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Is being small for gestational age a risk factor for retinopathy of prematurity? A study with 345 very low birth weight preterm infants

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Abstract

Objective: To analyze prevalence and risk factors for retinopathy of prematurity (ROP) among preterm infants born small for gestational age (SGA) and appropriate for gestational age (AGA).

Methods: A prospective cohort study included preterm infants with birth weight (BW) ≤ 1,500 grams and gestational age (GA) ≤ 32 weeks, divided into two groups: AGA or SGA. Prevalences and risk factors for ROP were determined in both groups. Logistic regression was used for the significant variables after univariate analysis.

Results: A total of 345 patients were examined: 199 included in the AGA group and 146 in the SGA. Mean BW and GA in the whole cohort (345 patients) were 1,128.12 grams (±239.9) and 29.7 weeks (±1.9), respectively. The prevalence of any stage ROP and severe ROP (needing treatment) was 29.6 and 7.0%, respectively. ROP in any evolutive stage developed in 66 AGA (33.2%) and in 36 SGA (24.7%) (p = 0.111). Severe ROP occurred in 15 AGA (7.5%) and in nine SGA (6.2%) (p = 0.779). After adjusted logistic regression, weight gain from birth to sixth week of life and need for blood transfusions were found to be significant risk factors for ROP in both groups.

Conclusions: This study has shown that being SGA was not a significant risk factor for any stage ROP or for severe ROP in this cohort and, also, that the risk factors for ROP were similar among SGA and AGA very-low-birth-weight preterm babies.

J Pediatr (Rio J). 2009;85(1):48-54: Prematurity, retinopathy of prematurity, very low birth weight infant, risk factors, small for gestational age, appropriate for gestational age.

Introduction

Retinopathy of prematurity (ROP) is in continuous study throughout the world due to the rise in survival rates among very low birth weight (VLBW) preterm infants, i.e., those born with weight ≤ 1,500 grams. This, which stems from the higher quality of perinatal care, has led to a significant increase in the presence of comorbidities related to preterm birth, some of which have important social consequences, such as blindness secondary to ROP.[1,2]

ROP is a vasoproliferative retinal disorder which affects preterm newborns. It can lead to blindness in its natural course, or when treatment is not provided in time. In Brazil, it

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is estimated that around 1,500 VLBW preterm infants are at risk of developing severe ROP, and that it may cause up to 500 new cases of blindness every year.[3]

ROP most often affects lower gestational age (GA) preterm infants, even those with few comorbidities, but it can also be found in larger, though sicker, babies.[4-6]

Currently, controversy still surrounds the significance of being small for GA (SGA) for the onset of ROP. This finding, which has been recently reported,[6-9] had already been publicized by the studies of Johnson et al. in 1976,[10] and Distefano et al. in 1993,[11] which described an association between infants born SGA and ROP.

ROP does not arise immediately after birth, but rather around the 34th or 35th week of postconceptional age (PCA). During that period, the disease can be identified by ophthalmologists through fundus examinations; if treated around the 37th or 39th week of PCA, there is still time to avoid severe and irreversible damage to vision. There is also controversy surrounding the issue of whether preterm SGA infants would develop ROP before expected,[12,13] which would mean that the optimal time for early ophthalmologic examinations, while screening ROP among SGA patients, should be earlier than recommended by the guidelines established in many industrialized countries and which have excellent results in neonatology.

Trying to answer existing issues in scientific knowledge about the subject of being SGA and the onset of ROP, starting on 2002, we designed a prospective study with the goals of analyzing the prevalence of any stage ROP and severe ROP which requires treatment, and potential risk factors for the onset of ROP among preterm infants born appropriate for GA (AGA) and preterm SGA infants, as well as determining the moment of onset of severe ROP which requires treatment among AGA and SGA patients.

Methods

This was a prospective, descriptive cohort study which included preterm infants with birth weight (BW) ≤ 1,500 grams and GA ≤ 32 weeks at birth admitted to the Neonatal Intensive Care Unit (NICU) of Hospital de Clínicas de Porto Alegre (HCPA) between October 2002 and August 2008 which survived initial ophthalmologic examination, performed between the fourth and sixth week of life, until the 42nd week of PCA, at which point temporal peripheral vascularization of the retina would be complete. This point was chosen as cross-sectional threshold for ROP prevalence. There were no exclusion criteria.

