RESEARCH PAPER

Pune Low Birth Weight Study – Growth from Birth to Adulthood

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Objective: To assess the growth, adiposity and blood pressure of non-handicapped low birthweight children at 18 years.

Design: Prospective cohort study.

Setting: Infants born between 1987-1989 with birthweight less than 2000g, discharged from a neonatal special care unit of a referral hospital and followed up till the age of 18 years.

Methods: The height, weight, and head circumference were measured. Measurements for adiposity, blood pressure, parental height and weight were recorded.

Results: The cohort of 161 low birth weight (LBW) infants was divided into three groups according to their gestation – preterm SGA (n=61), full term SGA (n=30) and preterm AGA (n=70). 71 full term AGA infants served as controls. Preterm SGA males had height of 164.5 cms (162-166.9, 95% CI) which was significantly less (mean deficit = 5.7 cms) than that of controls (P=0.02). However, PTSGA children were short inspite of normal mid-parental height. Preterm SGA and AGA children had smaller head circumference. There was no evidence of adiposity and no child had hypertension. Mid-parental height was an important determinant of height in LBW children. Both parents' weight and BMI were important determinants of weight and BMI, respectively in all LBW children.

Conclusion: Preterm SGA males were short, but there was no difference in the weight of the LBW group and controls. Preterms had smaller head circumference. There was no evidence of adiposity or hypertension.

Key words: *Blood pressure, Follow-up, Growth, India, Low birth weight.*

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Almost one-third of the children born in India are low birth weight [1] and a large percentage of them are small for gestational age (SGA). Infants with intrauterine growth restriction have been reported to have a seven-fold increased risk of growth failure [2,3] and subsequently adult short stature. In addition, they are prone to a number of disorders like type II diabetes, central obesity, hypertension and coronary heart disease in adulthood, collectively called the "metabolic syndrome"[4,5].

Although there are many recent reports on the growth of very low birth weight (VLBW) [6] and extremely low birth weight (ELBW) infants [7], less attention has been paid to the long term growth of moderately low birth weight (LBW) children. We have previously reported on the physical growth of LBW children at 12 years [8]. This study describes the growth at early adulthood of "non-disabled" LBW children who were born in the late eighties with birth weight less than 2000 grams. We have also tried to find out if there were any early predictors of metabolic syndrome, such as central obesity or hypertension. To the best of our knowledge, this is the only Indian study, where low birth weight children have been followed up till adulthood.

METHODS

The cohort consisted of infants weighing less than 2000g discharged from a neonatal special care unit during a 18 month period, between October 1987 to April 1989 and followed up prospectively till the age of 18 years [8-11]. The LBW infants were classified into AGA or SGA using the criteria of Singh, *et al*. [12]. Full term neonates born in the same hospital during the same period with birth weight ≥2500g with a normal antenatal, natal and postnatal course were enrolled as controls. All neonatal risk factors were recorded. A detailed socio-demographic background of each child was obtained by the social worker by making a home visit. Children with major neurologic sequelae like cerebral palsy and mental retardation were omitted from this study at the end of the three year follow up. So, the cohort now consisted of non-handicapped children, who looked "apparently normal".

Assessment of growth: Weight was measured by an electronic scale with an accuracy of ± 10g (ATCO Manufacturing Co., Ltd., Mumbai). Standing and sitting height was measured to the nearest 0.5cm by a wall-mounted stadiometer using standard technique [13]. Head circumference was measured using a nonstretchable tape measure. All anthropometric measurements were taken by trained medical staff. Z scores or SD scores were calculated for weight, height and head circumference using gender specific Indian standards [14,15]. An *X*-ray of the left hand including the wrist was taken at 12 years and bone age was determined in the LBW group, after taking parental consent. All *X*-rays were assessed by a single observer using TWII standards [16]. Final height was predicted using the TWII (RUS) scores [17]. This data was unmasked at 18 years, and correlated with the actual height.

Assessment of adiposity: BMI was calculated and categorized by the method described by Cole, *et al.* [18]. Waist circumference was measured by a nonstretchable tape to the nearest 0.1cm, midway between the lower costal margin and superior iliac crest in expiration. The reading was plotted using centiles given by McCarthy, *et al*. [19]. Hip circumference was measured at the point of maximum protuberance. A waist/hip ratio greater than 0.9 was considered as obese [20]. Waist/height ratio was also determined. A ratio of more than 0.5 was considered as obese [21]. Skinfold thickness was measured at 4 sites – biceps, triceps, subscapular and suprailiac. The sum of these 4 skinfold thickness was used to determine the percentage of body fat using Durnin equation [22].

