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RESEARCH ARTICLE

Prevalence, characteristics and maternal risk factors of small for gestational age fetuses in a tertiary care center from Kerala

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ABSTRACT

Objectives: This study was conducted to determine the prevalence and to understand the maternal characteristics and risk factors of small for gestational age (SGA) fetuses among booked antenatal mothers in the third trimester in a tertiary care hospital. **Methods:** 250 consecutive booked and singleton mothers at or above 28 weeks gestation were screened for SGA. Those who were diagnosed so, were matched 1:2 ratio with age matched controls and compared. **Results:** The prevalence of SGA was 13.6% (95% CI 9.4-17.8). Fifty-three percent were in the age group of 20-24 years, 68% were primigravida and 75% of multigravida women had previous history of SGA child. Mothers of SGA fetuses had median BMI of 22.4 kg/m^2 and gained 8 kg in pregnancy. Each kilogram gain in pre-pregnancy weight reduces the risk of having SGA fetus by 0.8%. Each earlier week of delivery increased the risk of LBW by 20%. Each gram of low hemoglobin increased the risk of having SGA fetus by 7.6%. Mothers with previous history of SGA had odds of 36 times to have SGA fetus in the current pregnancy. **Conclusions:** Apart from knowing the prevalence, this study also sheds light into fact that several social, educational and nutritional factors play a role in causation of a SGA fetus. Health policies aimed in improving adolescent health and education could be one of the primary preventive strategies.

Keywords: Fetal growth restriction, intrauterine growth restriction, South India.

Intrauterine growth restriction (IUGR) or fetal growth restriction (FGR) is a common complication of pregnancy leading to multiple adverse perinatal outcomes. The prevalence of FGR is variable but grossly affects 5–10 % of uncomplicated gestations and up to 25% in high risk gestation. Also it is the second most common cause of perinatal mortality[1]. FGR babies have an increased risk for perinatal mortality, complications of prematurity and birth adaptation. On a long-term basis, they have an increased risk for developing short stature, cognitive delay with decreased academic achievement and increased risk of neurologic disorders, including cerebral palsy[2]. FGR is now proven to be associated with increased rates of coronary heart disease, stroke, hypertension, PCOS in women and type 2 diabetes[3]. Hence, it is important to diagnose and mitigate this condition, as it would lead to substantial burden to the society on long-term basis.

Small for gestational age (SGA) is not synonymous with FGR but due to ease in diagnosis of SGA, we refer further discussions strictly to SGA. The prevalence of SGA fetuses is variable across the globe. In India, the estimates were up to 47% with high regional variation. Latest and largest study

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from south India comes from the state of Tamil Nadu, where the prevalence of SGA among about 37000 deliveries was 8.4%[4]. From the previous discussion; it is clearly evident that SGA has a huge impact on the future health of the individual. In order to prevent SGA, maternal correctable risk factors have to be established. Since both these states- Kerala and Tamil Nadu fare almost equally in health parameters, it is prudent to even compare the incidence of SGA. In order to tailor the health policies for the state, a proper investigation for the prevalence is required - this was the primary reason for the conduct of the study.

Maternal, fetal and placental risk factors lead to a 'stressed' fetus with high levels of inflammatory markers. Several markers like interleukin-6, tumour necrosis factor α, C reactive protein, myeloperoxidase and adiponectin levels have been demonstrated to be significantly high in cord blood samples [5,6]. Hence, this study was conducted to determine the prevalence of SGA fetuses among booked antenatal mothers in the third trimester in a tertiary care hospital.

Materials and methods

This was a hospital based cross sectional study with a nested case control comparison. The study was conducted from May 2018 to December 2018 in the outpatient department of Obstetrics and Gynecology. For the prevalence study, 250 consecutive booked and singleton antenatal mothers at or above 28 weeks were enrolled after getting voluntary consent. Twin or multiple gestation pregnancies, fetuses diagnosed with congenital anomalies and mothers referred from other hospitals were excluded. All antenatal mothers enrolled in the study were screened by ultrasonogram as per protocol. Antenatal mothers having estimated fetal weight less than the 10th percentile for their gestational age (reference for estimated fetal weight was taken from a study [7] were diagnosed to have SGA fetus and were enrolled for the second part of the study. The definitions of different variables are available in supplementary appendix.