Patients were divided into two groups: Group 1 consisted of all infants born with weights AGA. Group 2 (SGA) consisted of all infants born with weight < 10th percentile over GA, according to the tables from Alexander et al.,[14] which are used in our institution.

Ophthalmologic examination consisted of binocular indirect ophthalmoscopy under pupillary dilation, associated with eye drops tropicamide 0.5%, phenylephrine 2.5%, 28 dioptries lens (Nikon®, Melville, NY, EUA), and blepharostat (Alfonso Eye Speculum, Storz®, Bausch & Lomb Inc., San Dimas, CA, EUA). Scleral depression was used, when necessary, to better identify peripheral retinal alterations. Assessments were repeated periodically, according to Brazilian guidelines for examining and treating ROP.[15] All patients were initially examined at the NICU; after discharge, they were examined at the outpatient department up to the 42nd week of PCA or until the retinopathy was fully stabilized in the treated patients. All patients were examined by the same ophthalmologists (J.B.F.F., G.U.E., F.B.V.), all professionals qualified for performing the ROP screening. Every patient who developed ROP was treated by the same ophthalmologist (J.B.F.F.).

All patients were treated upon detection of threshold ROP, defined as the moment from which the risk of an unfavorable anatomical or functional outcome, or of leading into blindness, is seen in 50% of patients.[16]

The moment in which patients reached pre-threshold ROP was also noted in terms of PCA in weeks. Pre-threshold ROP was defined following guidelines from the Early Treatment for Retinopathy of Prematurity Cooperative Group (ET-ROP).[17]

Primary clinical outcomes were: ROP onset at any evolutionary stage and onset of severe ROP which requires treatment in both groups (AGA/SGA). Disease stages were recorded according to the 1984/1987 International Classification of ROP,[18] and correspond to the most severe degree of retinopathy found in either eye during follow-up. Severe ROP was defined as disease on stage 3, threshold or higher. ROP prevalence was calculated for both patient groups. As secondary outcomes, we observed mean GA upon treatment and pre-threshold disease onset.

The following variables were determined to analyze risk factors for ROP: BW, GA (assessed by clinical history, early obstetric echography, and confirmed by clinical examination), weight gain after birth to sixth week of life (defined as weight at sixth week of life minus BW), sex, twin pregnancy (born of single or multiple gestation), use of oxygen in mechanical ventilation or nasal continuous positive airway pressure (nasal CPAP), use of indomethacin, surfactant and erythropoietin, Apgar score at 5th minute, presence of intraventricular hemorrhage (from cranial ultrasound) and need for blood transfusions. We could not determine the duration and concentration of oxygen used. This variable, use of oxygen therapy, was considered dichotomous.

Univariate analysis was performed on the same set of variables for both groups. We used Student's *t* test to analyze continuous variables for independent samples; for categorical variables, we used the chi-square test with Yates' correction. Results were considered significant for $p < 0.05$.

Table 1 - Prevalence of ROP for the two patient groups, small (SGA) or appropriate for gestational age (AGA)

ROP stages	Group 1, AGA (n = 199) n (%)	Group 2, SGA (n = 146) n (%)	p
No ROP	133 (66.8)	110 (75.3)	
ROP	66 (33.2)	36 (24.7)	0.111
ROP 1	28 (14.1)	15 (10.3)	
ROP 2	23 (11.6)	12 (8.2)	
ROP 3*	15 (7.5)	7 (4.8)	
ROP 4*	0 (0.0)	1 (0.7)	0.779*
ROP 5*	0 (0.0)	1 (0.7)	

AGA = appropriate for gestational age; ROP = retinopathy of prematurity; SGA = small for gestational age.
* Severe ROP.

Logistic regression was performed after univariate analysis.

Statistical analyses were performed with the SPSS software (SPSS® 14.0 for Windows®, SPSS Inc., Chicago, IL, EUA). To determine test power, we used application PEPI (POWR, version 4.0).

The study protocol about risk factors for ROP was approved by the HCPA Research Ethics Committee under number 03-248 on August 20, 2003.

