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Research

Case-load, associated characteristics and outcomes of small for gestational age (SGA) neonates admitted to a tertiary hospital neonatal unit in Kigali, Rwanda: a cross-sectional study

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Abstract

Introduction: small for gestational age (SGA) is defined as birth weight less than the 10th percentile with a population prevalence of 17% in sub-Saharan Africa. Mortality and morbidity are worse in SGA neonates and there are long term implications from fetal growth restriction. Objective: the goal of this study was to evaluate and report the case-load, associated characteristics and outcomes of neonates admitted with SGA at the largest tertiary public hospital in Kigali, Rwanda. **Methods:** a prospective, cross-sectional, observational study was performed. We defined SGA as birth weight <10th percentile by gender according to the Alexander reference population. Eligible infants were identified through the neonatal registry. **Results:** of 1184 admitted neonates, 38% were SGA. Mortality in these SGA neonates (16%) was higher than appropriate for gestational age neonates (AGA, 13.4%) (AOR=2.03, CI: 1.1-3.5, p=0.011). SGA neonates, compared to their AGA peers, had a more extended hospital stay, and displayed faster postnatal growth. **Conclusion:** the case-load of SGA neonates in this reference hospital setting is high. The poorer outcomes in SGA neonates speaks to the need for: i. continued improvements in antenatal care throughout the health system to decrease the prevalence of small for gestation age and therefore case-load and ii. Optimisation of direct care for SGA neonates in order to minimise negative outcomes.

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Introduction

Small for gestational age (SGA) is defined as birth weight less than the 10th percentile or less than -2 standard deviations (SDs) by reference population [1-4]. Fetal growth restriction is found in term and preterm neonates, and in both groups has important adverse effects on future survival, health, growth and development [5-8]. Being born SGA is associated with fetal distress in labor and perinatal mortality and morbidity [9-11]. SGA neonates are associated with both early and late complications. Early complications include raised mortality, infection, hypoglycaemia, and more extended hospital stay [12-16] SGA neonates have a post-natal weight catch-up period from 6-months to 2-years before most attain normal growth [17,18]. However, 10% persist with short stature throughout their childhood [19]. To be born with SGA, increases the risks of insulin resistance, obesity, hyperlipidaemia and other metabolic disorders in later life contributing to poorer health outcomes in later adult life [1,20,21]. Demographic surveys have demonstrated that Rwanda has reduced neonatal mortality significantly between 1994 and 2014, from 44 to 20 neonates per 1000 live births [22]. However, no published data are available in Rwanda for the subgroup of SGA neonates who are admitted to neonatal units.

Objective: the goal of this study was to evaluate and report the case-load, associated characteristics and outcomes of neonates admitted with SGA at the largest tertiary public hospital in Kigali, Rwanda through the use of an electronic database (registry).

Methods

Study design: this was a cross-sectional, descriptive study where the reporting has been verified in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [23].

Location: this study was carried out in the neonatal unit at Kigali University Teaching Hospital (Centre Hospitalier Universitaire de Kigali, CHUK), located in Kigali (the capital city of Rwanda). CHUK is the largest, public, tertiary referral hospital in Rwanda, and serves as a teaching hospital for the University of Rwanda (UR). The hospital has approximately 2000 deliveries annually and is a referral centre for high-risk pregnancies and deliveries. The neonatology unit has approximately 560 admissions annually (with approximately 20-30 cot capacity). The majority of admissions are neonates born in the hospital ("in-born"). Some neonates transferred from District Hospitals ("out-born") are admitted but typically these are admitted to the general pediatric department due to bed capacity and space constraints for both neonatology and maternity units [24].

Participants: inclusion criteria were all neonates admitted in the neonatal unit who had the Rwandan Neonatal Database Collection Form (RNDCF) completed prospectively and had all three data-points available to identify SGA, namely; birth weight, sex, and gestation. Exclusion criteria were cases based on retrospective data or duplicated in the neonatal database.

