MORTALITY AND MORBIDITY PATTERN IN SMALL-FOR-GESTATIONAL AGE AND APPROPRIATE-FOR-GESTATIONAL AGE VERY PRETERM BABIES: A HOSPITAL BASED STUDY

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Background: Very preterm babies are important group of paediatric babies who require special attention. These babies are known to have increased risk of morbidity and mortality. Studying the morbidity and mortality pattern for this important paediatric group can help in better understanding of their care in the hospital settings. Objective of the study was to compare the mortality and morbidity pattern in Small-for-gestational age and appropriate–for-gestational age very preterm babies. This hospital based prospective (cohort) study was conducted at the department of Paediatrics, Postgraduate Medical Institute, Lady Reading Hospital, Peshawar from March 2008 to April 2009. **Methods:** One hundred Small-for-gestational age (SGA) live born very preterm babies were compared with 100 appropriate-for-gestational age (AGA) very preterm babies having similar gestational ages. Information regarding gestational age, birth weight, mortality, and morbidity (in terms of various biochemical and clinical markers) were recorded on a pre-designed questionnaire. Data analysis was done using SPSS version 15. Results were interpreted in terms of descriptive (mean, proportions, standard deviation) and inferential statistical tests (with *p*-values). **Results**: There was no difference between the two groups (SGA Vs AGA) with regards to gestational age and gender of the babies The mean weight of SGA babies was significantly lower as compared to AGA babies (1.1±0.16 Kg Vs 1.5±0.2 Kg; *p*=0.001). As compared to AGA babies, the SGA babies had a higher mortality (40% Vs 22%, *p*=0.006), and higher morbidity in terms of hyperbilirubinaemia (67% Vs 51%, *p*=0.02) and hypocalcaemia (24% Vs 10%, *p*=0.02). The difference in the mortality between the two groups was more prominent in babies with gestational age ≤31 weeks (71.4% for SGA as compared to 39.3 % for AGA very preterm babies with gestational age ≤31 weeks). **Conclusion:** Very preterm SGA infants have significantly higher mortality and morbidity in comparison to the AGA babies. In deciding for therapeutic management of these babies, they need special attention in terms of factors as gestational age and the biochemical markers, to improve the outcome for these babies in the hospital settings.

Keywords: Very preterm, SGA, AGA, mortality and morbidity

INTRODUCTION

Very preterm babies or those born before 33 completed weeks of gestation include both Small-for-gestational age (SGA) and Appropriate-for-gestational age (AGA) infants[1]. These very preterm babies are very important paediatric age group in terms of morbidity and mortality reported for this age group. For instance, in Western countries, while they represented about one percent of live births nevertheless they accounted for half of all neonatal mortality.[1]

The **v**ery preterm babies (SGA or AGA) also carry increased risk of neonatal morbidity or complications. These complications include respiratory distress syndrome (RDS)' intraventricular haemorrhage (IVH), sepsis, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), hyperbilirubinemia, feeding difficulties, temperature instability, hypoglycemia and hypocalcaemia.[2–6]

There are a number of studies comparing mortality and morbidity pattern in SGA and AGA very preterm infants. These studies show that SGA infants carry higher mortality than AGA infants[7–10], yet the differences regarding morbidity pattern are less clear, more importantly that of the respiratory morbidity and non respiratory morbidity (biochemical indicators). A few **s**tudies have shown that SGA infants have lower incidence of RDS but longer hospital stay than AGA infants.[8,9]

Mortality and morbidity (including prolonged hospital stay) of very preterm babies result in significant cost to parents, society and health sector. The small for gestational age group is also very important in terms of admission to NICU. There is generally a paucity of information regarding the mortality and morbidity patterns of very preterm babies from developing countries. Therefore, studying these very preterm babies becomes imperative for proper and timely decision-making in hospital settings in developing countries. The present study was aimed to identify the morbidity and mortality pattern in this high risk group in our setting.

SUBJECTS AND METHODS

This hospital based prospective (cohort) study was conducted at the Department of Paediatrics, Postgraduate Medical Institute Lady Reading Hospital, Peshawar from March 2008 to April 2009. Two hundred (100 in each exposed and unexposed

arm) very preterm singleton babies between 28–32 weeks gestation, without lethal congenital anomalies and birth weight >500gram were included. Detailed history, examination was carried out and relevant data was collected on pre-designed questionnaires.