Blood pressure: Blood pressure (BP) was measured with a standard sphygmomanometer. Subjects were seated and after 5 minutes of rest, the BP was measured with a cuff two thirds the size of the upper arm length. The mean of three readings of systolic and diastolic pressure was recorded. Hypertension was defined as systolic pressure above 140 mm Hg, and diastolic pressure above 90 mm Hg [23].

Socio-economic status was determined by using the revised Kuppuswamy Scale [24]. Height and weight of both parents was measured. Ethical permission was obtained from the hospital's Ethics Committee. Consent of both the parents was obtained at the time of enrollment in the study.

*Statistical analysis***:** The data was entered into the computer and statistical analysis was done using Statistical Package for Social Science (SPSS) for Windows (version 11.5). The linear association between the normally distributed variables was assessed by Pearson's correlation coefficients, otherwise Spearman's correlation coefficients were used. The partial correlation analysis was also used to test the independent associations between variables like age, sex and socio-economic status.

The LBW and the control groups were first compared by using analysis of variance (ANOVA) procedure with Bonferroni's method of correction for multiple group comparisons. The nonparametric test like Mann Whitney U test was performed to test the significance of difference between the means of two independent groups with non-normally distributed variables. For finding the independent predictors of several quantitative variables multivariate analysis was carried out by multiple linear regression technique. Standardized scores (SD scores) were calculated by taking appropriate standards [14,15] to assess the physical growth at 18 years of age.

RESULTS

From the 180 LBW and 90 controls reported upon at 12 years [11], five LBW children and 17 controls were lost to follow up, and fourteen LBW children refused to come for the assessment. So our final sample consisted of 161 LBW and 73 normal birth weight controls, who were followed up since birth. The children who dropped out of the study were similar to those who continued in the study and showed no statistically significant difference. Thus, out of the 201 LBW infants, 161 (80%) were available for the final follow up.

The cohort was divided into 4 groups – preterm SGA, preterm AGA, full term SGA, and full term AGA (controls). The birthweight of the study group ranged from 860-1999g (mean 1545 ± 243.9g). The gestation of the study group ranged from 28-40 weeks (mean 34.7 ± 2.7). The mean birth weight of the control group was 2835.3 ± 30.5g. There were 131 preterm and 30 full terms in the study group. Out of the 131 preterms, 61 were small for gestational age and 60 were appropriate for gestational age. Of the 91 SGA infants, 61 (67%) were preterm and 30 (33%) were full term. ***Table* I** shows the neonatal data and maternal socio-demographic data.

The anthropometric measurements of the cohort are shown in ***Table* II**. The PTSGA males were the shortest in the group and were significantly shorter (*P*=0.02) than controls. The preterm females showed a significantly smaller head circumference compared to that of controls, the preterm SGA more so (*P*=0.003) than the PTAGA (*P*=0.02). ***Fig*. 1** shows the *Z* scores of all the 4 parameters of growth. The preterm subjects had small head size compared to controls, as well as the smallest sitting height but none of the subjects showed any disproportion in stature compared to controls. ***Fig.* 2** and **3** show the sex specific growth trajectory of height and weight from birth to 18 years.

The bone age was assessed at 12 years and adult height was predicted. The actual height attained by the LBW children at 18 years was compared with the predicted height, and this showed a good correlation (r=0.821, *P*=0.001)

