RESEARCH PAPER

Growth and Neurodevelopmental Outcomes at 12 to 18 Months of Corrected Age in Preterm Infants Born Small for Gestational Age

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Objective: To compare the growth and neurodevelopmental outcomes at 12 to 18 months of corrected age in preterm infants (gestation < 35 wks) born appropriate for gestation (AGA) with those born small for gestation (SGA). **Methodology:** This cross sectional, study assessed the growth outcomes in terms of underweight, stunting, microcephaly, overweight and obesity. Development delay was defined as developmental quotient < 70 on DASII. **Results:** Out of 178 infants enrolled in the study 119 were AGA and 59 were SGA. The mean gestational age of the study cohort was 30.45 (2.08) weeks. More infants in the SGA group were underweight (59.3% vs. 37.8%, RR: 1.79, 95% CI: 1.16-2.74), stunted (62.7% vs. 30.25%, RR: 2.19, 95% CI: 1.42-3.36) and had higher incidence of motor (6.7% vs.0.8%, RR: 2.5, 95% CI: 1.5-4.1) and mental development (3% vs. 0, RR: 3.1, 95% CI: 2.5-3.8) delay. **Conclusion:** Preterm SGA infants are at an increased risk of underweight, stunting, motor and mental development delay when compared with preterm AGA infants in early childhood.

Keywords: *Obesity, Development quotient, Stunting, Underweight.*

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The rate of preterm birth ranges from 5% to 18% and India is the biggest contributor to the world's prematurity burden [1]. Neonates born preterm are more susceptible to growth and neurodevelopmental abnormalities when compared with neonates born at term gestation [2,3]. Preterm neonates who are SGA at birth are at double jeopardy because of their shortened gestation period and growth restriction [4]. A higher incidence of prenatal and perinatal complications, as well as lower cognitive scores and poorer growth during first years of life, has been reported in preterm small for gestation age (SGA) infants compared with those born appropriate for gestational age (AGA) at birth. This study was designed to assess the growth and neurodevelopment outcomes in preterm SGA infants (gestation <35 week) in comparison to their AGA counterparts when assessed at 12 to 18 months of corrected age.

METHODS

This was a cross-sectional study conducted in the outpatient follow-up clinic of Fernandez hospital, Hyderabad after obtaining clearance from ethical committee and informed written consent from one of the parents. The study was conducted over a period of 2 years from May, 2016 to May, 2018. All preterm infants (till 34 6/7 days of gestation) born after May, 2015 with a corrected age of 12-18 months were eligible for enrollment. AGA and SGA were categorized based on infant's birthweight falling between 10th and 90th percentile and less than 10th percentile for gestational age on Fernandez growth charts [5], respectively. Infants with major congenital malformations were excluded from the study. The antenatal, perinatal and neonatal details of enrolled infants were collected in a predesigned proforma from the discharge summary, computerized database and case files. Feeding details during the first 6 months and that of complementary feeding were collected from the parents by asking direct or leading questions. A list of eligible infants was prepared from the existing computer database and parents of these infants were contacted on phone (maximum of 3 reminders) for a scheduled visit when they attained a corrected age of 12 months. During the visit growth was assessed by measuring weight, length, head circumference and mid upper arm circumference. These measurements were analyzed using WHO AnthroPlus software [6]. Developmental

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assessment was by Developmental Assessment Scale for Indian Infants (DASII) by a certified pediatrician blinded to the baseline neonatal variables. Tone abnormalities were identified by detailed neurological examination of the child and neurosensory evaluation by a need for hearing aids and need for visual aids or blindness in one or both eyes.

Assuming the incidence of malnutrition to be (weight deviation for age > 2 z score from the reference mean for age) 40% in preterm SGA group and 20% in preterm AGA group [7], with an alpha error at 5% and a desired power set at 80%, with 2:1 ratio of AGA to SGA infants, the required sample size was 116 infants in the AGA group and 58 infants in the SGA group.

Statistical analyses: All the data was analyzed using software SPSS ver.20. Data was expressed as mean (with standard deviation) and proportions as appropriate. Chi square test and student *t* test were applied for qualitative and quantitative data respectively. A *P*-value of <0.05 was considered significant.

Incidence of undernutrition (underweight) defined as weight/age Z score >2 standard deviations below the reference mean (WHO Growth charts) [8] for that age and sex was the primary study outcome. Incidence of stunting (length/age Z-score ≤-2.00), wasting (weight/length Z-score ≤-2.00), microcephaly (head circumference/age Z-score ≤-3.00), overweight (Body mass index (BMI)/age between 85-95 percentile) and obesity (Body mass index (BMI)/age ≥95 percentile) and incidence of developmental delay defined as Motor Developmental quotient and mental developmental quotient <70 were the secondary study outcomes.