Babies were categorized as SGA (birth weight less than 10^{th} centile) & AGA (birth weight between 10^{th}-90^{th} centile) based on foetal growth charts developed by Lubchenco *et al.*[11] SGA babies were considered as exposed group while AGA as unexposed group. For each SGA baby admitted, the subsequent AGA admission of same gestational age was identified as a comparison group.

Gestational age (recorded as completed weeks) was assessed from maternal last menstrual period (LMP), ultrasound scan in the first trimester & Dubowitz examination results.[12] If there was discrepancy for more than two weeks between these three methods then Dubowitz examination results alone were used to determine gestational age.

Weight of baby was done within 24 hrs of birth and measured in decimal of kilograms. We followed both SGA (exposed) and AGA babies for 1 week after birth, and noted the mortality and morbidity during this period. In case if a baby died before this time, mortality was noted for him. All the babies who were still admitted after 1 week of birth were followed till the time of their discharge and any mortality noted if it took place. Babies were discharged when able to maintain temperature, having no apnoeic spells and tolerated full NG feed. X-ray chest and echocardiography were done based upon clinical suspicion. Complete blood count, blood cultures were sent as well as blood glucose, total serum calcium and serum bilirubin level were also measured. Informed consent was taken from parents.

WHO sample size calculation manual for Health studies was used for calculation of sample size for hypothesis testing. The estimated proportion of disease (very preterm babies) amongst non-exposed was taken at 25% based on clinical observations. For testing hypothesis for estimated relative risk of 1.75 for infant mortality in exposed group (small for gestational age) as compared to unexposed group (appropriate for gestational age), at power of 80% and level of significance of 5%, the required sample size was of 100 patients in each cohort.[13,14]

Data were processed using SPSS-15. Mean±SD was calculated for weight. Frequencies as percentages are presented for gender, hypoglycaemia, hypocalcaemia, indirect hyper-bilirubinaemia, PDA, sepsis, RDS, resuscitation, meconium aspiration syndrome (MAS), Polycythemia and mortality. Chi-square test and Independent sample *t*-test was used to compare the two groups (SGA and AGA) in regards to various study variables. A *p*-value <0.05 was considered significant.

RESULTS

Table-1 summarizes the results for the study. Out of the total 200 patients, an equal number (n=100) of patients were exposed (Small for gestational Age) and un-exposed (Appropriate for the gestational age).

A higher percentage of the 'very preterm babies' included in the study were males (120, 60%), as compared to females 80 (40%). The mean gestational age of very preterm babies was 31.4±1.0 weeks. There was no significant difference between the two study groups in regard to the gender (p=0.77) and gestational age of the babies (p=0.9).

The mean weight of all (n=200) the 'very preterm babies' was 1.3±0.3 Kg. The mean weight of the babies in the 'SGA' arm was 1.1±0.16 Kg, and was significantly lower (p=0.001) as compared to 'AGA' group for which the mean weight of babies was 1.5±0.2 Kg.

The morbidity of the babies during the length of stay at the hospital was higher in the 'SGA' babies as compared to 'AGA' babies. The morbidity of the babies was measured by a number of biochemical and clinical indicators (measures).

A significantly higher (p=0.02) proportion of children were jaundiced (hyper-bilirubinaemia) in the 'SGA' babies as compared to the 'AGA' babies (67% Vs 51% babies). Similarly a significantly higher (p=0.02) proportion of small for gestational age patients had lower blood calcium levels as compared to the 'AGA' (24% vs 12%). There was a significant difference (p=0.03) in blood sugar levels of the exposed and unexposed groups, with 15% of small for gestational age babies being hypoglycaemic as compared to 27% in the appropriate for gestational age group.

However, when we run further analysis on the very term babies that were hypoglycaemic (n=42, 21%), we found that the mean glucose level for the SGA babies was significantly lower than that of AGA babies (20.4 mg/dl VS 33.1 mg/dl; p=0.0001). Considering the gestational ages of the very preterm babies and dichotomizing the hypoglycaemia into low (26–39 mg/dl) and very low (25 mg/dl and lesser), we found that there were significantly higher babies with very low blood glucose levels in SGA group as compared to AGA group in both gestational age categorizes as depicted in Table-2.

