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Impact of Being Born as a Small for Gestational Age on Neonatal Outcomes - Can it be Generalised

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Abstract

Small for Gestational Age (SGA) is a term used as a proxy for poor intrauterine fetal growth and is associated with higher perinatal mortality and morbidity. A retrospective cohort study was carried out analysing outcomes amongst SGA neonates born over 2 years in a tertiary-care referral teaching hospital. Out of 21086 neonates born during the study period, 3229 (15.3%) were Small for Gestational Age (SGA); defined as birth weight between 3rd-10th centile and 2289 (10.9%) had severe SGA; with birth weight below 3rd centile as per Fenton's intrauterine growth charts. The need for hospitalisation beyond initial 72 hours was needed in 31.1% (1005/3229) of SGA and 42.5% (973/2289) of severe SGA. It was observed that the Odds of developing morbidities such as symptomatic hypoglycaemia, meconium aspiration syndrome, pulmonary haemorrhage, transient feed intolerance, polycythaemia and death before hospital discharge were at least twice more likely in SGA neonates. Neonates who were severe SGA had odds of mortality further two times higher than the moderate SGA group. In addition, severe SGA were also noted to be at a higher risk of early and late onset neonatal sepsis, acute kidney injury, hypoxic ischemic encephalopathy, seizures, patent ductus arteriosus and necrotizing enterocolitis. This study emphasises the need to identify separately the neonates born as severe SGA. This distinct high - risk group from amongst the vulnerable set of SGA population needs more cautious monitoring and intensive management for improving chances of their overall intact survival.

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Introduction

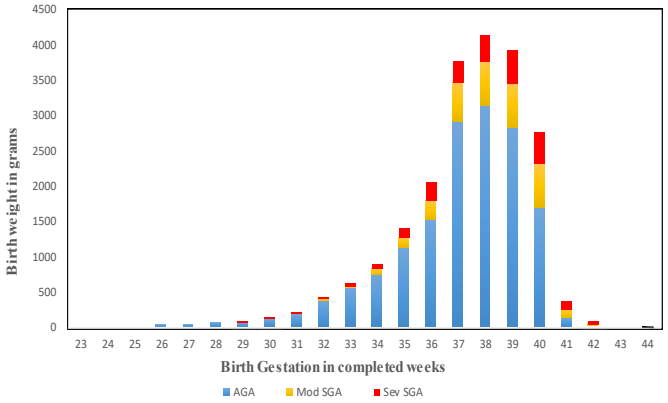
Low birth weight has been defined by World Health Organisation (WHO) as birth weight of less than 2500 grams regardless of gestational age [1]. Nearly 15% of babies are born annually with low-birth weight worldwide. Out of a total estimated 20.5 million Low birth weight (LBW) neonates globally, 95% are born in Low-Middle Income Countries (LMICs) [2]. India alone accounts for 7.5 million i.e. 42% of global burden [3]. Apart from prematurity, Fetal growth restriction contributes to 60% of this LBW population [4]. Intrauterine Growth Restriction (IUGR) and SGA (Small for gestational age) terms have been used interchangeably in the literature, however are not similar. While SGA are those which have birth weight <10th centile or ≤ 2 standard deviations below the mean for a particular gestation age and gender as per standard reference growth charts; IUGR are defined by presence of clinical features of malnutrition at birth irrespective of birth weight [5]. Based upon birth weight, SGA can be further classified as moderate (birth weight between 3rd-10th centile) or severe (birth weight <3rd centile). A myriad of maternal, fetal, placental, genetic and endocrine causes have been identified as causative of Fetal growth restriction [6]. In the presence of compromised nutrients, blood and oxygen supply in utero, these foetuses respond by reducing their overall fat, glycogen, muscle mass and bone mineral content in an attempt to preserve growth of vital organs. All these factors predispose them to hypoxia and acidosis hence increasing their risk of neonatal complications [7]. Literature shows higher risk of prematurity and perinatal complications in small for gestational age neonates, however studies differentiating effect of moderate and severe growth restriction on neonates are lacking [8]. Through our study we have tried to evaluate strength of association of various morbidities and mortality with severity of growth restriction.

