

## Small for gestational age: A risk factor for the development of hypertension in childhood?

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### ABSTRACT

**Background:** There is evidence regarding the association of elevated blood pressure and small for gestational age (SGA) status. Most studies showing positive association have demonstrated this in children above 7 years. **Objectives:** The objectives of the study were to determine a significant difference between children aged from 3 to 5 years, born SGA, and those born appropriate for gestational age (AGA) developing hypertension. **Methodology:** The cross-sectional study was carried out at a private tertiary care hospital. Clinically healthy children (age: 3–5 years) were enrolled and grouped as those born SGA and those born AGA. Blood pressure was recorded with an oscillometric device and the procedure was repeated 3 times at an interval of at least 10 min. The mean of three blood pressure recordings was the participant's true blood pressure. The demographic characteristics of the study population were summarized using descriptive statistics. Categorical outcomes were compared using Chi-square or Fisher's exact test. For continuous outcomes, "t test" was used.  $p < 0.05$  was considered statistically significant. **Results:** The study enrolled 27 SGA born children and 27 AGA born children. Nine children (33.33%) in the SGA group and 1 child (3.7%) in the AGA group developed hypertension ( $p = 0.011$ ). The systolic blood pressure in the SGA group ( $103.20 \pm 8.62$  mmHg) was significantly higher than that in the AGA group ( $98.58 \pm 6.60$  mmHg) ( $p = 0.031$ ). The diastolic blood pressure (mean  $\pm$  SD) in the SGA group was  $62.75 \pm 9.19$  mmHg. There was no difference between the diastolic blood pressures in the two groups (AGA:  $59.00 \pm 5.11$  mmHg and SGA:  $62.75 \pm 9.19$ ;  $p = 0.07$ ). **Conclusion:** Being born with SGA is a risk factor for hypertension in children between the ages of 3 and 5 years.

**Key words:** Appropriate for gestational age, Children, Hypertension, Low birth weight, Small for gestational age

Small for gestational age (SGA) defined as birth weight  $< 10^{\text{th}}$  centile for that particular gestational age [1]. This burden is disproportionately higher in India, where 46.9% of babies are born SGA [2].

Infants born SGA are at a higher risk of mortality and morbidity in the neonatal period and beyond. They are more likely to have neonatal infections, polycythemia, hypoglycemia, perinatal respiratory depression, jaundice, poor feeding pattern, and hypothermia [3]. In adult life, SGA babies are at high risk of developing obesity and diabetes [4]. Many studies have identified SGA status at birth as a risk factor for childhood hypertension [1,5,6], but there is no unanimity in this regard [1,7,8]. The association has been found and noted in children (over the age of 7 years), adolescents, and young adults. Hypertension in children is of importance, as it tracks into adulthood and increases the risk for cardiovascular morbidity and mortality throughout

life [9,10]. Hence, we decided to conduct a study to determine the association between SGA status and hypertension at the age of 3–5 years.

### MATERIALS AND METHODS

#### Study Site

The study was conducted in the outpatient department (OPD) of a private tertiary care hospital in Mumbai, affiliated to National Board of Examination and the State Health University. The hospital has a 105-bedded NICU with approximately 900 admissions annually. It provides newborns with conditions such as extreme prematurity, underweight babies, infants with congenital anomalies, and respiratory distress syndrome. It is equipped with 15 ventilators (including five high-frequency oscillatory ventilators), 10 heated humidified high-flow nasal cannula, 22 continuous positive airway pressure machines, and a milk bank. The NICU graduates and babies born in the hospital follow-up

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at the hospital's OPD as per the schedule depending on the age, NICU course (if any), risk factors, and physician's advice. The observational study was conducted for 19 months beginning from June 2018.

### Study Design

This was a cross-sectional observational analytical study design.

### Eligibility Criteria

Children aged from 3 to 5 years, born SGA or appropriate for gestational age (AGA), were enrolled in the study. Children with congenital anomalies, chromosomal aberration, syndrome abnormalities, severe neurological deficits; those with arrhythmia, congenital heart disease, or malignancy; those with the conditions of hypertension, for example, neurofibromatosis, tuberous sclerosis, or ambiguous genitalia; and those with a family history of hypertension or congenital renal disorders were excluded from the study.

### Methodology

Consecutive children (age: 3–5 years) attending the OPD were included in the study. The participants' age and status with SGA/AGA status were determined on the basis of medical records and birth records available with the parent/guardian. The exclusion criteria were determined on the basis of history, clinical examination, and medical records provided by the parent/guardian. Method of the measurement of blood pressure: The blood pressure in the right brachial artery was evaluated when the child was calm and cooperative and in the supine position. It was measured 3 times at an interval of at least 10 min using an oscillometric device "Vista 120, Drager Medical GmbH." The mean of three blood pressure recordings was the participant's true blood pressure [11].