The neonatal database/registry (data collection and management): the CHUK neonatal registry was established in 2013 and the description of its development and use has previously been described in the literature [24-27]. A robust newborn admission record (NAR), was introduced between July and August 2012 and facilitates data-collection. Data from the paper data-collection tool is inputted into the electronic

Rwanda Neonatal Database (NDB), held in a password-protected Microsoft Access database. Pediatric residents and paediatricians on-duty for the neonatal unit complete the data-collection.

Data protection and confidentiality: all data were maintained in a secure area in a password protected database. Names or other patient identification information was not disclosed or accessible publicly.

Data quality: to assess the quality of recruitment of admitted newborns, the nursing admission book was cross-checked with the NDB at the end of the study period to retrospectively identify basic demographic information on any missing cases (Figure 1). The RNDCF was designed with a tick-box to document if a pathology or risk was present; however, multiple negative options for each outcome (i.e. No or Unknown) were not completed during data-collection [24].

Variables and outcomes: the primary outcome of this study was to assess the case-load of SGA in neonates admitted to the newborn unit. Secondary outcomes were risk factors associated with SGA birth, morbidity, mortality and confounding factors. Outcomes included the length of stay (LOS), growth rate (g/kg/day to the point of discharge), admission temperature, episodes of hypoglycaemia, and episodes of infection.

How were outcomes defined? SGA neonates were defined using the Alexander reference population as those neonates with birth weight less than 10th percentile by sex [4]. The length of stay was defined as the number of days from the date of admission to the date of discharge or death. The growth rate (g/kg/day) was defined as the weight gained or lost from the date of admission to the date of discharge divided by the length of stay and the birth weight of the neonate.

Sample size (power calculation): the primary outcome of this study was to assess the case-load of SGA of neonates admitted to the neonatal unit and not prevalence in all births. Annual admission rates are approximately 560 per year. Assuming a case-load of 24% [2] with a confidence limit of 5%, a sample size of 188 neonates is required for each year of study (4 years). A total sample of 752 was therefore required. This was surpassed by the prospective data available in the NDB.

Statistical analysis: the data was analyzed using Statistical Package for the Social Sciences (SPSS) version 24.0. Comparison of means was undertaken with independent, two-sided, t-tests. Comparison of categorical variables was undertaken with bivariate analysis with Chi-square test and description of unadjusted odds ratios (OR). This was followed by multivariate logistical regression and presentation of Adjusted Odds Ratios (AOR) with 95% confidence intervals. All risk factors were included in the multivariate analysis. All outcomes, along with the significantly associated characteristics ($p<0.05$), were included in the multivariate analysis of outcomes.

Ethical approval and consent to participate: informed consent was waived based on this being a data review with no patient interaction. The research protocol was reviewed and granted approved by the the CHUK Research Ethical Committee (Ref: EC/CHUK/300/2017) on 17th March 2017. Subjects did not receive any incentive for this study, and there were no significant physical, legal, emotional, financial and/or social risks to the subjects identified during this study.

Results

Participants: a total of 2535 neonates were available in the NDB for the study period. Of these, 1351 neonates were excluded due to duplication of cases (n=292), SGA status

unknown (n=236), and retrospectively data-inputted neonates (n=823). A total of 1184 neonates were therefore included in the analysis (Figure 1).

Data quality: the data were collected prospectively, however, not all data-points were available in all eligible neonates (Figure 1). For example, in order to calculate weight gain in g/kg/day, three variables were required and data not always available, namely; birth weight (n=43), discharge weight (n=316), admission date (n=12) and discharge date (n=155).

Case-load of SGA and baseline data: 444 (38%) of the 1184 included neonates were SGA (Table 1). There was no significance between the SGA and AGA groups with regards to sex or place of birth.

Characteristics associated with SGA: on bivariate analysis, characteristics associated with SGA were gestation and maternal hypertension (Table 2). On multivariate logistical regression analysis, the risk factors associated with SGA were prematurity, maternal hypertension, and place of birth. Mild prematurity (32-37 weeks) had the strongest association with SGA (AOR: 4.0, p<0.001).