There was no significant difference in other morbidity indicators like RDS, sepsis, meconium aspiration syndrome, PDA and polycythaemia between the SGA and AGA babies.

Table-1: Morbidity and mortality of Very Preterm babies (n=200) in Paediatric Nursery of Lady Reading Hospital, Peshawar

	Over All n=200 (Mean±SD)	Small for gestational Age n=100 (Mean± SD)	Appropriate for Gestational Age n=100 (Mean±SD)	*p*-Value
Weight of baby (in Kg)	1.3 ± 0.3	1.1 ± 0.16	1.5 ± 0.2	0.001
	N (%)	N (%)	N (%)	
Gender				0.77
Males	120 (60)	59 (59)	61 (61)	
Females	80 (40)	41 (41)	39 (39)	
Hypoglycaemia*				0.03
Yes	42 (21.0)	15 (15)	27 (27)	
No	158 (79.0)	85 (85)	73 (73)	
Hypocalcemia**				0.02
Yes	34 (17.0)	24 (24)	10 (10)	
No	166 (83.0)	76 (76)	90 (90)	
Hyper-bilirubinemia***				
Yes	118 (59.0)	67 (67)	51(51)	0.02
No	82 (41.0)	33 (33)	49 (49)	
Polycythemia****				
Yes	10 (5.0)	5 (5)	5 (5)	1.0
No	190 (95.0)	95 (95)	95 (95)	
Respiratory Distress Syndrome†				0.15
Yes	84 (42)	37 (37)	47 (47)	
No	116 (58)	63 (63)	53 (53)	
Patent Ductus arteriosus				1.0
Yes	8 (4)	4 (4)	4 (4)	
No	192 (96)	96 (96)	96 (96)	
Meconium aspiration syndrome				0.3
Yes	4 (2)	3 (3)	1 (1)	
No	196 (98)	97 (97)	99 (99)	
Resuscitation				
Yes	12 (6)	7 (7)	5 (5)	0.5
No	188 (94)	93 (93)	95 (95)	
Sepsis‡				
Yes	20 (10)	11 (11)	9 (9)	0.6
No	180 (90)	89 (89)	91 (91)	
Mortality				0.006
Yes	62 (31)	40 (40)	22 (22)	
No	138 (69)	60 (60)	78 (78)	

*random blood glucose level <40 mg/dl; **total serum calcium level <7 mg/dl; ***indirect bilirubin level ≥10 mg/dl; ****Hct ≥65%
†Signs of respiratory distress developing within 6 hrs of birth and/or radiological evidence; ‡Based on positive blood culture

Table-2: Comparison of Hypoglycaemic pattern in Exposed (SGA) and Unexposed (AGA) very preterm babies across categories of gestational age

Categories	Hypoglycaemia	SGA N (%)	AGA N (%)	*p*-Value
Gestational age 31 weeks and lesser	Very low blood glucose (25 mg/dl and lesser)	9 (100)	1 (10)	0.0001
	low blood glucose (26–39 mg/dl)	0 (0)	9 (90)	
Gestational age 32 weeks	Very low blood glucose (25 mg/dl and lesser)	4 (66.7)	1(6)	0.0077
	low blood glucose (26–39 mg/dl)	2 (33.3)	16 (94)	

The mortality trends for the 'very preterm babies' are presented in Table-1 and Figure-1. Considering the outcomes, the overall mortality for the 'very preterm babies' included in the study was 62 (31%). There was a significantly lower mortality in the 'AGA group as compared to 'SGA group' (22% Vs 40% respectively). The difference in the mortality between the two groups was more prominent in babies with gestational age ≤31 weeks (71.4% for SGA as compared to 39.3 % for AGA very preterm babies with gestational age ≤31weeks, p=0.015) (Table-3 and Figure-2). For babies with gestational age of 32 weeks, there was no significant difference at 5% level of significance between the exposed and unexposed babies (p=0.06). The mortality in the small for gestational age babies however was higher as compared to age appropriate babies with gestational age of 32 weeks (27.8% Vs 15.3%). (Table-3 and Figure-3).