All antenatal mothers with fetus diagnosed to have SGA by definition from the prevalence study were taken as cases. Mothers with AGA fetus were randomly chosen by simple random numbers from the remaining sample and were taken as controls for comparison (cases: controls = 1:2). For the case-control study, details of antenatal mothers with SGA – residential, nutritional, medical and socioeconomic - were noted. Anthropometry and complete examination was performed. Biochemical tests - hemoglobin, TSH, glucose challenge test and CRP were performed. AFI levels and placental insufficiency indices in USG; PAPP-A and β hCG levels (when available) were recorded. For the controls (who were selected by random numbers from the prevalence cohort), all the above said details were recorded except for CRP.

The antenatal mothers labeled cases were followed up till confinement. Additional nutritional supplements given to them were recorded. Maternal outcomes in terms of mode of delivery and timing of delivery were recorded. Immediate neonatal outcomes in terms of APGAR score, admission in NICU and duration of hospital stay were recorded.

Statistical analysis: Expected proportion of SGA as per previous study from CMC Vellore was 8.4% [4]. With total width of confidence interval (W) being 0.1 and confidence level (CL) of 99 %, the sample size was 204 [8]. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range whichever is appropriate. Frequencies and percentages were used for categorical data. Distribution of variables was checked for normality with Shapiro-Wilk test. Pearson's Chi–square test was used to assess differences in groups for categorical data. Normative data was compared by student-t test and non-normative by Mann Whitney U test. Spearman's correlation was done to assess the relation between fetal birth weight and maternal parameters. Variables showing significant correlation and other relevant parameters were entered into stepwise backward binary logistic regression to calculate odds ratio. Data was analyzed by the Statistical Package for the Social Sciences software (version 23.0, IBM, SPSS Statistics). A p value of < 0.05 was considered statistically significant.

Results

Description of SGA pregnancies: The prevalence of SGA in our study was 13.6% (95% CI 9.4-17.8) in 250 consecutive antenatal mothers. Of 34 SGA fetuses, 33 had birth weight less than 2.5 kg. None of the 68 randomly selected controls had low birth weight. Fifty-three percent of mothers were between 20 -24 years of age (Figure 1). About 60% were graduates and 18% were employed. Half of them were residing in urban areas. Except for one, all mothers conceived naturally. Majority was primigravida (68%) and there was inter-pregnancy spacing of > 3 years in 75% of multigravida mothers. Previous history of SGA was present in 75% of multigravida women. About 25% had chronic medical disorders prior to pregnancy (Figure 2). Sixty-two percent were already on nutritional supplements prior to consultation. While the timing of delivery, birth weight and

Table 1: Antenatal details of cases and controls

Parameters	Cases N = 34	Controls N = 68	P value
Age in years	24 (22,29)	25 (23,27)	0.5
Educational status			
▪ High school	13	11	0.03
▪ Graduation	21	57	
Occupation			
▪ Housewife	28	45	0.08
▪ Employed	6	23	
Residence			
▪ Rural	16	34	1
▪ Urban	18	34	
Mode of conception			
▪ Spontaneous	33	65	1
▪ Assisted	1	3	
Obstetric score			
▪ Primigravida	23	43	0.8
▪ Multigravida	11	23	
Inter pregnancy spacing in multigravida			
▪ < 3years	2/8	9/20	0.5
▪ >3 years	6/8	11/20	
Previous FGR in multigravida	6/8	2/26	<0.001
Nutritional supplementation	21	1	<0.001
Chronic medical disorders	9	8	0.06
Medical disorders complicating pregnancy	22	31	0.07
Abnormal doppler study	11	1	<0.001
Oligohydramnios	10	3	0.001