Outcomes in SGA neonates: on bivariate analysis SGA was not associated with mortality (OR=1.25, CI: 0.9 to 1.7, p=0.18) but was associated with admission hypothermia (OR=1.4, CI: 1.0 to 1.9, p=0.02) (Table 3). Multivariate analysis revealed that mortality (AOR=2.01, CI: 1.1-3.5, p=0.01) and hyperglycaemia (AOR=3.7, CI: 1.0-13.1, p=0.03) were positively associated with SGA, while infections, hypoglycaemia, hypothermia, and need for respiratory support were not significantly associated.

Weight gain and length of stay: Infants who die during admission will have their length of stay and weight gain impacted by their death, they were therefore removed from the analysis of weight gain and length of stay. Surviving SGA infants were found to have faster weight gain during their entire stay, and a longer length of stay compared to surviving AGA neonates (Table 4).

Discussion

The goal of this study was to evaluate and report the case-load, associated factors and outcomes of neonates admitted with SGA. We demonstrated that SGA neonates made up a large proportion (38%) of the neonatal case-load. In 2012, an estimated 5.6 million infants born in sub-Saharan Africa were SGA, with a population prevalence of 17% [7,10,28]. The case-load in our centre is therefore double the likely population prevalence. A likely reason for this increased case-rate is that CHUK is one of the specialised centres in Rwanda with the capacity and expertise to manage high risk pregnancies. Hence, reflecting the health needs of these infants have after birth and the burden of care they provide on health facilities and their families.

Associated characteristics: in our cohort of admitted neonates, the characteristics associated with SGA birth were: prematurity, maternal hypertension, and place of birth. Mild prematurity (32-37 weeks gestation) had the strongest association with SGA (AOR: 4.0, p<0.001). It is well known that conditions which cause uteroplacental insufficiency such as maternal hypertension result in prematurity and increase the risk of SGA [5,29]. The prevalence of SGA in the term infant group may, potentially, be biased by the prevalence of infants with Hypoxic Ischemic Encephalopathy (HIE) in this group. Identifying associated factors, such as maternal hypertension, highlight the importance of maternal health, improving pre-conception and antenatal care, in order to reduce the case-burden of SGA and its associated outcomes in settings such as Rwanda.

Outcomes: completely preventing SGA delivery is unrealistic, therefore understanding the outcomes in these neonates is

important. Outcomes for SGA neonates reported in the literature demonstrate increased risk of death, hypothermia and hypoglycaemia [11,15,16,30]. Knowing that there is a high case-load, is pertinent to local health system planning. We identified that the mortality rate was significantly higher in SGA vs. AGA neonates (AOR=2.03, p=0.011), a rate consistent with others studies [9,11,28,31-34]. This further highlights the need for prevention, through good antenatal care. It also highlights the importance of recognising these infants and optimisation of care. Hyperglycaemia was to be more significance on multivariate analysis, and further study is needed to explore this and determine whether the significance holds or a clinical explanation is revealed. Our subsequent clinical observation is that this situation has been largely eliminated in our nursery due to the introduction of syringe pumps and more careful monitoring and choice of fluids. Consistent with previous reports, this study demonstrates no difference in early and late-onset infection rate between SGA and AGA neonates and conflicts with reports from India where SGA status increases sepsis risk [11,35,36].

Weight gain and length of stay: weight gain and length of stay in surviving neonates were stratified by gestational group. Consistent with other recent studies, the length of stay was significantly higher for SGA neonates [11,32,33]. This large dataset was able to demonstrate a significantly increased rate of growth throughout the hospital stay for the SGA infants compared to their AGA peers and is consistent with evidence from US and Swedish population-based studies demonstrating more rapid growth of SGA infants in the first 6 months of life, reflecting catch up growth [17,18]. Feeding in SGA infants is often conservative due to fears related to necrotising enterocolitis, a significant complication of prematurity. In resource-limited settings length of stay places high cost on families, places extra burden on stretched nursing teams and places infants at risk of nosocomial infections. Therefore, feeding strategies need to be identified that optimise growth and minimise length of stay.