The child was considered to have hypertension if systolic or diastolic blood pressure (DBP) was above 95<sup>th</sup> centile (for children between the ages of 1 and 12 years) [11]. For adolescents  $\geq 13$  years old, hypertension was considered as  $\geq 130/80$  mmHg [11]. Children with hypertension should have a close follow-up as advised.

The study was approved by the Institutional Ethics Committee and eligible children were enrolled in the study only after obtaining written informed consent from a parent or guardian.

### Outcome Measures

The comparison between the children of ages 3 and 5 years born SGA or AGA having hypertension was the primary measure for the study. Subgroup analysis was carried out for the same variable (hypertension) in different subsets of the study populations such as those born SGA-term and SGA-preterm, AGA-term and AGA-preterm, SGA-LBW (SGA-low birth weight [LBW]) and SGA-non-LBW, and AGA-LBW and AGA-non-LBW.

### Statistical Plan

Twenty-seven participants in each group (born SGA and born AGA) were estimated using the formula for two proportions with the assumptions for hypertension in AGA and SGA groups being 16% and 50%, respectively [1], and an  $\alpha$ -error of 0.05 and power of 80%.

The demographic characteristics of the study population were done using descriptive statistics. Categorical outcomes were compared using Chi-square or Fisher's exact test, as appropriate. For continuous outcomes, two-sample "t-test" was used.  $p < 0.05$  was considered statistically significant.

### RESULTS

The observational study was conducted over a 19-month period beginning from June 2018. Fifty-four children (AGA: SGA=1:1) aged between 3 and 5 years were enrolled in this study. As shown in Table 1, there was a significant difference between the two groups in terms of birth weight and height and weight at the time of enrollment. There was no statistical difference between the two groups in terms of gestation age, proportion of preterm babies, gender distribution, mode of delivery, and age at enrollment.

As shown in Table 1, there was a difference in the proportion of children with hypertension in the two groups (nine in SGA group vs. one in AGA group,  $p=0.011$ ). The mean systolic blood pressure (SBP) was different between the two groups, as well. Five (50.00%) out of 10 children with hypertension had both systolic and diastolic hypertension, one baby had only systolic hypertension, and four babies had only diastolic hypertension. Thus, overall in the study population, six children demonstrated systolic hypertension (with or without diastolic hypertension) and nine children demonstrated diastolic hypertension (with or without systolic hypertension). All the six babies with systolic hypertension were born as SGA. Eight of the nine babies with diastolic hypertension were born SGA, while the remaining one was born as an AGA baby.

As shown in Table 2, there was no significant difference in the proportions of children with hypertension between term-SGA and preterm-SGA, between term-AGA and preterm-AGA, between SGA-LBW and SGA with SGA-non-LBW, and between AGA-LBW and AGA-non-LBW.

### DISCUSSION

Six children born SGA developed elevated SBP and eight children born SGA developed elevated DBP. Only one participant born AGA showed elevated DBP. No child born AGA had elevated SBP. A significantly higher proportion of children between the ages of 3 and 5 years born SGA had hypertension (systolic and/or diastolic) than those born AGA. Furthermore, the mean SBP in SGA born children was higher than that in children born AGA.

Data concerning SGA children at risk for hypertension have provided contradictory results. Although most studies suggest that the SGA child is at a greater risk for the development of hypertension [1,6,12], they have established this association for

**Table 1: Baseline characteristics and primary outcome measure**

Parameter	SGA (n=27)	AGA (n=27)	p-value
Birth weight			
Birth weight (kg)	2.22±0.39	2.98±0.60	<0.001*
BW<2.5 kg	20 (74.07)	4 (14.81)	<0.001*
BW≥2.5	7 (25.93)	23 (85.19)	
Gestational age at birth (GAAB)			
Gestational age (weeks)	37.80±2.98	37.77±2.56	0.97
Preterm	5 (18.52)	8 (29.62)	0.53
Term	22 (81.48)	19 (70.37)	
Gender			
Male	14 (51.85)	14 (51.85)	1.00
Female	13 (48.15)	13 (48.15)	
Mode of delivery			
Vaginal	6 (22.22)	7 (25.93)	0.95
Vacuum-assisted vaginal delivery	1 (3.70)	1 (3.70)	
LSCS	20 (74.07)	19 (70.37)	
Age at the time of examination			
Age (months)	48.11±8.49	51.85±7.10	0.08
Anthropometric measurements			
Height (cm)	97.33±5.65	103.44±7.41	0.001*
Weight (kg)	13.15±1.71	15.71±3.42	0.001*
Primary outcome: Hypertension in the study groups			
Hypertension (n=10)	9 (33.33)	1 (3.7)	0.011*
Systolic BP (mean±SD, mm Hg)	103.20±8.62	98.58±6.60	0.031*
Diastolic BP (mean±SD, mm Hg)	62.75±9.19	59.00±5.11	0.07