Results

A total of 450 VLBW (born with weight ≤ 1,500 grams and/or GA ≤ 32 weeks) were examined at the HCPA NICU during screening sessions for detection of ROP throughout the period of the study. The 450 correspond to approximately 93% of patients admitted to the institution according to the inclusion criteria of the ROP neonatal screening program, as defined for Brazil.[15]

The study included 345 patients with BW ≤ 1,500 grams and GA ≤ 32 weeks. Group 1 (AGA) consisted of 199 patients, while Group 2 consisted of 146 (SGA). Mean BW among preterm infants in the AGA group was 1,155.30±230.2 grams, while for SGA group it was 1,091.10±248.6 grams, p = 0.014. Mean GA among AGA patients was 28.8±1.8 weeks, while for SGA patients it was 30.9±1.3 weeks, p < 0.001. Mean weight gain after birth to sixth week of life was 556.10±277.2 grams for AGA patients and 625.60±219.1 for SGA ones, p = 0,013

Table 1 shows data for onset of any stage ROP and severe ROP for groups AGA and SGA. There was no significant difference among groups in terms of ROP occurrence at any stage or of severe ROP.

Table 2 presents the univariate analysis of the main risk factors for ROP in both groups. Among those AGA, BW (p < 0.001), GA (p < 0.001), and weight gain until sixth week of life (p = 0.001) were significantly lower for patients which developed ROP, while the use of oxygen therapy in mechanical ventilation (p = 0.016), use of indomethacin (p = 0.010) and need for blood transfusions (p < 0.001) were significantly more common among those who developed ROP. Among those SGA, BW (p = 0.001), GA (p = 0.036), and weight gain after birth to sixth week of life were significantly lower for patients who developed ROP (p < 0.001). The need for blood transfusions was significantly more common among patients who developed ROP at any evolutionary stage (p < 0.001).

After logistic regression adjustments, weight gain after birth to sixth week of life (odds ratio or OR = 0.997; 95%CI 0.996-0.999; p < 0.001) and need for blood transfusions (OR = 2.958; 95%CI 1.575-5.558; p = 0.001) were considered significant for onset of ROP among the cohort (Table 3).

Mean GA at which pre-threshold ROP was detected was 35.9±2.7 weeks among AGA patients and 38.3±1.6 weeks among SGA one, p = 0.61. Mean PCA upon treatment was 37.4±2.7 weeks for AGA patients and 39.9±1.2 weeks for SGA, p = 0,052. Pre-threshold ROP and threshold ROP diagnoses occurred, on average, after 9.1±2.1 weeks of life for AGA patients and after 8.3±1.5 weeks of life for SGA ones, p = 0.356 and p = 0.140, respectively.

Test power for determining the 8.5 percentage point differential in ROP prevalence between Groups AGA and SGA was estimated at 40%.

Discussion

Due to the 40% test power of our study, the results allow us to conclude that being SGA may not be a significant risk factor for any stage ROP or for severe ROP among VLBW preterm patients. The study has also shown that diagnoses of pre-threshold and threshold ROP (illnesses in more severe stages and which require treatment) were found after the initial periodic examinations for ROP detection in both patient groups (AGA and SGA), and that criteria for ROP detection

Table 2 - Risk factors significant for ROP in groups 1 (AGA) and 2 (SGA) after univariate analysis

Factors	Group 1, AGA (n = 199)			Group 2, SGA (n = 146)		
	Patients without ROP (n = 133)	Patients with ROP (n = 66)	p	Patients without ROP (n = 110)	Patients with ROP (n = 36)	p
Birth weight (grams)*	1,202.5±199.0	1,060.1±259.3	< 0.001	1,128.7±240.8	976.0±239.6	0.001
Gestational age (weeks)*	29.1±1.6	28.1±1.9	< 0.001	31.0±1.3	30.4±1.5	0.036
Absolute weight gain (grams)*	602.0±261.9	463.6±286.1	0.001	681.8±198.1	453.7±190.4	< 0.001
Use of oxygen in mechanical ventilation†	63 (47.4%)	44 (66.7%)	0.016	-	-	-
Use of indomethacin†	40 (30.1%)	33 (50.0%)	0.010	-	-	-
Blood transfusions†	73 (54.9%)	54 (81.8%)	< 0.001	54 (49.1%)	31 (86.1%)	< 0.001

AGA = appropriate for gestational age; ROP = retinopathy of prematurity; SGA = small for gestational age.
* Mean ± standard deviation (Student's *t* test).
† Chi-square test.