Study strengths: there are several strengths to this description of SGA case-load. It is a large sample size prospectively collected by physicians into a well-described database. The data reflects neonates born over a long period of time, minimizing short term differences in medical providers or their care, and the process of eliminating incomplete records from the database resulted in a dataset that is still quite large. This public referral teaching hospital is likely representative of many centers in LMIC principal cities where high risk obstetric and neonatal cases are transferred in from within the surrounding metropolitan area and the more distant district hospitals.

Data collection and analysis leading to systems improvements at the clinical level is imperative in LMIC neonatal centers. One powerful result of this study is demonstrating that a database can be created, maintained, and used to generate relevant data, even in a nascent neonatal unit in an LMIC teaching site in a large public teaching hospital. The data collection form and the electronic database are easy to develop, but this effort also shows that there must be institutional support [24].

Limitations: the limitations of our neonatal registry have been fully described, in particular it is limited by the data-quality [24]. Related to this study, the database requires the co-operation and effort of residents who are encouraged to complete the data-collection process on daily rounds during the neonate´s admission in order to increase the capture of pertinent variables in real time. However, our experience suggests that many forms are completed at the point of discharge, therefore data points are not always available or completed. It is well described in the literature that hypertensive disorder of pregnancy, smoking, maternal SGA are factors associated with SGA, however, our limited variable set precluded the ability to determine the association, and potential confounding, with several important antecedent maternal and demographic characteristics, such as smoking status, maternal age, history of personal and previous delivery

SGA status, and intrapartum risks that have been linked to the delivery of an SGA infant [5]. Other limitations include the fact that CHUK is not representative of the many smaller district, regional, and private hospitals in LMIC settings and can not generate a national rate for any particular variable. No long term follow-up monitoring was performed and, therefore, the ability to study growth and development over a prolonged period are not available from our cohort. We used the US-based Alexander reference in order to classify the newborns as SGA or AGA, and the cut-offs would likely be different if there were a similar reference based on data from LMIC settings.

Conclusion

To conclude, we have identified a large case-load and mortality associated with SGA birth in our public referral teaching neonatal unit in Rwanda. Continued efforts are required to prevent fetal growth restriction by improving maternal care at all levels of the Rwandan health system, from the village community health workers and local Health Centers to the District hospitals. This should be concurrent with optimisation of direct care for SGA neonates to minimise negative outcomes.

What is known about the topic

- An estimated 5.6 million infants born in sub-Saharan Africa were born small for gestational age (SGA) in 2012, with a population prevalence of 17%;
- Factors associated with SGA birth include; advanced maternal age, primigravida state, maternal tobacco smoking, parental SGA, maternal hypertension, uteroplacental insufficiency, previous SGA neonates, low social-economic status, and maternal age <20-years;
- The mortality rate increases steadily with decreasing birth weight, and mortality is more common in male than females.

What this study adds

- The case-rate of SGA in admitted neonates is high (38%) in a Rwandan tertiary hospital;
- Mortality rate was significantly higher in SGA vs. AGA neonates (AOR=2.03, p=0.011).

Competing interests

The authors declare no competing interest.

Authors' contributions

The study was undertaken as the undergraduate thesis of the Principal Investigator (RD). RD was supported and supervised by the three authors (PC, FA & CO). CO and RT created the database. RD, JC and FU contributed to data-collection. RT was engaged in the project conception and early data-collection. MK, FU, and RD assisted the data-collection and analysis. RD and PC undertook the analysis. All authors were significant contributors in writing the manuscript. All authors read and approved the final manuscript.

