16.7)	146/1522 (9.6)	2.3 (1.6, 3.3)

_RDS – Respiratory distress syndrome BPD- Bronchopulmonary dysplasia IVH- Intraventricular haemorrhage NEC- Necrotizing enterocolitis ROP- Retinopathy of prematurity

TABLE 3: Incidence of neonatal morbidities among survivors in very low birth weight infants classified as SGA or Non-SGA. Risk ratios for association between SGA and AGA (reference group) adjusted for sex, antenatal steroids, and gestational age at birth.

	SGA (N=170)	**Non-SGA (N=1337)**	**aRR (95% CI)**
	n/N (%)	n/N (%)	
RDS	53/170 (31.2)	538/1336 (40.3)	0.9 (0.7, 1.2)
BPD	24/170 (14.1)	56/1328 (4.2)	4.0 (2.5, 6.7)
IVH (Grades III,IV)	1/168 (0.6)	45/1280 (3.5)	0.2 (0.0, 1.6)
NEC	10/170 (5.9)	54/1336 (4.0)	1.7 (0.9, 3.5)
ROP (Stages III-V)	3/77 (3.9)	15/568 (2.6)	2.5 (0.7, 9.2)
Early onset sepsis	2/170 (1.2)	16/1336 (1.2)	1.1 (0.2, 5.0)
Late onset sepsis	26/170 (15.3)	86/1331 (6.5)	3.3 (2.1, 5.2)

Figure 1: Fenton growth illustrating SGA (blue) and non-SGA (green) between 501-1500g