Results are expressed as number of cases/controls or median (interquartile range) as appropriate

neonatal complications were not affected; those mothers of SGA infants with abnormal doppler studies had significantly higher rates of cesarean section (81% vs 40% in those without abnormal doppler). Anthropometrically, mothers had median BMI of 22.4 kg/m^2 and gained 8 kg in pregnancy. Details of mode of delivery of the mothers have been elaborated in figure 3. Median gestational age at the time of delivery was 37 weeks and median birth weight of neonates was 2.3 kg. There were 3 babies with more than one neonatal complication. Two babies required ventilator support and one baby was delivered after intrauterine death. Comparison of mothers of SGA infants with controls: The median age was not different between cases and controls (Table 1). Proportionately, 84% of controls were graduate or higher in

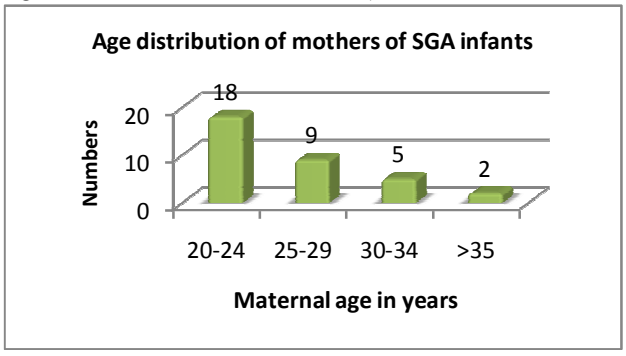

Figure 1: Age distribution of mothers of SGA infants

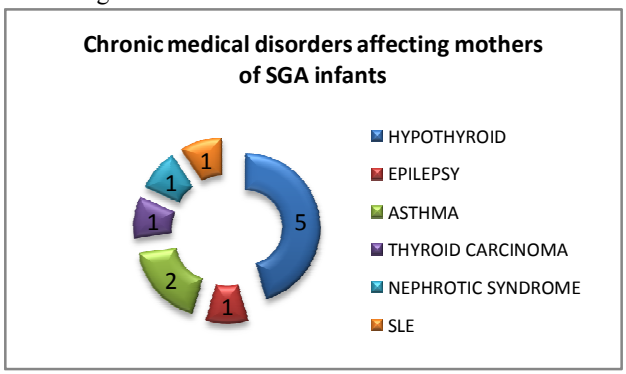

Figure 2: Chronic medical disorders affecting mothers of SGA infants

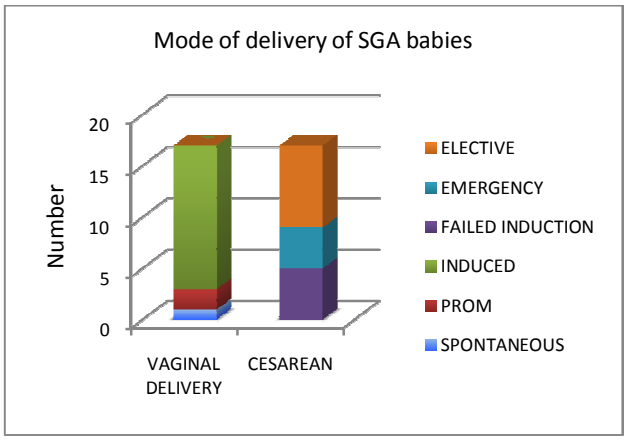

Figure 3: Mode of delivery of SGA babies

qualification whereas it was only 61% in cases. There was significantly higher number of mothers in SGA group with previous SGA births. While 21 of 34 in SGA group were on nutritional supplementation already, only 1 of 68 in control group was on supplementation. There was significant difference in pre-pregnancy weight between two groups (Table 2). Cases were significantly more stunted than controls. As a result of these changes, BMI, a fraction involving both height and weight was not different between two groups. A significant weight gain difference of 3 kg was present between controls and cases. Median hemoglobin level was lower in cases. With respect to perinatal outcomes, the timing of delivery was significantly earlier in cases – median of 37 weeks as compared to 39 weeks in controls. As expected, number of cesarean section was higher in cases 55%.