Table 3 - Odds ratio for ROP onset after adjusted logistic regression

Factors	OR	95%CI	p
Gestational age	0.887	0.749-1.051	0.166
Absolute weight gain	0.997	0.996-0.999	< 0.001
Use of oxygen in mechanical ventilation	1.446	0.831-2.514	0.192
Use of indomethacin	1.276	0.722-2.253	0.402
Need for blood transfusions	2.958	1.575-5.558	0.001
Being SGA	1.024	0.552-1.897	0.941

95%CI = 95% confidence interval; OR = odds ratio; ROP = retinopathy of prematurity; SGA = small for gestational age.

through ophthalmologic examination between the fourth and sixth week of life, as recommended for Brazil,[15] were able to detect all cases which required treatment in time for its administration, both for AGA and SGA patients.

The World Health Organization, in its Vision 2020 program, has identified ROP as an important cause of blindness in countries with low infant mortality rates. Gilbert et al.[19] suggest that ROP is predominant among preterm infants born with BW < 1,000 grams in industrialized countries, and is on the rise as an important cause of childhood blindness in developing nations such as Brazil, as well as other Latin American countries, Asia and Eastern Europe, to the higher survival rates for VLBW preterm infants.

Studies suggest that the incidence and severity of ROP show an inverted relationship with BW and GA, and few cases of severe ROP are diagnosed in preterm patients with BW > 1,500 grams or GA > 32 weeks.[20] Severe ROP, which requires treatment, has greater incidence among patients born at GA < 28 weeks or with BW < 1,000 grams, though the disease is still found among babies born at GA 34-35 weeks and BW > 1,500 grams, especially in the presence of several comorbidities, as reported in India, China, and emerging Eastern European economies.[21-24]

Our institution is a tertiary referral university hospital, located at a metropolitan region with population of circa 4 million. ROP prevalence at HCPA has been previously reported as 24.7% for infants with BW ≤ 1,500 grams and/or GA ≤ 32 weeks between 2002 and 2006.[25] In the present study, the prevalence of severe ROP was 7.5% among AGA patients and 6.2% among SGA ones.

Recent studies in developed countries suggest that the first ophthalmologic examination of SGA patients should be the fourth week of life, since most cases of threshold ROP were identified before the 34th week PCA.[12,13] Our results diverge from such statements, however, because we have not found any statistically significant differences between the onset of pre-threshold and threshold ROP between AGA and SGA patients in our cohort of 345 VLBW preterm newborns. Mean

PCA upon onset of pre-threshold ROP was 35.9±2.7 weeks for AGA and 38.3±1.6 weeks for SGA patients. Mean PCA upon treatment was 37.4±2.7 weeks for AGA patients and 39.9±1.2 weeks for SGA ones. In our cohort, all diagnoses of indications for ROP treatment were found after the initial ophthalmologic examination, as per Brazilian guidelines. Pre-threshold and threshold ROP diagnoses were made, on average, after 9.1±2.1 weeks of life for AGA patients and after 8.3±1.5 weeks for SGA patients, respectively.

All of our patients were treated at threshold ROP. At the end of 2003, after our data collection process began, the first results of ET-ROP were published, suggesting ROP treatment at pre-threshold ROP. ET-ROP results showed significant improvements in functional and anatomical outcomes (decrease from 19.5 to 14.5% in loss of visual acuity and from 15.6 to 9.1% in residual retinal damage after nine months) for patients treated at pre-threshold ROP when compared with patients treated at threshold ROP.[17] We chose to keep the classic indication for treatment upon onset of threshold ROP during our study, since, in 2003, ET-ROP results were still considered preliminary, with only nine months of follow-up.

There are many studies which analyze risk factors for ROP. Low GA, low BW, maternal essential hypertension before pregnancy,[6,26,27] presence of bronchopulmonary dysplasia,[6] sepsis, and need for oxygen therapy in mechanical ventilation have been the factors most often related to the onset of ROP. In a controlled clinical study, Patz et al.[28] clearly showed the cause and effect relation between oxygen therapy and the onset of ROP. Hypoxia and hyperoxia, as well as fluctuations in oxygen blood pressure, have been implicated as etiological factors for ROP. In our study, the use of oxygen therapy in mechanical ventilation was considered a risk factor for ROP among AGA patients, but the same was not found for SGA ones. At our institution, control over oxygen therapy follows very strict parameters. Preterm patients are permanently controlled via pulse oxymetry with saturation pressure standards between 88 and 94%. The nursing staff is periodically trained on the relationship between efficient oxygen control and onset of ROP, and on the need of avoiding fluctuation to prevent the onset of severe ROP in many cases with these simples procedures.

