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Is being small for gestational age at birth a predictive risk factor for retinopathy of prematurity? A study in Central Maharashtra, India

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ABSTRACT

BACKGROUND: Retinopathy of prematurity (ROP) is a leading cause of avoidable blindness in preterm infants. Born preterm with small gestation age (SGA) may be an additional risk factor for developing ROP. The study was conducted to evaluate the incidence, risk factors, and severity of ROP in SGA newborns admitted to the newborn nursery.
MATERIALS AND METHODS: 91 preterm infants were screened for ROP in a prospective observational study conducted in a teaching hospital in central Maharashtra, India using the National Neonatology Forum of India criteria (NNF, 2010). Systemic risk factors and ocular findings were documented. The incidence, risk factors, and severity of ROP were compared between the SGA and appropriate for gestational age (AGA) newborns.
RESULTS: The incidence of ROP was 36.26% (total), 39.62% (SGA), and 31.57% (AGA) amongst screened infants. ROP was more common in babies with higher gestational age (35.4 weeks; $p = 0.064$) in the SGA group, and it was more in babies with lesser gestational age (32.2 weeks; $p = 0.033$) in the AGA group. There was no difference in the risk factors between the two groups on univariate and multivariate analysis.
CONCLUSIONS: The incidence of ROP was higher in SGA infants than AGA infants in the present study. However, there was no difference in the risk factors and severity of ROP between the two groups.

KEY WORDS: retinopathy of prematurity; small gestation age (SGA); appropriate for gestational age (AGA)

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INTRODUCTION

Retinopathy of prematurity is a significant cause of avoidable blindness in children [1]. In particular, India is experiencing the third epidemic of blindness due to ROP [2]. It is projected that approximately 18,000 infants will go blind every year in India due to ROP [3]

Retinopathy of prematurity occurs in infants with low gestational age (GA) and low birth weight (BW). However, infants with comparatively higher gestational age and higher birth weight in developing countries like India also develop ROP [4–6].

Along with low birth weight and low gestational age, respiratory distress syndrome, unregulated use

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of oxygen, chronic lung disease, fetal hemorrhage, sepsis, transfusion of blood products, patent ductus arteriosus are some of the other significant risk factors which play an essential role in the development of ROP [7, 8]. Studies have shown that SGA may contribute to the above long list of risk factors [8–10]. The present study was conducted to evaluate the incidence, risk factors, and severity of ROP in SGA infants.

MATERIAL AND METHODS

This prospective observational study was conducted in a teaching hospital in central Maharashtra, India, between December 2015 and July 2018. The study was approved by the institutional ethics committee and adhered to the guidelines of the Declaration of Helsinki. Informed consent was obtained from parents of all neonates included in the study.

Inclusion criteria

Inclusion criteria were as follows:

- preterm neonates with ≤ 34 weeks of gestational age and/or birth weight ≤ 1750 g;
- preterm neonates with 34–36 weeks of gestational age and/or birth weight between 1751 and 2000 g who are at a high risk of developing ROP with risk factors such as the need for cardiorespiratory support or prolonged oxygen therapy, blood transfusion, apnea of prematurity, anemia requiring blood transfusion, or neonatal sepsis

  OR
- any neonate believed at risk of ROP by the attending pediatrician.

Exclusion criteria

Neonates who died before complete vascularization of the retina or lost to follow-up were excluded from the study.

Study procedure

A total of 91 preterm neonates meeting the screening criterion during the study period were included. The screening was performed by a pediatric ophthalmologist and or a retina specialist in the neonatal intensive care unit (NICU). The first screening was conducted between the 20th and 30th days of life. Pupils were dilated with 0.4% tropicamide, and 2.5% phenylephrine eye drops instilled twice at an interval of 10 minutes. A third drop was instilled if the pupil was not sufficiently dilated. The retinal screening was performed using an indirect ophthalmoscope with a 20D lens under topical anesthesia and monitoring vital signs. A pediatric speculum with scleral depression was used to examine the retina. The screening was carried out until:

1 — complete retinal vascularization;

2 — regression of ROP was noted with complete retinal vascularization, or

3 — zone-III retinal vascularization was attained without previous zone I or II ROP.