TABLE I NEONATAL AND SOCIO-DEMOGRAPHIC DATA OF THE STUDY SUBJECTS

	Cases (n=161)		*Controls (n=73)*	
	Male (n=91)	*Female (n=70)*	*Male (n=43)*	*Female (n=30)*
Birthweight (g)*	1568.9 (223.3)	1515.1 (267.0)	2898.8 (337.0)	2744.3 (230.4)
Gestation age (wks)*	34.8 (2.6)	34.9 (2.9)	39.9 (0.54)	39.9 (0.51)
Small for gestational age	49 (53.8%)	42 (60.0%)	0	0
Appropriate for gestational age	42 (46.2%)	28 (40.0%)	43 (100.0)	30 (100.0)
Mother's height (cm)*	152.5 (6.7)	151.2 (7.2)	152.2 (6.2)	153.3 (6.2)
Father's height (cm)*	161.4 (7.9)	161.8 (9.8)	162.9 (5.8)	162.4 (5.6)
Mother's weight (kg)*	56.9 (12.7)	57.0 (11.4)	57.6 (10.1)	58.3 (11.4)
Father's weight (kg)*	68.1 (15.7)	64.2 (14.6)	66.3 (12.3)	67.2 (11.5)
Socio-economic status#				
Higher	14 (15.7%)	16 (23.5%)	5 (12.2%)	4 (14.3%)
Upper middle	23 (25.8%)	18 (26.5%)	7 (17.1%)	8 (28.6%)
Lower middle	36 (40.4%)	22 (32.4%)	16 (39.0%)	13 (46.4%)
Lower	16 (18.0%)	12 (17.6%)	13 (31.7%)	3 (10.7%)
Maternal education<10^{th}Std	42 (47.2%)	23 (33.8%)	19 (46.3%)	11 (39.3%)
Father's education<10^{th}Std	25 (28.1%)	12 (17.7%)	10 (25.0%)	4 (14.3%)

**Values are mean (SD). Rest of the values are n (%); #No significant difference between the LBW and control subjects in the socio-demographic data.*

TABLE II COMPARISON OF ANTHROPOMETRIC MEASUREMENTS OF STUDY GROUPS WITH CONTROLS

Category	*Sex*	*Height (cms)*	*Weight (kg)*	*Sitting Height (cms)*	*HC (cms)*
PT SGA (*n*=61)	Male (*n*=34)	164.5 (7.3)* (162.0-166.9)	53.8 (11.5) (49.9-57.7)	83.8 (3.6) (82.6-85.0)	53.4 (2.1)* (52.7-54.1)
	Female (*n*=27)	152.9 (6.8) (150.3-155.5)	44.6 (8.9) (41.2-47.9)	78.2 (3.9) (76.7-79.7)	51.3 (1.6)* (50.6-51.9)
FT SGA (*n*=30)	Male (*n*=15)	168.9 (6.3) (165.7-172.1)	54.9 (8.2) (50.7-59.0)	85.6 (3.6) (83.8-87.4)	53.5 (1.2) (52.9-54.1)
	Female (*n*=15)	155.6 (3.6) (153.8-157.4)	45.3 (8.8) (40.8-49.8)	78.7 (2.5) (77.4-79.9)	51.8 (1.8) (50.9-52.7)
PT AGA (*n*=70)	Male (*n*=42)	168.6 (6.5) (166.7-170.6)	55.5 (10.1) (52.4-58.6)	85.2 (3.1) (84.3-86.1)	54.1 (1.9)* (53.5-54.7)
	Female (*n*=28)	153.8 (6.2) (151.5-156.1)	49.3 (10.6) (45.4-53.2)	79.0 (2.9) (77.9-80.1)	51.8 (1.7)* (51.2-52.4)
Controls (*n*=73)	Male (*n*=43)	170.2 (5.8) (168.5-171.9)	56.3 (10.6) (53.1- 59.5)	86.0 (2.9) (85.1-86.9)	54.6 (1.6) (54.1-55.1)
	Female (*n*=30)	156.3 (6.4) (154.0-158.6)	48.1 (9.7) (44.6- 51.6)	80.3 (3.3) (79.1-81.4)	53.6 (1.8) (52.9-54.2)

*Values are mean (SD), (95% CI of mean); * P<0.05 significantly different from controls; HC=Head circumference.*

The sex specific adiposity parameters at 18 years are shown in ***Table* III**. There was no significant difference in these measurements in the PTSGA, FTSGA and PTAGA groups and controls. Similarly, there was no evidence of adiposity when the BMI and body fat as a percentage of body weight of these 3 groups was compared with controls. Only two subjects had hypertension for which no cause could be found inspite of thorough investigations.