Methods

During this retrospective cohort study, data was analyzed from December 2013 to December 2015 for all neonates born during the study period. Neonates were weighed within first 24 hours of their birth. A tabletop electronic baby weighing scale with Liquid-Crystal Display (LCD) display having measurement range of 0.01-15 kilograms, with accuracy of 5 grams, resolution of 1 gram was used for recording birth weights in neonatal birth performa. Neonates were then categorized as having birth weight for gestation between 3rd and 10th centile [moderate small for gestational age (SGA group)], less than 3rd centile (severe SGA group) and between 10th and 50th centile [Appropriate for gestational age (AGA group)] using gender-specific Fenton's intrauterine growth charts. Neonatal hospital records were accessed to analyze neonatal outcomes. Odd's ratios along with its 95% Confidence Intervals were calculated for various neonatal morbidities; namely hypoglycemia, polycythemia, meconium aspiration syndrome, pulmonary hemorrhage, transient feed intolerance, early and late onset sepsis, acute kidney injury, hypoxic ischemic encephalopathy, seizures, patent ductus arteriosus, necrotizing enterocolitis and neonatal mortality in neonates with moderate and severe SGA as compared to neonates weighing more than 10th centile for gestation at birth. Data was analyzed using Stata version 12.1 (StataCorp. 2011, College Station, TX, USA). As prevalence of growth restriction varied with gestation, the measures of association were adjusted for gestation at birth.

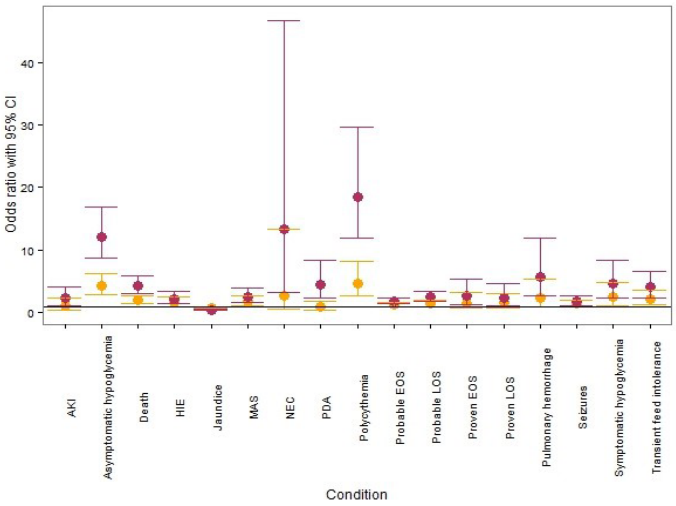
Results

Amongst 21086 neonates born during the study period, 3229 (15.3%) were moderate SGA, 2289 (10.9%) were severe SGA while 15568 (73.8%) were born as AGA. Gestation wise distribution was suggestive of increasing incidence of SGA with increasing gestational age from 28 to 40 weeks (Figure 1). Out of total of 21086 neonates born, 20683(98%) neonates survived and 7109 (33.7%) needed admission in intensive care unit. Incidence of mortality and major morbidities such as hypoglycemia, polycythemia, meconium aspiration syndrome, pulmonary hemorrhage, hypoxic ischemic encephalopathy before hospital discharge were increased in SGA neonates, more so in neonates with severe SGA group (Table 1). In addition, only neonates with severe IUGR were at higher risk of developing early and late onset sepsis, acute kidney injury, hypoxic ischemic encephalopathy, seizures, patent ductus arteriosus and necrotizing enterocolitis (Figure 2).



AGA: Appropriate for Gestational Age
Mod SGA: Moderate Small for Gestational Age
Severe SGA: Severe Small for Gestational Age

Figure 1: Gestation wise distribution of neonates as per birth weight categorisation.



Orange colour: Neonates with Moderate SGA, Red colour: Neonates with Severe SGA
AKI: Acute Kidney Injury; HIE: Hypoxic Ischemic Encephalopathy; MAS: Meconium Aspiration syndrome; NEC: Necrotising Enterocolitis: PDA: Patent Ductus Arteriosus; EOS: Early Onset Sepsis; LOS: Late Onset Sepsis.

Figure 2: Odds ratio and 95% confidence interval of neonatal morbidities and mortality in moderate and severe SGA neonates.

Table 1: Incidence of neonatal morbidities and mortality amongst hospitalised cohort.

Neonatal morbidities	AGA^ (n=5131) n (%)	Moderate SGA* (n=1005) n (%)	Severe SGA* (n=973) n (%)	P value
Asymptomatic hypoglycemia	77 (1.5)	51 (5.1)	973 (11.6)	<0.00001
Symptomatic hypoglycemia	30 (0.6)	15 (1.5)	26 (2.7)	<0.00001
Polycythemia	40 (0.8)	27 (2.7)	91 (9.3)	<0.00001
Meconium aspiration syndrome	85 (1.6)	37 (3.7)	49 (5)	<0.00001
Pulmonary hemorrhage	50 (0.9)	10 (0.9)	19 (1.9)	0.026
Transient feed intolerance	93 (1.8)	23 (2.3)	29 (2.9)	0.05
Hypoxic ischemic encephalopathy	101 (1.9)	28 (2.7)	38 (3.9)	0.0008
Jaundice needing treatment	3673 (71.6)	660 (65.7)	539 (55.4)	<0.00001
Respiratory distress syndrome (RDS)	316 (6.2)	28 (2.8)	32 (3.3)	<0.00001
TTNB#	323 (6.3)	66 (6.6)	89 (9.1)	0.0049
Probable EONS@	680 (13.2)	107 (10.6)	136 (13.9)	0.048
Proven EONS@	56 (1)	11 (1)	12 (1.2)	0.92
Probable LONS$	272 (5.3)	46 (4.6)	78 (8)	0.001
Proven LONS$	53 (1)	14 (1.4)	21 (2.1)	0.012
Renal failure	55 (1.1)	15 (1.5)	22 (2.2)	0.009
Respiratory failure	354 (6.9)	64 (6.4)	86 (8.8)	0.06
PPHN~	65 (1.3)	12 (1.2)	17 (1.7)	0.45
Septic shock	123 (2.4)	19 (1.9)	35 (3.6)	0.037
Seizures	117 (2.3)	33 (3.3)	39 (4)	0.0036
Sclerema	34 (0.6)	1 (0.09)	7 (0.7)	0.03
Death	305/15568 (1.9)	62/3229 (1.9)	81/2289 (3.5)	<0.00001