\*Statistically significant. Data expressed as mean±standard deviation (for continuous outcome), number, and percentage (for categorical outcome) as applicable. Figures in parentheses indicate percentages. AGA: Appropriate for gestational age, SGA: Small for gestational age, SD: Standard deviation

**Table 2: Secondary outcome of study**

Parameter	Hypertension	No hypertension	p-value
SGA (n=27)			
Term (n=22)	7 (31.82)	15 (68.19)	1.0
Preterm (n=5)	2 (40.00)	3 (60.00)	
AGA (n=27)			
Term (n=19)	0 (0)	19 (100)	0.29
Preterm (n=8)	1 (12.50)	7 (87.50)	
SGA (n=27)			
LBW (n=20)	8 (40)	12 (60)	0.363
Non-LBW (n=7)	1 (14.29)	6 (85.71)	
AGA (n=27)			
LBW (n=4)	1 (25)	3 (75)	0.148
Non-LBW (n=23)	0 (0)	23 (100)	

Figures in parentheses indicate percentages. AGA: Appropriate for gestational age; LBW: Low birth weight; non-LBW: Non-low birth weight; SGA: Small for gestational age

adolescents, adults, and children aged above 7 years and many with some caveats.

For example, Pocobelli *et al.* [12] found this association only in individuals between the ages of 15 and 24 years but

not in younger children between the ages of 8 and 14 years. A recent study reported that there was no significant difference between children born SGA or AGA regarding the SBP and DBP recorded at daytime, night, and as 24 h ambulatory record [7]. Weres *et al.* [8] also did not show significant difference in the prevalence of hypertension in children (born AGA, SGA, or LGA) at the age of 4–6, 7–11, and 12–15 years. Our study shows the presence of an association between SGA status and hypertension in childhood. This evidence is especially noteworthy, since there is hardly any Indian data available in this regard. An earlier study carried out in India [13] and reported that hypertension was not recognized as a major issue in the cohort of 161 SGA and AGA babies. Wang *et al.* [5] have demonstrated an association between SGA status and elevated blood pressure in children between the ages of 3 and 9 years, an age group similar to the one studied by us. Determining that SGA babies are at higher risk of developing elevated blood pressure at a younger age is important, as if this persists; they may have higher probability of developing consequences of hypertension such as left ventricular hypertrophy, congestive heart failure, and stroke, among others. The hypothesis proposed to explain this predisposition of SGA babies to develop hypertension in childhood and adulthood is compensatory hypertrophy of the nephrons (as a part of metabolic programming), secondary to the adaptation of the fetus to the challenging environment encountered *in utero* [1].

The study also showed no significant difference in terms of proportion of various groups of children developing hypertension (Table 2). However, considering the small number of participants in each group; these observations can only be considered as exploratory, requiring further confirmatory research study.

The study has addressed the issue of paucity of Indian data. It proved the association of SGA and subsequent hypertension in children younger than 5 years. A sufficient number of participants (as provided by formal sample size estimation) were enrolled for drawing inferences. All the readings were taken by the same observer using the same instrument obviating the possibility of interobserver variations. Oscillometry is known for the ease of use, reliability, reproducibility, accuracy, and freedom from observer bias [14]. The study was limited by the fact that high blood pressure was diagnosed on the basis of observation at a single time point. In our study, we found that a number of children with low birth weight were more in SGA group than AGA group with  $p<0.001$ . This difference could be expected as SGA tend to have more LBW than AGA group. Its effect on blood pressure should be done in a different study. The extent of differential proportion of LBW babies in the AGA and SGA groups is not known. The association of LBW with blood pressure, nevertheless, has been a controversial one with different studies providing contrasting results [5,15]. We calculated the sample size keeping the primary objective in mind. This may not be adequate for determining answers for the secondary objectives. Thus, a larger study should be conducted to determine the association of prematurity and LBW with hypertension in this age group.

On the basis of the analysis of the literature and the data generated by the study, it can be surmised that SGA status is a

risk factor for the development of hypertension in childhood, as early as at 3–5 years of age. As hypertension in children is predictive for the development of hypertension, coronary artery disease, atherosclerosis, stroke, and other complications related to hypertension later in life [16], this study finding has implications for clinical practice. This calls for a regular monitoring of blood pressure, especially, in children born SGA. The American Academy of Pediatrics clinical practice guidelines for screening and management of high blood pressure in children and adolescents recommend that blood pressure must be routinely measured from the age of 3 years [10]. Our study supports this recommendation and suggests that SGA status be added to the list of groups of individuals who are prone to develop high blood pressure.

## CONCLUSION

SGA is a risk factor for childhood hypertension from the age of 3 years. Blood pressure should be monitored in children born SGA right from that age.

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