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Risk and clinical course of retinopathy of prematurity in 78 infants of gestational age 22–25 weeks

Marijean M. Miller, MD^{a,b}, Mary E. Revenis, MD^b, Michael M. Lai, MD, PhD^{c,d}, Annal D. Meleth, MD, MS^a, Elaine S. Jeffress, MSN, APRN^a, Ana Carrera, BA^a, Yao I. Cheng, MS^e, Ann M. Sill, BA^e, and Robert McCarter, ScD^{e,f}

^aDepartment of Ophthalmology, Children's National Medical Center and The George Washington University, Washington, DC

^bDepartment of Pediatrics, Children's National Medical Center and The George Washington University, Washington, DC

^cThe Retina Group of Washington, Washington DC

^dDepartment of Ophthalmology, Georgetown University, Washington, DC

^eDivision of Biostatistics and Study Methodology, Children's National Medical Center, Washington, DC

^fBiostatistics and Epidemiology, The George Washington University, Washington, DC

Abstract

Purpose—To characterize the retinopathy of prematurity (ROP) and survival of infants born at gestational age (GA) of 22–25 weeks.

Methods—This study was a comparative case series for the total set of 78 infants < 25 GA screened for ROP at a level IV NICU during a 21-month period. Data are presented on infants screened for ROP from 6 weeks after birth for 22 and 23 weeks' GA infants and from 5 weeks after birth for 24 and 25 weeks' GA. Accounting for the competing risk of mortality, we implemented Cox CR regression models to assess birth weight, GA, and admission diagnosis as potential risk factors for the following time to event outcomes: type 1 disease, aggressive posterior ROP (AP-ROP), plus disease, first presentation of ROP, and worst ROP observed.

Results—Risk of laser treatment (subhazard ratio [SHR] = 0.56, $P = 0.007$) and of plus disease (SHR = 0.49, $P = 0.001$) was increased among those born at lower GA. Twenty infants required laser for type 1 disease at median postmenstrual age (PMA) of 35.8 weeks (range, 33.0–42.7);

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Correspondence: Marijean Miller, MD, Director of Neonatal Ophthalmology, Children's National Medical Center, 111 Michigan Ave., Washington, DC 20010-2970 (mmiller@childrensnational.org).

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infants with AP-ROP had laser at PMA of 34.5 weeks (range, 33.0–36.9), 2 weeks earlier than infants without AP-ROP at PMA 36.5 weeks (range, 33.9–42.7). The cumulative probability of receiving laser therapy approached 46% (22 or 23 weeks' GA), 30% (24 weeks' GA), and 18% (25 weeks' GA).

Conclusions—This study confirms the 2013 screening guidelines appear to be appropriate for infants of 22 and 23 weeks' GA when ROP screening begins at PMA 31 weeks.

The risk of retinopathy of prematurity (ROP) is not well characterized in infants born at 22–25 weeks' gestational age (GA), and the timing of the first screening for infants born at 22 and 23 weeks' GA remains provisional¹ even though survival of this cohort has improved. The purpose of this study was to evaluate the risk of ROP and related outcomes in a cohort of low (< 25 weeks) gestational age infants to assess both the adequacy of the provisional criteria for the timing of screening evaluations and to assess the role of prominent risk factors for these outcomes. During the study period, the neonatal intensive care unit (NICU) guidelines initiated diagnostic ROP screening on many infants earlier than the 2006 guidelines.² We present earlier ROP information on infants born at 22–25 weeks' GA than is available at many centers.

Subjects and Methods

With the approval of the institutional review board committee and in accordance with the US Health Insurance Portability and Accountability Act of 1996, the medical records of all infants of < 25 weeks' GA evaluated for ROP in the level IV Neonatal Intensive Care Unit (NICU) at Children's National Medical Center in Washington, DC, from September 2006 to June 2008 were retrospectively reviewed. All infants are transferred to Children's via ambulance or helicopter from regional nurseries due to critical change in medical status. Children's has no delivery ward, and infants of <25 weeks' GA with limited prenatal care are frequently treated.

The gestational age used in this study is the one assigned by the neonatologist at the birth hospital, taking into account the date of the mother's last menstrual period (if known), prenatal ultrasound (if performed, and especially if performed early), and physical examination on the day of birth. When transfer occurred on the day of birth, the admission physical examination at Children's was compared for the determination of GA. GA is assigned in full weeks rounded down, according to the American Academy of Pediatrics policy statement for age assignment in the perinatal period.³

In this study, the timing of the first ROP examination was 6 weeks after birth for infants of 22 and 23 weeks' GA when clinical condition allowed and 5 weeks after birth for those of 24 and 25 weeks' GA. The 2006 joint policy statement of the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus² suggested tentative versus evidence-based initiation of ROP examinations for infants of 22 and 23 weeks' GA at 31 weeks' PMA. Due to the illness of our cohort, we choose to be more conservative, with earlier initiation of ROP examinations.