Systemic risk factors and ocular findings were documented. Retinopathy of prematurity was classified according to the International Classification of ROP (ICROP). All the preterm neonates included in the study were further subdivided into two categories — appropriate for gestational age (AGA) and small for gestational age (SGA) using Fenton's Criteria [12]. Weight, head circumference, and length of the neonate were marked on specific separate charts for girls and boys.

All babies diagnosed with type 1 ROP were treated as per early treatment of ROP protocol (ETROP), while those with aggressive posterior ROP (APROP) were treated with intravitreal anti-VEGF agents after taking informed consent. Statistical analysis

Collected data was compiled in an MS Excel sheet. The collected data were analyzed with statistical packages for social science v.20 (SPSS). Quantitative data are represented in the form of mean and standard deviation. Odds ratio, univariate analysis, and chi-square test were applied to assess the significant association between risk factors and ROP development. Multivariate analysis was applied to check significant risk factors development of ROP. P-value was checked at a 5% level of significance.

RESULTS

Ninety-one preterm neonates met the screening criteria in the study. Of these, 53 (58.24%) were SGA, and 38 (41.75%) were AGA infants. 36.26% (33 out of 91) developed ROP. The incidence of ROP in the SGA group was 39.62% (21 out of 53) and 31.57% (12 out of 38) in the AGA group. This was statistically significant ($X2 = 0.61$; $DF = 1$; $p = 0.043$; $p < 0.05$)

Retinopathy of prematurity was observed in babies with higher gestational age (35.4 weeks; $p = 0.064$) in the SGA group as compared to the

Table 1. Incidence of retinopathy of prematurity (ROP) according to gestational age (GA) in neonates with small gestation age (SGA) and appropriate for gestational age (AGA)

GA [weeks]	ROP positive	ROP negative	Total	Mean GA		T-value	p-value
				ROP positive	ROP negative		
SGA							
< 30	02	01	03	35.4	34.2	3.14	0.064 NS
30–34	09	14	23				
> 34	11	16	27				
Total	21	32	53				
AGA							
< 30	06	01	07	32.2	36.6	3.14	0.033 S
30–34	04	13	17				
> 34	02	12	14				
Total	12	26	38				

NS — non significant

AGA group, and it was more in babies with lesser gestational age (32.2 weeks; p = 0.033) (Tab. 1). The mean birth weight was lower amongst ROP positive babies (1207.11 ± 19.21 grams in the AGA group and 1412.11 ± 21.92 grams in the SGA group) as compared to non-ROP babies (1712.11 ± 21.92 g in the AGA group and 1680.11 ± 19.21 g in the SGA group) in both groups (p = 0.043 for the AGA group and p = 0.048 for the SGA group) (Tab. 2).

Type 1 ROP as per the ETROP classification occurred in 10.98% (10/91 preterm neonates). The incidence of type 1 ROP in SGA and AGA groups was 33.3% and 25%, respectively, with 7/21 babies in the SGA group and 3/12 babies in the AGA group having treatable ROP but was not statistically significant. Of the seven babies with type 1 ROP in the SGA group, 2 had aggressive posterior ROP (APROP).

On univariate analysis, the risk factors for ROP development in both the SGA and AGA groups were similar (Tab. 3).

On multivariate analysis, blood transfusion was identified as a risk factor for the SGA group only (Tab. 4, 5).