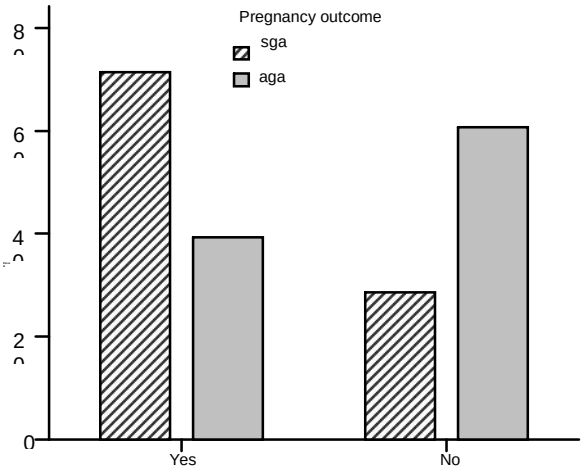

Figure-1: Mortality trends in the 'SGA' Vs appropriate for gestational age

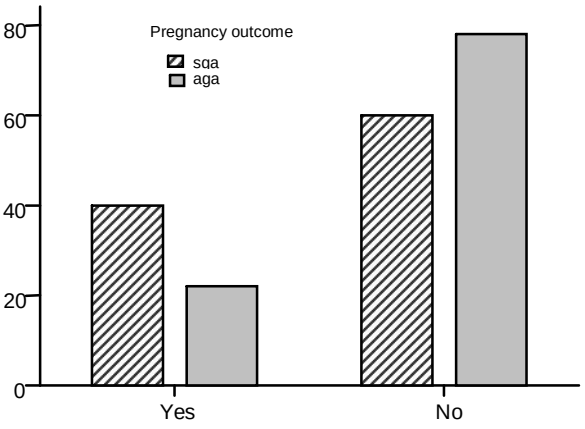

Figure-2: Mortality pattern for gestational age 31 weeks and lesser

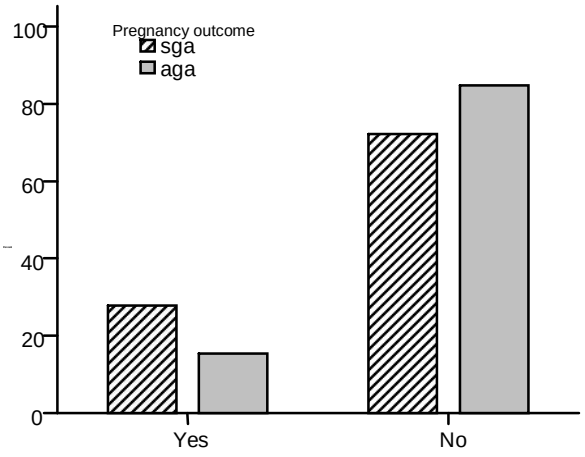

Figure-3: Mortality pattern for gestational age 32 weeks

Table-3: Comparison of mortality pattern in Exposed (SGA) and Unexposed (AGA) very preterm babies across categories of gestational age

Categories of gestational age	Mortality Pattern in the preterm babies	Small for gestational age No. (%)	Appropriate for gestational age No. (%)	*p*-Value
Gestational age 31 weeks and lesser	Preterm babies died	20 (71.4)	11 (39.3)	0.015
	Preterm babies alive	8 (28.6)	17 (60.7)	
Gestational age 32 weeks	Preterm babies died	20 (27.8)	11 (15.3)	0.06
	Preterm babies alive	52 (72.2)	61 (84.7)	

DISCUSSION

Studies have shown that SGA infants carry higher mortality than AGA infants[7–10], yet the results on comparison of morbidity patterns among the two groups are wide-ranging. Some of the studies have reported higher mortality and morbidity for AGA vs SGA babies, still others have reported no difference in the morbidity and mortality between the two groups of very preterm babies.[8]

Our study has found a higher mortality and higher morbidity (hyperbilirubinaemia, hypocalcaemia, and severe hypoglycaemia) in SGA babies as compared to AGA babies.

The difference in the mortality between the two groups was more prominent in babies with gestational age ≤31 weeks.