Once ROP diagnostic examination was initiated, both our screening and treatment guidelines precisely followed the 2006 policy statement.² Screening was performed by a pediatric ophthalmologist who had more than 15 years of ROP experience. Infants were examined every 1–2 weeks and examinations were only spaced to a 2–3 week interval for stage 1 or 2 in zone III, regressing ROP in zone III, or in premature infants born near term with immature vascularization in anterior zone II or zone III. Rate of ROP disease progression was closely noted, and laser treatment was administered in the following cases: type 1 threshold disease; zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; and zone II, stage 2 or 3 ROP with plus disease, according to the early treatment for ROP randomized trial.⁴ Once the screening ophthalmologist deemed laser treatment was required, a pediatric retina specialist was consulted to perform laser treatment. Thus the clinical diagnosis of type 1 threshold as the criteria for laser treatment was independently determined by two clinicians.

Cases of aggressive posterior ROP (AP-ROP) were identified in this record review from notes in the clinical record and confirmed for the purpose of the study in a separate record review by a retina specialist who was masked to patient identity. AP-ROP cases were identified using criteria established by the revised international classification of ROP.⁵ Features of AP-ROP include rapidly progressive disease course, involvement of zone I or posterior zone II, and flat network of neovascularization with plus disease.

The ROP data collected was from first examination to the date of highest ROP disease or date of laser treatment. All available ROP screening data were abstracted from the medical records. GA and birth weight were collected for each infant. For each examination, data included age, and for each eye, ROP zone (I, II, or III), ROP stage (1, 2, 3, 4a, 4b, 5) and clock hours (1–12), and whether plus was present. Data for the worst eye is reported. ROP outcomes were collected by postnatal age for each outcome. Time to initial presentation of ROP was the age at which any ROP was first seen in either eye when a prior examination documented an immature retina. Worst ROP examination was the peak level of ROP in the worst eye: for laser treated infants, worst examination age was the age at laser treatment, and for infants with ROP that regressed, age of worst ROP was the point of highest stage with most clock hours in the worst eye with a documented follow-up examination recording less severe ROP. Plus was noted as the age when first identified. AP-ROP was the date of laser for AP-ROP.

Transfer admission diagnosis to Children's National Medical Center was collected. Data on the diagnoses of patent ductus arteriosus, severe respiratory distress syndrome that could not be managed in the birth hospital NICU, necrotizing enterocolitis, and bowel perforation were identified in this cohort with sufficient frequency to allow statistical analysis.

The effect of each independent variable, GA, birth weight, and transfer admission diagnosis was evaluated using competing-risk (CR) regression analysis⁶ to account for the substantial competing risk of mortality in these high-risk infants. Analysis assessed the time to event outcomes: type 1 disease, AP-ROP, plus disease, first presentation of ROP, and worst ROP examination observed. Competing risk survival analysis was used rather than standard survival analysis (Kaplan-Meier Cox models) because death is frequent in this population

and had we considered every patient who died to have little or no risk of ophthalmic outcomes, the risk of ophthalmic outcomes would probably have been underestimated. With competing risk analysis, we are allowed to use all the data to account for the unobserved but likely substantial ophthalmic outcome risk in the group who died. The subhazard estimate presents a cause-specific hazard ratio and so provides an estimate of what unobserved risk might have been among those who died before manifestation of ophthalmic outcomes. The underlying assumption is that the risk of ophthalmic outcomes is uniform in those who die and thus can be estimated in those who experience an ophthalmic outcome event before death. Competing risk survival analysis may still underestimate ophthalmic outcome risk, but it represents an improvement over treating those who die early as having essentially no risk of ophthalmic outcome. Competing risk survival analysis was performed for the age unit day of life (DOL) for each outcome to provide information on the events of interest during the NICU course. Survival data was abstracted from patient records and was analyzed using completing-risks regression analysis in STATA (StataCorp LP, College Station, TX).