RESULTS

During the study period, 610 infants were eligible for enrollment in the study but only 178 infants could be enrolled in the study. Of the 178 infants enrolled in the study, 119 infants were AGA and 59 infants were SGA at birth. ***Table* I** provides the baseline characteristics for the study population. Most neonatal morbidities were similar in infants of both the groups. The duration of exclusive breast feeding was similar between both groups, but complementary feeding was initiated one month earlier in SGA infants.

The mean corrected age at follow up in the study population was 14.4 months. ***Table* II** provides the outcomes for the study population. More infants in the

Table I Baseline Variables In Preterm Small for Gestational Age Babies (*N*=178)

Variable	*Overall (n=178)*	*AGA group (n=119)*	*SGA group (n=59)*	*P-Value*
Gestation (wk)[#]	30.4 (2.08)	30.1 (2.15)	31.0 (1.80)	0.006
Birth weight (g)[#]	1242.1 (354.4)	1349.7 (355.1)	1025.0 (234.6)	<0.001
Birth length (cm)[#]	38.2 (3.2)	39.0 (3.0)	36.5 (3.0)	<0.001
Head circumference (cm)[#]	27.4 (2.1)	27.7 (2.2)	26.6 (1.7)	<0.001
Male sex (%)	95 (53.4)	65 (54.6)	30 (54.2)	0.63
Multiple pregnancy (%)	50 (28)	42 (35.3)	8 (13.5)	0.002
Neonatal seizures (%)	5 (2.8)	2 (1.6)	3 (5)	0.19
Culture positive sepsis (%)	44 (24.7)	26 (21.8)	18 (30.5)	0.20
hsPDA (%)	35 (19.6)	25 (21)	10 (16.9)	0.52
NEC IIA or more (%)	9 (5)	2 (1.6)	7 (11.8)	0.004
ROP requiring treatment (%)	4 (2.2)	4 (3.3)	0 (0)	–
BPD (%)	17 (9.5)	11 (9.2)	6 (10.1)	0.84
Cystic PVL (%)	3 (1.6)	3 (2.5)	0	0.21
IVH grade 3 or more (%)	2 (1.1)	2 (1.7)	0	–
Time to reach full feeds (d)[#]	7.8 (5.4)	6.6 (4.8)	10.3 (5.8)	<0.001
Time to regain birth weight (d)[#]	13.0 (4.79)	14.0 (4.55)	10.9 (4.6)	<0.001
Duration of hospitalization (d)[#]	26.6 (21.3)	27.1 (22.1)	34.6 (18.9)	0.02
Duration of exclusive breast feeding (mo)[#]	3.6 (2.2)	3.5 (2.3)	3.8 (2.0)	0.37
Initiation of complementary feeding (mo)[#]	6.96 (0.95)	7.12 (0.92)	6.64 (0.96)	0.002

hsPDA: Hemodynamically significant patent ductus arteriosus; NEC: Necrotizing enterocolitis: ROP: Retinopathy of prematurity; BPD: Bronchopulmonary dysplasia; IVH: Intraventricular hemorrhage; PVL: Periventricular leukomalacia; [#]Mean (SD).

Table II Growth and Neurodevelopmental Outcomes of Preterm Small for Gestational Age Infants at the Corrected Age of 12-18 Month

Variable	*Overall (n=178)*	*AGA group (n=119)*	*SGA group (n=59)*	*P value*
Age at follow up (mo)[#]	14.4 (2.2)	14.4 (2.3)	14.4 (2.1)	0.99
Weight (kg)[#]	8.5 (1.4)	8.8 (1.5)	7.8 (1.0)	<0.001
Length (cm)[#]	74.2 (4.8)	75.1 (4.9)	72.4 (4.0)	<0.001
Head circumference (cm)[#]	44.0 (1.7)	44.4 (1.7)	43.3 (1.5)	<0.001
Underweight (%)	80 (45)	45 (37.8)	35 (59.3)	0.007
Wasting (%)	34 (19.1)	21 (17.6)	13 (22.03)	0.48
Stunting (%)	73 (41.01)	36 (30.25)	37 (62.7)	<0.001
Microcephaly (%)	15 (8.4)	10 (8.4)	5 (8.4)	0.98
Mean BMI (kg/m^2)[#]	15.3 (1.3)	15.5 (1.4)	14.9 (1.1)	0.004
Overweight (%)	9 (5.0)	7 (5.8)	2 (3.3)	0.47
Obesity (%)	2 (1.1)	2 (1.6)	0 (0)	0.31
Mean MUAC (cm)[#]	12.5 (1.1)	12.7 (1.1)	12.2 (0.9)	0.002
Mean motor age (mo)[#]	13.5 (2.6)	13.7 (2.6)	13.0 (2.5)	0.1
Mean motor developmental quotient[#]	93.1 (9.5)	94.5 (8.3)	90.2 (11.2)	0.005
MoDQ <70 (%)	5 (2.8)	1 (0.8)	4 (6.7)	0.02
MoDQ 71-85 (%)	20 (11.2)	12 (10)	8 (13.5)	0.48
MoDQ >85 (%)	153 (85.9)	106 (89)	47 (79.6)	0.09
Mean mental age (mo)[#]	13.7 (2.6)	13.9 (2.6)	13.1 (2.4)	0.048
Mean mental developmental quotient[#]	94.7 (8.6)	96.6 (7.9)	90.8 (8.8)	<0.001
MeDQ <70 (%)	3 (1.6)	0 (0)	3 (5.0)	0.03
MeDQ 71- 85 (%)	19 (10.6)	10 (8.4)	9 (15.2)	0.16
MeDQ >85 (%)	156 (87.6)	109 (91.5)	47 (76.2)	0.005
Tone abnormalities (hyper/hypotonia) (%)	39 (22)	27 (22.6)	12 (20.3)	0.72