Correlation and regression: One of the hypotheses that, maternal inflammatory markers would be related to fetal weight was not found to be true. However, there were correlations between maternal weight ($r = +0.27$, $p = 0.006$), weight gain during pregnancy ($r = +0.36$, $p < 0.001$) and maternal height ($r = +0.37$, $p < 0.001$) with birth weight. When analyzed with univariate general linear model, the adjusted R^2 was 0.65, meaning that the predicted estimate was very significant. Each kilogram gain in pre-pregnancy weight reduces the risk of having SGA fetus by 0.8%. Time of delivery has been very well correlated with birth weight. In our study, each earlier week of delivery increased the risk of LBW by 20%. Each gram of low hemoglobin increased the risk of having SGA fetus by 7.6%. Babies born out of vaginal delivery had 14% reduced risk of LBW. In logistic regression of multigravida women, it was seen that mothers

Table 2: Anthropometric, biochemical and perinatal details of cases and controls

Parameters	Cases N = 34	Controls N = 68	P value
Prepregnancy weight in Kg	50.5 (42,59)	58.5 (50.3,67)	0.001
Height in cm	151 ± 6	157 ± 6	<0.001
BMI in Kg/m^2	22.4 (18.5,25.5)	23.9 (20.9,26.7)	0.07
Weight gain in pregnancy in Kg	8 (5.7,11)	11 (9.3,13)	<0.001
Hemoglobin in g/dL	11.6 ± 1.2	12.1 ± 1	0.04
TSH in mIU/mL	2.2 (1.4,3.5)	2.2 (1.4,3.6)	0.8
Glucose challenge test in mg/dL	124 (112,138)	127 (111,157)	0.6
PAPP-A in MoM	1.03 (0.67,1.31) N = 22	0.94 (0.67,1.62) N = 34	0.9
Free β hCG in MoM	1.1 (0.8,1.6)	0.7 (0.4,1.4)	0.07
CRP in mg/L	5 (3.4,7.4)	NA	NA
Timing of delivery in weeks	37 (36.5,37.7)	39 (38,39.4)	<0.001
Mode of delivery			
▪ Vaginal	16	52	0.006
▪ LSCS	18	16	
Gender of baby (female)	20	37	0.6
Birth weight in Kg	2.3 (2.1,2.4)	3.2 (3,3.5)	<0.001
APGAR score	9 (8,9)	9 (9,9)	<0.001
NICU stay in days	2 (0,4)	0 (0,0)	<0.001

Results are expressed as number of cases/controls, median (interquartile range) or mean ± standard deviation as appropriate.

Abbreviations: BMI – body mass index, TSH – thyroid stimulating hormone, PAPP-A – pregnancy associated plasma protein – A, MoM – multiples of median, hCG – human chorionic gonadotropin, CRP – C reactive protein, LSCS – lower segment cesarean section, NICU – neonatal intensive care unit

with previous history of SGA had odds of 36 times to have SGA fetus in the current pregnancy.

Discussion

The prevalence of SGA fetuses in the current study was 13.6%. This figure closely resembled that obtained in a large retrospective study comprising about >36000 deliveries done in a tertiary care center in Tamil Nadu. However, SGA was defined based on birth weight <10th centile in that study [4]. The prevalence was 11.4 % in 1996 and 8.4% in 2010. Considering the same health related indices, socioeconomic factors and almost similar ethnicity, these results were comparable.