^ AGA: Appropriate for Gestational Age; *SGA: Small for Gestational Age; #: Transient Tachypnoea of Newborn; @EONS: Early Onset Neonatal Sepsis; $LONS: Late Onset Neonatal Sepsis; ~PPHN: Persistent Pulmonary Hypertension of Newborn.

Discussion

Incidence of SGA reported in studies varies from 10-20% depending upon gestational age of cohort and country of origin [7,8]. Manning FA et al have demonstrated a significant relationship between neonatal mortality and morbidity with decreasing centile of birth weight. The mortality increases from 5 to 15 % in those with SGA and severe SGA, while morbidities from 10 % to 45 % which is in concordance with our findings [9]. In the resource limited countries more than 20% of neonatal deaths have been reported amongst SGA population [7]. Systematic review of association of birth weight with neonatal mortality has shown an Odds ratio of 48.6(95% CI 28.6-82.5) for neonates born with birth weight ≤ 1500 grams [10]. Apart from increased mortality these neonates are prone to suffer from perinatal asphyxia at least twice more than controls [11]. Similarly incidence of hypothermia and hypoglycaemia have been seen to be two to five folds higher in the affected population [11,12]. In a recently published multicentric study the odds of necrotising enterocolitis (NEC) 2.3 (1.2 to 4.1), polycythaemia 3.0 (1.6 to 5.4), late-onset neonatal sepsis (LOS) 3.6 (1.1 to 10.9)) and prolonged hospitalisation 2.9 (2.0 to 4.2) have been found to be significantly higher in SGA preterm population born between 28-36 weeks of gestational age [13]. Studies from LMIC have frequently reported higher occurrence of adverse outcomes such as hypothermia, hypocalcaemia, respiratory distress syndrome and hypoglycaemia in SGA cohort [14]. Many centres have also resorted to the use of customised growth charts as compared to standard growth charts with a perspective to clearly identify at risk SGA infants [15]. However not only they lack generalisability but can artifactually increase the worse outcomes if based on alone premature neonates [16]. Use of Lubchenco growth charts have not been able to differentiate neonates with severe SGA from those with moderate SGA and hence clubbing them together undermines the severity of perinatal complications faced by the former cohort [17]. The INTERGROWTH-21st standards based on multicentre, multiethnic population cohort, have followed rigorous standardised measurement methods and are currently being recommended for appropriate identification and follow up of growth restriction amongst neonates [18]. Study conducted by Tunzun et al found that although the rate of detection of SGA was significantly higher with Intergrowth charts but risk of morbidities did not increase in this newly identified cohort [19]. Furthermore it was found that Extra uterine growth restriction was less prevalent with Intergrowth charts as the sample size of very preterm infants enrolled under the Preterm Postnatal Follow-up Study (PPFS) conducted under Intergrowth project was very small therefore authors have urged for better validation of these charts with long term studies in this subgroup before universal application [20]. Majority of studies conducted in LMIC countries are focussed on Low birth neonates, which have been be-

yond doubt proven to be are at higher risk of all early neonatal morbidities and mortality [21]. Limitations of our study are lack of detailed demographic variables such as maternal age and risk factors related to growth restriction. Strengths are standardised weight recording, at birth identification for SGA status and close follow up for morbidities in a large cohort of neonates.

Conclusions

Our study aims to highlight the need to identify subgroup of neonates born with severe SGA as a separate high- risk group from amongst SGA population using Fenton's growth chart till Intergrowth charts are more widely accepted and validated. Also, to sensitise the care providers towards cautious monitoring of neonates born at ≥ 39 weeks with a birth weight of ≤2500 grams who are erroneously regarded as apparently healthy neonates, however are severe SGA and hence at risk of all the aforementioned morbidities and increased perinatal mortality.

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