Morbidity data: Six subjects had myopia and were wearing glasses. Four subjects had sensori-neural hearing

TABLE III SEX SPECIFIC ADIPOSITY PARAMETERS AT 18 YEARS OF AGE BY WEIGHT FOR GESTATIONAL AGE

Category	*Sex*	*Sum of 4 skinfolds*	*Waist / Height*	**Body fat*
PT SGA (*n*=61)	Male (*n*=34)	52.3 (24.9) (43.9-60.7)	0.44 (0.061) (0.42-0.46)	18.5 (5.7) (16.6-20.4)
	Female (*n*=26)	66.8 (25.3) (57.1-76.5)	0.44 (0.049) (0.42-0.46)	29.0 (5.4) (26.9-31.1)
FT SGA (*n*=30)	Male (*n*=15)	47.2 (24.7) (34.7-59.7)	0.43 (0.058) (0.40-0.46)	17.4 (5.4) (14.7-20.1)
	Female (*n*=14)	69.7 (23.3) (57.4-81.9)	0.44 (0.047) (0.42-0.46)	29.2 (5.3) (26.4-31.9)
PT AGA (*n*=70)	Male (*n*=42)	55.9 (28.4) (47.3-64.5)	0.43 (0.057) (0.42-0.45)	19.2 (6.1) (17.4-21.0)
	Female (*n*=27)	80.5 (25.0) (71.1-89.9)	0.46 (0.064) (0.44- 0.48)	31.9 (4.7) (30.1-33.7)
Controls (*n*=73)	Male (*n*=43)	49.9 (25.0) (42.4-57.4)	0.43 (0.060) (0.41- 0.45)	17.9 (5.5) (16.3-19.5)
	Female (*n*=30)	67.6 (20.4) (60.2-74.9)	0.44 (0.059) (0.42-0.46)	29.5 (4.0) (28.1-30.9)

*Values are mean (SD) (95% CI of mean); No statistically significant difference between adiposity parameters of all four groups.*Durnin's equation.*

loss and were wearing hearing aids. Two subjects had epilepsy, but were well controlled on drugs. Two subjects who had hypertension were controlled on drugs. Five girls had menstrual problems – 3 had irregular bleeding, 1 had dysmenorrhoea, and 1 had menorrhagia. USG abdomen did not show any polycystic ovarian syndrome. This morbidity did not cause any significant abnormality of growth.

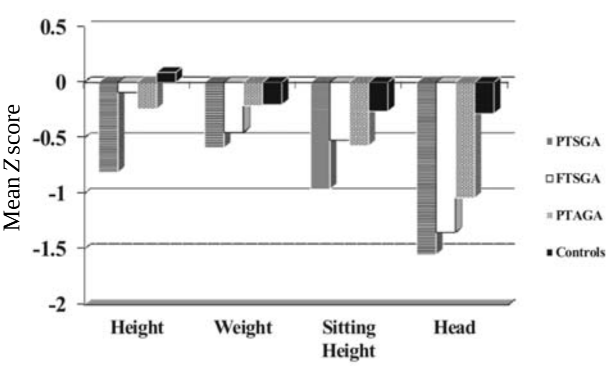

FIG. 1 *Growth at 18 years by weight for gestational age (Agarwal, et al. [15] standards).*

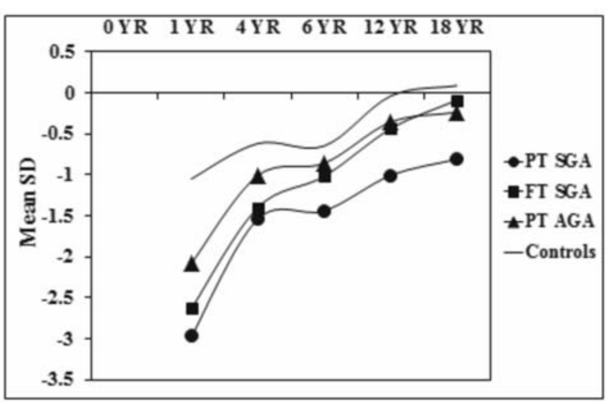

FIG. 2 *Growth trajectory (height) with sex-specific SD scores.*

Four separate multiple regression models were created with height, weight, head circumference and BMI, as dependent variables. The independent variables were grouped as (*i*) Birth parameters – weight, sex and AGA/SGA status; (*ii*) Neonatal risk factors; and (*iii*) genetic factors (*a*) midparental height for the height model, (*b*) mother's and father's weight for the weight model, and (*c*) mother's and father's BMI for the BMI model.

The major determinants for height, weight, head circumference and BMI in the whole LBW group were derived by a multiple regression analysis. Out of a total variance of 20.7% for height, midparental height contributed 17.1% variance. For weight, mother's weight contributed 23.2% variance out of a total variance of 31.3%. Birthweight was an important determinant of head circumference. Mother's and father's BMI were found to be important predictors of their children's BMI.