DISCUSSION

In addition to prematurity, SGA infants are a high-risk population, being vulnerable due to many causes for developing ROP. All babies with weight less than 2000 grams irrespective of their gestational age at birth are screened routinely for ROP at our institute. Our study attempts to

Table 2. Incidence of retinopathy of prematurity (ROP) according to birth weight (BW) in neonates with small gestation age (SGA) and appropriate for gestational age (AGA)

BW [g]	ROP positive	ROP negative	Total	Mean BW		T-value	p-value
				ROP positive	ROP negative		
SGA							
< 1000	01	04	04	1412.11 ± 21.92	1680.11 ± 19.21	2.46	0.048 S
1000–1750	12	16	28				
> 1750	08	12	20				
Total	21	32	53				
AGA							
< 1000	03	00	03	1207.11 ± 19.2	1712.11 ± 21.92	2.64	0.043 S
1000–1750	06	07	13				
> 1750	03	19	22				
Total	12	26	38				

Table 3. Univariate analysis of fetal risk factors for retinopathy of prematurity (ROP) in in neonates with small gestation age (SGA) and appropriate for gestational age (AGA)

Risk factor	SGA babies with ROP		p-value	AGA babies with ROP		p-value
	Present	Absent		Present	Absent	
Multiple pregnancy	6/21	15/21	0.03	5/12	7/12	0.041
Eclampsia	3/21	18/21	0.07	2/12	10/12	0.08
RDS	5/21	16/21	0.043	9/12	3/12	0.003
Apnoic spell	2/21	19/21	0.071	3/12	9/12	0.073
O_2 supplementation	14/21	7/21	0.001	7/12	5/12	0.01
Ventilation	3/21	18/21	0.07	2/12	10/12	0.08
Sepsis	7/21	14/21	0.04	4/12	8/12	0.047
Intraventricular hemorrhage	00/21	21/21	–	1/12	11/12	0.10
Blood transfusion	8/21	13/21	0.02	4/12	8/12	0.047
Fetal distress	3/21	18/21	0.07	3/12	9/12	0.073
Phototherapy	2/21	19/21	0.071	1/12	11/12	0.10
Surfactant administration	3/21	18/21	0.07	1/12	11/12	0.10
Congenital heart disease	00/21	21/21	–	1/12	11/12	0.10
Anemia	5/21	16/21	0.043	4/12	8/12	0.047
Thrombocytopenia	2/21	19/21	0.071	1/12	11/12	0.10
Neonatal jaundice	00/21	21/21	–	2/12	10/12	0.08
Hypoglycemia	1/21	20/21	0.09	00/12	12/12	–

RDS — respiratory distress syndrome

Table 4. Multivariate analysis of fetal risk factors for retinopathy of prematurity (ROP) in neonates with small gestation age (SGA)

Variables	β	SE	Wald	p-value	OR	95% CI for OR	
						Lower	Upper
Gestational age	1.341	0.311	7.631	0.005	2.131	1.009	3.617
Birth weight	1.712	0.183	6.542	0.002	3.111	1.213	4.124
Multiple pregnancy	1.612	0.256	9.219	0.006	1.354	1.004	2.871
Eclampsia	0.256	0.277	0.857	0.354	0.774	0.450	1.331
Sepsis	2.394	0.315	2.560	0.002	2.483	1.799	3.752
RDS	0.935	0.284	10.822	0.001	1.393	1.093	2.685
O_2 supplementation	1.921	0.265	52.597	0.000	6.380	4.063	11.479
Fetal distress	1.264	0.243	27.160	0.000	3.540	2.201	5.695
Phototherapy	0.252	0.260	0.943	0.332	1.287	0.773	2.141
Ventilation	0.274	0.341	2.912	0.041	1.023	1.007	2.411
Blood transfusion	1.256	0.277	1.857	0.004	0.774	0.450	1.331
Surfactant	1.612	0.191	0.219	0.053	0.854	0.704	2.112
Anaemia	1.254	0.5511	12.781	0.000	1.672	1.016	2.114
Thrombocytopenia	0.462	0.234	0.982	0.056	0.891	0.678	1.412
Hypoglycemia	0.256	0.277	0.857	0.354	0.774	0.450	1.331

$p < 0.05$ = statistically significant; RDS — respiratory distress syndrome; SE — standard error; OR — odds ratio; CI — confidence interval

assess any difference in the incidence, risk factors, and severity of ROP amongst the AGA and SGA infants.