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Tables and figure

Table 1: baseline data of SGA and AGA neonates

Table 2: risk factors for SGA

Table 3: outcomes in SGA neonates

Table 4: weight gain and length of stay in surviving neonates (SGA versus AGA neonates)

Figure 1: consort diagram of participants

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Table 1: baseline data of SGA and AGA neonates			
	SGA n=444 (37.5%)	**AGA n=740 (62.5%)**	**p-value X**
Gender (n=1184)			
Female	191 (36.6%)	330 (63.4%)	
Male	253 (38.1%)	410 (61.9%)	p=0.59 (df=1)
Birth Place (n=1165)			
In	365 (36.1%)	645 (63.9%)	p=0.089
Out	67 (42.6%)	88 (57.4%)	(df=1)
Gestational groups (n=1184)			
Extremely preterm (<28 weeks)	4 (6.6%)	56 (94.4%)	
Very preterm (28 to <32 weeks)	57 (29%)	139 (71%)	
Moderate to late preterm (32 to <36+6 weeks)	244 (59.9%)	163 (40.1%)	
Term (>37)	139 (26.6%)	382 (73.4%)	p<0.001 (df=3)
Birth weight category (n=1184)			
Low birth weight (<2500 g).	231 (60.3%)	152 (39.7%)	
Very Low Birth Weight (VLBW): <1500g	95 (47.5%)	105 (52.5%)	
Extremely Low Birth Weight (ELBW): <1000g	45 (40.9%)	70 (59.1%)	
Normal Birth Weight	73 (15%)	413 (85%)	p<0.001(df=3)
XPearson Chi-squared;			

Table 2: risk factors for SGA				
		SGA Case-load	**Odds RatioX**	**Adjusted Odds Ratio (AOR)* X**
Gestation (n=1184)	<28	4/60 (6.6%)	OR=0.20 (CI:0.07 to 0.55)	AOR=0.12 (CI:0.04-0.40)
			p=0.002 (df=1)	p<0.001 (df=3)
	28-32	57/196 (29.0%)	OR=1.12 (CI:0.78 to 1.61)	AOR=0.91 (CI:0.61-1.35)
			p=0.520 (df=1)	p=0.628 (df=3)
	32-37	244/407 (59.9%)	OR=4.08 (CI:3.10 to 5.39)	AOR=4.04 (CI:2.99-5.45)
			p<0.001 (df=1)	p<0.001 (df=3)
	Term	139/521 (26.6%)		-
Maternal hypertension (eclampsia or preeclampsia) (n=1184)	Yes	106/207 (61.2%)	OR=1.98 (CI:1.47 to 2.69)	AOR=2.09 (CI:1.45-3.00)
			p<0.001 (df=1)	p<0.001 (df=1)
	No	338/977 (33.9 %)		
Mode of delivery (n=1115)	Vaginal	182/494 (36.8%)	OR=0.97 (CI:0.76 to 1.24)	AOR=1.21 (CI:0.92-1.60)
			p=0.816 (df=1)	P=0.177 (df=1)
	LSCS	233/621 (37.5%)		
Place of birth (n=1166)	Out-born	68/156 (43.6%)	OR=1.37 (CI:0.97 to 1.92)	AOR=2.19 (CI:1.48-3.26)
			p=0.073 (df=1)	p<0.001 (df=1)
	In-born	365/1010 (36.1%)		
XPearson Chi-squared; CI=95% confidence interval; df=degrees of freedom; LSCS=Lower Segment Caesarean Section; *Multivariate analysis: all variables in table included in the multivariate analysis				