The Z scores of midparental height were compared in the four groups. There was no statistically significant difference between the midparental height of the PTSGA, FTSGA, PTAGA groups and controls. When the actual height was plotted against three tertiles of midparental height, PTSGA children were shorter than controls inspite of having similar midparental heights.

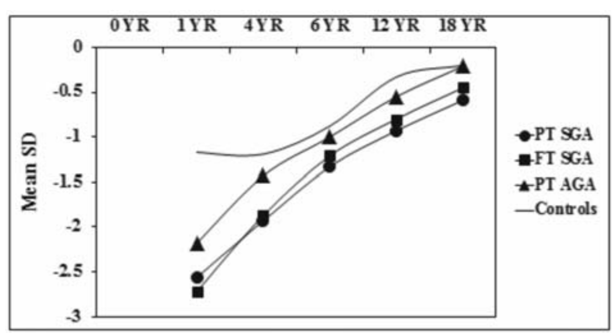

FIG. 3 *Gowth trajectory (weight) with sex-specific SD scores.*

WHAT IS ALREADY KNOWN?

- Preterm SGA children have short stature in adulthood.

WHAT THIS STUDY ADDS?

- Parental height, weight and BMI are important factors in determining the same in LBW children at early adulthood.
- Central obesity and hypertension were not found at 18 years of age.
- Bone age at 12 years can predict height at adulthood, even in preterm SGA children.

DISCUSSION

This was the last phase of a long term study spanning 18 years, with a 80% followup of the original cohort. This is the first Indian report of gender-specific trajectory of growth of low birth infants born in the late eighties. Our study showed that preterm SGA males were significantly shorter than controls. There was no difference in the weight, BMI, and measurements for adiposity in the LBW and control group. Preterm females showed a smaller head circumference, the preterm SGA more so than preterm AGA.

Ranke, *et al*. [25] reported that there was no difference in the growth of SGA and AGA children at 3.5 years. PTSGA children in this study remained shorter than controls at 18 years. Similar findings have been reported by Hack, *et al*. [6] in VLBW children at 20 years, and Saigal, *et al*. [7] in ELBW children. On multiple regression analysis, midparental height was found to be an important predictor of height at 18 years for the whole LBW group. In a recent study of moderately low birthweight children, Odberg, *et al*. [23] found that parental height was an important determinant of height. However, in our study, inspite of normal midparental height, the PTSGA children were significantly shorter.

There was no difference in the weight of the study and control group. Hack, *et al*. [6] reported lower weights in VLBW males at 20 years, as well as lower BMI. There was no difference in the BMI and measurements of adiposity between the LBW and control group. Both weight and BMI were predicted by mother's and father's weight and BMI, respectively. We found little evidence in our cohort of a relationship between socio-economic status and growth. Similar findings were reported previously in VLBW children [6].

Birthweight was the only important biological factor as a predictor of head circumference. Prediction of adult height from bone age done at 12 years in LBW children has not been described before. It was interesting to see the agreement between predicted height and actual height, even amongst SGA children.

Barker, *et al*. [4] have described the tendency of low birthweight children (especially with intrauterine growth restriction) to develop metabolic syndrome in adulthood. We found no evidence of adiposity, at least in early adulthood, and no hypertension. Several studies have reported higher blood pressure in VLBW infants in late adolescence [26] and in VLBW infants at early adulthood [27]. We plan to follow up these children further to look for early predictors of the metabolic syndrome.

The strengths of this longitudinal study include its gender specificity, and the use of *Z* scores which are comparable across ages and provide a more sensitive assessment of deviations of growth, than the use of percentiles or cut offs of subnormal growth. A major strength was the high participation rate over time and complete parental information in the form of height, weight, education and socio-economic status. Adults who were moderately premature and moderately low birth weight were included, a group that is rarely considered in follow up studies. Since the study started in the preventilation era in India, a weakness was the small number of extremely low birth weight babies in the cohort.

Contributors: SC: conceived the study, supervised it, wrote the manuscript and is the guarantor of the paper. MO: supervised data collection and analysed data. BK: collected data. AP: supervised the project. MH: Made home visits, ensured appointments, MGS.. did statistical analysis.
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