Considering the national average of SGA at birth being up to 47%, it is important to know the proportion during gestation in order to allocate health resources. Detection of SGA fetus gives an ample opportunity for the obstetrician to anticipate and prepare adequately for perinatal complications [1]. However, until recently there were no specific interventions to treat a SGA fetus so as to normalize its weight by birth. Nutritional supplementation/ modification in 4665 women from 13 trials did increase the birth weight minimally and reduce the SGA infants modestly (RR 0.68, 95% CI 0.56 – 0.84). Paradoxically, there was no additional benefit in nutritionally deprived section [9]. In another meta-analysis comprising >137000 pregnancies from low to middle-income countries, multiple micronutrient supplementation resulted in reduction of SGA neonates (RR 0.92, 95% CI 0.86 – 0.98). There was no significance difference when micronutrients were compared with iron/folate supplementation [10]. These studies again confirm that as of now there are few evidences to support iron and folate supplementation for treating SGA fetus to prevent LBW.

Social factors had great impact in deciding the outcome of fetal weight. In our study, educational status played a major role. As it can be appreciated from the final predictive model equation, educational status of high school was tending towards significance to predict the risk of SGA fetus. The green top guideline from NICE does not recognize this as a risk factor probably because in such a developed country educational status may not be a risk factor. But, in developing country such as India, through our study, we propose to include educational status as one of the risk factor of determination of SGA fetus in third trimester. Though it is grossly emphasized that education of girls is important for improvement of society, there is objective evidence from our study that empowering women with higher education pays off by improving the health of future generation.

Two-thirds of mothers of SGA infants were primigravida and half were between 20-24 years. These findings again vouch for improving the general health status of girls from birth so that they are healthy during reproductive years. Though elderly age group is a risk factor, none of the mothers of SGA infants had age >40 years. Contrary of general perception, in our study, the urban and rural mothers fared equally in the incidence of SGA fetus. Probably in the areas catered by this tertiary care hospital, the socioeconomic division does not exist.

Another important risk factor is the previous history of SGA birth. Compared to mothers with previous AGA births, mothers with previous SGA births had higher risk (RR - 3.9, 95% CI 3.4 – 4.6) [11]. In our study, the odds ratio was very high (OR 36, 95% CI 4 – 310). Such a wide confidence interval was probably due to small size. It's important to educate women about adequate spacing and regarding the risk of subsequent SGA birth. If identified in 1st trimester, such high-risk pregnancies should be referred to expert tertiary care center for management.

Anthropometric measures of weight and height were significantly low in mothers of SGA infants in comparison with controls. Since both were lower than controls, BMI as a ratio was not different between the two groups. In a study done in Brazil, 2200 mother-child pairs were assessed for relationship with SGA status. Short stature of mother and underweight status had odds of 3 and 2.3 respectively for the development of SGA infant [12]. In our study, maternal height, pre-pregnancy weight and weight gain during pregnancy had correlation coefficient of 0.36, 0.27 and 0.37 respectively. Moreover, while height was not a significant influencer, pre-pregnancy weight influenced the infant's birth weight – every kilogram gain in weight by the mother reduced the risk of SGA infant by 0.8%.

Inflammatory markers were hypothesized to play a role in predicting SGA fetuses. One study looked at the trend of change of CRP during pregnancy and concluded that the rate of change of CRP was negatively correlated with birth weight centiles (β = -3.7, 95% CI -5.5 to – 2.1) [13]. In our study, probably due to very small numbers we were not able to show correlation between the third trimester CRP levels in the mothers of SGA infants with any outcomes.

There were several limitations in the current study and are enlisted below. The sample size of the study was calculated for prevalence study and not for case control

study. Hence, some common correlations had not turned out to be significant. The definition of SGA was according to generally accepted <10th centile of estimated weight and not based much more stricter customized growth charts. PAPP-A and β-hCG levels were not significantly low in our study. Firstly, sample size was not calculated for these tests as a primary endpoint. Secondly, only a few mothers opted for this test in 1st trimester and hence the numbers were small.

Conclusion

The prevalence of SGA fetuses in a tertiary care hospital in Kerala is 14%. Mothers of SGA infants were leaner, stunted, had low hemoglobin, had less weight gain during pregnancy, delivered early and had higher cesarean rates. Health programs have to be strengthened to educate women regarding their adolescent health, as pre-pregnancy parameters were one of the most important determinants of SGA status of the fetus.

Conflict of interest: None. **Disclaimer:** Nil.

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