Table 4: weight gain and length of stay in surviving neonates (SGA versus AGA neonates)					
		SGA	**AGA**	**Difference**	**p-valuet**
Weight gain in mean g/kg/day (St Dev)%	**<28 weeks**	(n=0)	16.22 (±3.1) (n=13)	NA	NA
	28 to <32 weeks	16.07 (±7.4) (n=26)	10.7 (±9.6) (n=69)	5.2 (CI:1.5 to 9.0)	p=0.007
	32 to <36+6 weeks	4.4 (±9.1) (n=185)	-0.36 (±11.7) (n=117)	4.8 (CI:2.2 to 7.3)	p<0.001
	>37	3.91 (±9.4) (n=80)	0.05 (±11.3) (n=231)	3.8 (CI:1.3 to 6.4)	p=0.003
	All	5.34 (±9.6) (n=291)	2.15 (±11.9) (n=430)	3.1 (CI:1.6 to 4.7)	p<0.001
Length of stay, mean in Days (St Dev)#	**<28 weeks**	(n=0)	49.13 (±35.4) (n=16)	NA	NA
	28 to <32 weeks	52.0 (±18.8) (n=27)	36.84 (±20.1) (n=86)	15.1 (CI:6.6 to 23.6)	p=0.001
	32 to <36+6 weeks	19.5 (±17.1) (n=207)	13.16 (±14.1) (n=146)	6.4 (CI:3.1 to 9.7)	p<0.001
	>37	7.48 (±7.3) (n=120)	6.91 (±9.4) (n=355)	0.5 (CI: -0.3 to 2.4)	p=0.500
	All	17.95 (±18.5) (n=354)	13.81 (±17.6) (n=603)	4.1 (CI:1.7 to 6.5)	p=0.001
CI=95% confidence interval; t2-sided t-test; ±Standard deviation					

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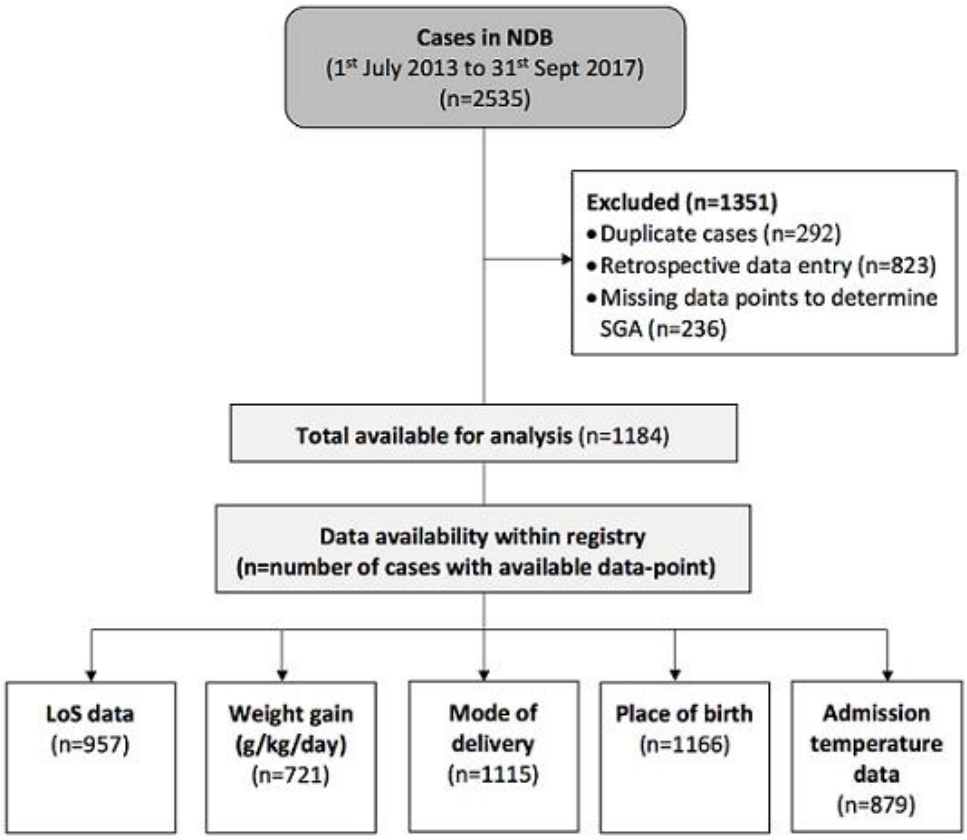

Figure 1: consort diagram of participants