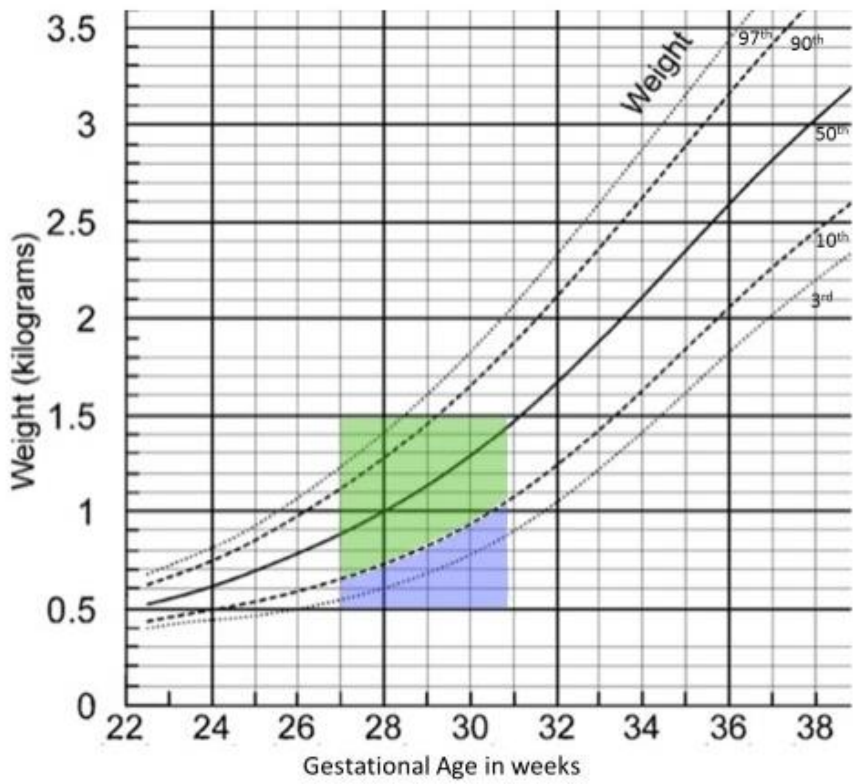
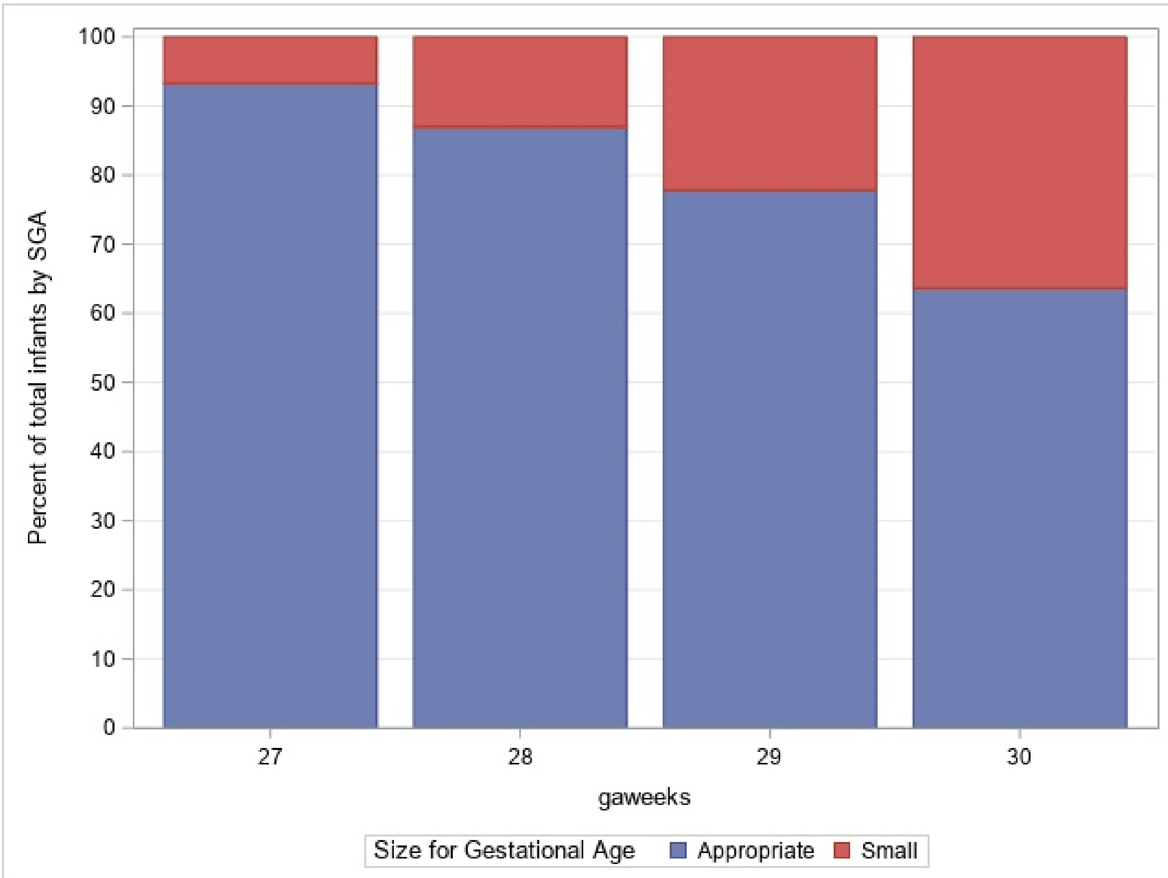


Figure 2: Percent of total infants by SGA (blue) and non-SGA (red)



APPENDICES

ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 March 2019

HREC REF: 102/2019

Dr L Tooke
Neonatal Department
H-Floor
GSH

Dear Dr Tooke

PROJECT TITLE: MORBIDITY AND MORTALITY IN SMALL FOR GESTATIONAL AGE VERY LOW BIRTH WEIGHT INFANTS. (MPHIL NEONATOLOGY CANDIDATE: DR. M MANGIZA)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

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

Approval is granted for one year until the 30 March 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Marcia Mangiza will also be involved in this study.

Please quote the HREC REF number in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
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HREC 102/2019

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A structured abstract is required for original articles and a standard abstract format is required for other types of articles. An abbreviated unformatted abstract is preferred for Review articles. For clinical trials, the abstract should also include details of where and when the trial was registered, and the Clinical Trial Number.

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Acknowledgements

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This is an example for a systematic review: MAJ was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, updating reference lists and creating 'Summary of findings' tables. SBM was responsible for designing the review protocol and screening potentially eligible studies. She contributed to writing the report, extracting and analyzing data, interpreting results and creating 'Summary of findings' tables. DIH conducted the meta-regression analyses and contributed to the design of the review protocol, writing the report, arbitrating potentially eligible studies, extracting and analyzing data and interpreting results. NAL contributed to data extraction and provided feedback on the report. FRT and RAL provided feedback on the report.

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