W/A: weight for age; L/A: length for age; HC/A: head circumference of age; W/L: weight for length; BMI: Body massindex; MUAC: Mid upper arm circumference; MUAC/A: Mid upper arm circumference for age; MoDQ: Motor developmental quotient; MeDQ: Mental developmental quotient; [#]Mean (SD).

SGA group were underweight (59.3% and 37.8%, RR: 1.57 and CI 1.15 - 2.14) and stunted (62.7% and 30.25%, RR: 2.07 and CI 1.48-2.90) when compared to AGA infants. Frequency of wasting (17.6% and 22.03% RR: 1.25 and CI 0.67-2.3), microcephaly (8.4% and 8.4%, RR: 1.0 and CI 0.36-2.81) and overweight (5.8% and 3.3% RR: 0.57 and CI 0.12-2.68) were similar in both AGA and SGA groups. Adjusting for birth gestation, gender, multiple pregnancy, mode of delivery and resuscitation at birth SGA independently predicted long term undernutrition (odds ratio: 2.5, 95%CI: 1.25-5). Infants in the SGA group had significantly lower motor and mental developmental quotients when compared to infants of AGA group.

DISCUSSION

The present study observed that preterm SGA infants were at higher risk for underweight, stunting, motor and mental developmental delay when compared with preterm AGA infants at corrected age of 12 to 18 months. The observations on the nutritional status reported in the present study are similar to that reported by Sharma, *et al*. [9] but different from that reported by Mukhopadhyay, *et al*. [10]. The differences in the incidence of long term growth outcomes between the studies is mainly due to the differences in study population, age at assessment and reference standards [11]. In a meta- analysis [12] of 19 birth cohorts from low and middle income countries it was noted that 12-60 months age, preterm SGA infants had the highest odds of stunting (4.51; 3.42, 5.93), wasting (4.19; 2.90-6.05) and underweight (5.35; 4.39-6.53).

In a prospective cohort study from northern India [12] that reported neurodevelopmental outcome at 1 year of corrected age, in preterm (≤34 wk/infants <1500 g), it was noted that average motor and mental scores were similar between preterm AGA and SGA infants. In a study [14] that compared the neurodevelopmental outcomes of 45

WHAT THIS STUDY ADDS?

- This study highlights the vulnerability of preterm SGA infants for poor growth and neurodevelopmental outcomes compared to preterm AGA infants.

preterm (<34 weeks) SGA infants with 46 preterm AGA infants matched for gender and gestation (±2 weeks) at 1 year of corrected age, the incidence of motor (2.7% *vs*. 8.3%) and mental developmental delay (18.9% *vs*. 16.7%) was similar between the SGA and AGA preterm infants, respectively. In a review [15] that reports the effect of gestation on long term neurodevelopmental outcomes of SGA/IUGR infants, preterm SGA infants were at higher risk of adverse neuromotor, cognitive, behavioral and scholastic achievement compared with preterm non-SGA infants. Studies of preterm infants revealed that IQ scores were on average approximately 5 to 7 points (0.5 SD) lower for preterm SGA infants compared with preterm AGA infants [19]. The observations of the latter studies are similar to the observations in the present study.

The main limitation of the present study is its cross-sectional design. However, the strength lies in the standardized protocol used to evaluate growth and neurodevelopment outcomes.

Preterm SGA infants are at an increased risk of underweight, stunting and lower motor and mental development scores when compared to AGA infants at a corrected age of 12 to 18 months. This suggests that preterm SGA infants probably need more intense follow-up and early and appropriate interventions to improve their outcomes.

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