Regarding mortality, our study confirmed the higher mortality in SGA babies (40% Vs 22%, p=0.006). These findings are consistent with various previous studies. Like our study, Bartels *et al*[9] and Susan *et al*[15] have reported highly significant difference in the proportion of mortality between the SGA and appropriate for gestational age babies. Bartels *et al*[9] has reported 25.5% Vs 10.5% mortality whereas Susan *et al*[15] has reported 20% Vs 0% mortality for SGA as compared to AGA babies. Similarly study by Thompson *et al*[16] has reported higher mortality for SGA very preterm babies. The study by Bardin *et al*[17] however did not observe any significant difference between the two groups, although the mortality was still higher for SGA babies.

The difference in the mortality between the two groups was more prominent in babies with gestational age ≤31 weeks (71.4% for SGA as compared to 39.3 % for AGA very preterm babies with gestational age ≤31 weeks). This finding is again consistent with some studies conducted previously.[8,18,19]

This higher mortality clearly pinpoints the importance of increased care and parental counselling after the birth of SGA very preterm baby in light of increased difficulties potentially faced by these babies. Efforts should be directed at standardizing the management of these babies in order to reduce the mortality among the children. It is clearly important for a country like Pakistan where neonatal mortality is already very high.

Our study also found that there is increased morbidity among the SGA Vs AGA very pre- term babies. Infant morbidity from prematurity is much more varied in its response to the addition of poor growth. Indirect hyperbilirubinaemia (jaundice) known to be associated with growth restriction in term infants, was found significantly higher in the IUGR babies as compared to AGA babies (67% Vs 51%, *p*-value 0.02).These findings are also consistent with those of Susan *et al*[15].This hyperbilirubinaemia may be due to decrease in liver size as well as immaturity of liver function as evident from the data of experimental animal models of IUGR[19,20].Blood calcium level was significantly low in SGA than AGA babies (24% Vs 10%, *p*=0.02), a finding again similar to those reported by Kramer *et al*[18].This may be multifactorial including cessation of maternal calcium flow, diminished responsiveness to parathyroid hormone, hypomagnesaemia and vitamin D deficiency.

There was no significant difference in other morbidity indicators like RDS, sepsis, meconium aspiration syndrome, PDA, resuscitation and polycythemia.

It is a general assumption that SGA have lower incidence of Respiratory Distress Syndrome (RDS) as compared to age appropriate babies. This is believed on the basis of assumption that SGA babies have accelerated lung maturation due to stressful intrauterine environment. However there is still no consensus on the outcomes of premature SGA infants. There are conflicting reports in different studies. Some authors have found increased risk in SGA infants while others have reported the opposite effect.

Procianoy *et al*[21] had shown decreased incidence of RDS in SGA infants as compared to AGA infants in babies born ≤32 weeks gestational age. However, other studies have found no significant difference between the two groups in regards to RDS.[14,17,22]

We found no difference in the sepsis of very preterm babies between the two groups. About 10 % of very preterm babies were found to be septic in our study. Bardin *et al*[17] found increased risk of sepsis in SGA infants. This difference may be due to strict criteria of sepsis (based on culture & sensitivity) in our study.

This study is one of very few research studies on this topic from Pakistan. We compared babies of same gestational age, singletons and having no major anomalies in order to minimize potential confounders.

These morbidity results are to be interpreted with caution. Firstly, the numbers of cases studied are small for generalization to be made for all very preterm babies in the country. This calls for further studies on large sample size to compare morbidity indicators separately in these groups and with more robust statistical techniques including regression analysis. Secondly, our study group was limited to infants between 28–32 weeks gestation, perhaps excluding infants at greatest risk of morbidity below 28 weeks. Thirdly, blood sample analysis in laboratory may have provided inaccurate biochemical indices in our study. It would have been interesting also to compare these groups for necrotizing enterocolitis and intraventricular haemorrhage. Unfortunately due to strict definition and/or limitation of facilities, it was impossible at the moment.

The prospective nature of our study does provide good evidence in regards to problem studied.

CONCLUSION

In conclusion, very preterm SGA infants have significantly higher mortality and morbidity in comparison to the AGA babies. Based on our study we recommend that in deciding for therapeutic management of these babies, they need special attention in terms of factors as gestational age and the biochemical markers, to improve the outcome for these babies in the hospital settings.

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