The overall incidence of ROP in our study was 36.26%. Our results are similar to the current trends [15–18] in developing countries. The incidence of

Table 5. Multivariate analysis of fetal risk factors for retinopathy of prematurity (ROP) in neonates with appropriate for gestational age (AGA)

Variables	β	SE	Wald	p-value	OR	95% CI for OR	
						Lower	Upper
Gestational age	1.141	0.311	7.631	0.005	2.131	1.009	3.617
Birth weight	1.712	1.183	6.542	0.002	3.111	1.213	4.124
Multiple pregnancy	1.818	0.216	5.864	0.02	2.354	1.712	4.619
Eclampsia	0.256	0.277	0857	0.354	0.774	0.450	1.331
Sepsis	2.394	0.315	2.560	0.002	2.483	1.799	3.752
RDS	0.935	0.284	10.822	0.001	1.393	1.093	2.685
O2 supplementation	1.921	0.265	52.597	0.000	6.380	4.063	11.479
Fetal distress	1.264	0.243	27.160	0.000	3.540	2.201	5.695
Phototherapy	0.252	0.260	0.943	0.332	1.287	0.773	2.141
Ventilation	0.274	0.341	2.912	0.041	1.023	1.007	2.411
Blood transfusion	1.256	0.277	0.857	0.354	0.774	0.450	1.331
Surfactant	1.612	0.191	0.219	0.053	0.854	0.704	2.112
Anaemia	1.254	0.5511	12.781	0.000	1.672	1.016	2.114
Thrombocytopenia	0.462	0.234	0.982	0.056	0.891	0.678	1.412

$p < 0.05$ = statistically significant; RDS — respiratory distress syndrome; SE — standard error; OR — odds ratio; CI — confidence interval

any stage ROP in the SGA group was significantly higher than in the AGA group. The incidence of type 1 ROP in our study was 10.98%. (33% in the SGA group and 25% in the AGA group). Dhaliwal et al. [19], in their study, observed that SGA infants were not only prone to develop any stage ROP ($p < 0.01$), but they were also prone to develop type 1 ROP ($p = 0.01$). Kavurt et al. [20] (28.2% incidence of ROP in SGA) and Raj et al. [17] (40% incidence of ROP in SGA) have also observed SGA as a significant risk factor for the development of ROP. A systematic review [21] concluded that SGA is a strong risk factor for the development of any stage as well as ROP needing treatment. The increased incidence of ROP in SGA infants is postulated to be due to intrauterine growth restriction. This makes the infants prone to changes in organ development because of fetal hypoxemia, nutrient restriction, and an altered endocrine environment [21]. These infants tend to be sicker, requiring a more extended stay in the NICU and maybe more supplemental oxygen. They also have lower insulin-like growth factor 1 (IGF1) levels which play an important role in the pathogenesis of ROP [23]. In addition, genetic factors also have been implicated [24, 25].

Lundgren et al. observed that infants born more mature but are growth restricted are more prone to develop ROP [10, 26]. This is in concurrence with our observation that older SGA infants are more prone to develop ROP.

The problem unique to countries in the developing world is that these affected infants are far older and far heavier than the infants in the western world. One of the reasons for the same could be the poor survival rate of infants born less than 28 weeks in low to middle-income countries. In our study itself, there was only one infant with GA at 27 weeks and three born at 28 weeks GA in the AGA group, whereas, in the SGA group, there was only one infant born at 28 weeks of GA. Similarly, in our study in the SGA group, there were only three infants with weight less than 1000 grams (800, 900, and 945 g, respectively), while in the AGA group, there were only two infants of less than 1000 grams (800 and 1000 g, respectively).

On univariate analysis, the risk factors for ROP development in both the SGA and AGA groups were the same. On multivariate analysis, blood transfusion was noted to be a risk factor for the SGA group only. Similar findings were observed by Fortes Filho et al. [27].

The drawbacks of our study are the relatively small patient population and single center-based.

CONCLUSION

The incidence of ROP was higher in SGA infants compared to AGA infants in the present study. However, there was no difference in the risk factors and severity of ROP between the two groups.

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