Some believe that the onset of ROP takes place among preterm patients with more comorbidities, but SGA patients are not always sicker than AGA ones, they only have lower BW for their respective GA. Being SGA, therefore, can correspond to an anthropometric measure which does not necessarily have adverse implications for studying the overall health of a preterm infant.[29] For patients in our study, median GA for SGA patients was two weeks higher than the median for AGA ones (31 vs. 29 weeks, respectively). Among the 14 variables considered as potential risk factors for ROP in the study, six were significant among AGA patients, while only four of the same set of variables were at all significant for the SGA Group. SGA patients showed no statistical significance for ROP regarding the use of oxygen therapy or to the need for use of indomethacin (significant variables among AGA patients), which allows us to conclude that, eventually, the patients were less sick than patients from the AGA group in our study (Table 2). We have also found that AGA patients had less weight gain after birth to sixth week of life than SGA ones (556.1±277.2 grams versus 625.6±219.1 grams, respectively; that fact may also be an indication that AGA patients in our study presented more comorbidities during their stay in the NICU. On the other hand, some studies show that preterm SGA patients have higher mortality rates, and higher probability of developing bronchopulmonary dysplasia and other comorbidities, such as ROP, and need longer hospital stays.[30]

Current knowledge about ROP considers it a multifactorial disease. In our study, the main risk factors associated to the onset of ROP, after univariate analysis, were: low GA, low BW, low weight gain after birth to sixth week of life, and need of blood transfusions, for both patient groups (AGA/SGA), and use of indomethacin and need for use of oxygen therapy with mechanical ventilation only for AGA patients. After adjusted logistic regression, only low weight gain after birth to sixth week of life and need for blood transfusions were significant for onset of ROP among our patients (Table 3).

Being preterm SGA as a risk factor for ROP, as it is in other studies,[7,8,30] was not confirmed by our prospective study; despite including a significant number of patients (345), there were no statistically significant differences between patients born AGA or SGA and the onset of ROP at any stage or severe ROP which requires treatment. Due to the 40% test power of our study, our current hypothesis is that being SGA may not be a risk factor for ROP. In the future, with a larger number of patients, there may come new contributions to this study from the attainment of ROP prevalence data adjusted for the various GA of the patients. Recently, Dhaliwal et al.[31] analyzed the prevalence of ROP among 1,084 AGA patients and 329 SGA ones, in a cohort from three different secondary and tertiary hospitals, observed from 1990 to 2004. The authors, who included patients with BW ≤ 1,500 grams and GA ≤ 32 weeks in their study, showed that SGA patients had higher probability of developing ROP at any stage, as well as more severe forms of the disease. The cohort described by Dhaliwal et al. points at infants smaller than those observed among our HCPA patients, because their median BW and GA were 890 grams and 27 weeks for AGA and 1,035 grams and 31 weeks for SGA ones, while our study had medians of 1,170 grams and 29 weeks for AGA patients and 1,112.5 grams and 31 weeks for SGA ones.

Other studies which also sought to analyze the risk of ROP among SGA patients and found positive results on that front have made findings in patient groups with different population features than those from our group, such as: retrospective studies which focus on studying patients with 24-26

weeks of GA[8]; or studies based on greater restrictions on growth (< 25th percentile for GA) [32]; or different patient inclusion criteria or different percentiles for GA (< 9th percentile for GA) when defining the SGA group.[12]

Among other possible limitations of our study, we should stress that our observations are based on data from a single NICU, at a single tertiary referral hospital which excels in perinatal care. We should also stress that prospective clinical studies show findings related to a specific population. Its results and conclusions should not be extrapolated for patients born at units with different characteristics or different possibilities in terms of perinatal care practiced at such institutions.

Our data highlight the importance of neonatal screening for ROP detection, as well as that the criteria defined for Brazil[15] have been effective in finding all 24 threshold cases from the cohort. The only unfavorable outcome (ROP 5) was due to loss of patient in follow-up after hospital discharge, with the patient not showing up for scheduled treatment (Table 2). ROP prevalence in the study is comparable to studies from industrialized countries.[33,34]

The implementation of screening programs for early detection and treatment of ROP in other Brazilian hospitals, as well as better training in ophthalmologic services for properly following up these young patients, would greatly contribute to lowering the primary cause of avoidable childhood blindness in Brazil.

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