Results

During the 21-month study period, 1,206 infants were admitted to the NICU. Of these, 78 were 25 weeks and 6/7 days' GA. A total of 20 infants died: 17 before the median time of type 1 laser; 3, after laser treatment. Infants ranged from 22 to 25 weeks' GA and 464 g to 1120 g at birth. For statistical analysis, GA and birth weight were stratified into tertiles (Table 1). In order of prevalence, infants presented with the following transfer admission diagnoses: patent ductus arteriosus (34%), severe respiratory distress syndrome (17%), bowel perforation (12%), necrotizing enterocolitis (8%) and a variety of others (29%).

The study cohort was very ill at birth and during NICU course. Together, laser treated and laser untreated infants had high rates of low 1-minute Apgar scores at birth (mean plus or minus standard deviation of 3.4 ± 2.3 [normal, 7–10]); low 5-minute Apgar scores (mean, 5.8 ± 1.9 [normal 7–10]); need for cardiopulmonary resuscitation at birth (31%); need for epinephrine (33%); need for dopamine (64%); intraventricular hemorrhage (63%); and hydrocephalus (22%); at least one surgical procedure in the operating room (68%); and the need for high-frequency oscillator ventilation for respiratory failure (41%). None of these acuity factors reached statistical significance between laser treated and laser untreated groups. Acuity remained high during the 28 days prior to the worst ROP examination regarding the number of packed red blood cell transfusions (mean number of transfusions, 2.7 ± 1.9); maximum fraction of inspired oxygen required (mean, 0.68 ± 0.28); and need for antibiotics (75%). Again, none of these factors reached statistical significance between the laser treated and untreated groups.

Only 2 infants had no ROP during the full screening period. The initial presentation of any level of ROP was documented in 34 infants at median PMA of 33.0 weeks (range, 30.1–38.7), which was a median DOL of 65 (range, 48–103). This subset of infants had at least one examination record documenting immature retinas before ROP presentation; thus the onset of first ROP is known.

Worst ROP examination was observed for 51 infants (laser treated and laser untreated) at a median PMA of 36.1 weeks (range, 32.3–46.3 weeks), or DOL of 87 (range, 58–149). For both initial ROP examination date and worst ROP examination date, not all infants had complete records because of transfer in or out of the NICU.

Twenty infants required laser for type 1 disease at median PMA of 35.8 weeks (range, 33.0–42.7 weeks), or a median DOL of 89 (range, 63–131). The cohort of infants born at 22 to 23 weeks' GA ($n = 8$) had laser at median PMA of 35.1 weeks (range, 33.4–36.7 weeks); those born at 24 weeks' GA ($n = 11$) had laser at median PMA of 36.7 weeks (range, 33–42.7); and the 1 infant born at 25 weeks' infant had laser at PMA of 42.7 weeks.

The subset of laser-treated infants with AP-ROP ($n = 8$) had laser for AP-ROP at a median PMA of 34.5 weeks (range, 33–36.9 weeks). The subset of laser-treated infants without AP-ROP ($n = 12$) had laser at a median PMA of 36.5 weeks (range, 33.9–42.7 weeks).

Plus disease was recorded in 21 infants at a median PMA of 36 weeks (range, 31.3–44.7 weeks). The subset of infants born at 22–23 weeks' GA ($n = 10$) had plus disease at a median PMA of 35.6 weeks (range, 31.3–40.7 weeks); those born at 24 weeks' GA ($n = 10$) had plus at a median PMA of 36.9 weeks (range, 34–42.7 weeks); the infant born at 25 weeks' GA had plus at 44.7 weeks. Table 2 summarizes the descriptive statistics for ROP outcomes by DOL, the age unit used in competing risk survival analysis. Of the 20 infants that died, the date of worst ROP examination was unknown in 7 cases (3 had laser; 4 did not).

The risk of ROP outcomes was assessed for GA, birth weight, and admission transfer diagnosis by competing risk survival analysis. Day of life (DOL) was the age unit used to provide information during the NICU course. The results of competing-risks regression in the presence of possible mortality for all ROP outcomes are shown in Table 3. Infants presenting with any one of the transfer admission diagnoses had slightly earlier onset of any level of ROP ($P = 0.11$) by competing-risks regression. These admission diagnoses did not relate to other ROP events.

As shown in Table 3, DOL competing risk survival analysis demonstrated that time to initial ROP was not predicted by either GA or birth weight. DOL time to worst examination was not predicted by GA; however, higher birth weight was associated with the shorter DOL time to worst examination ($P = 0.044$). The largest birth weight tertile had a worst examination documented at a median of 83 days (range, 58–149 days), whereas the smallest tertile had a worst examination documented at 87 days (range, 69–124 days). Calculated PMAs for the birth weight tertiles at the time of worst examination suggest that when the fetal time is considered using PMA rather than DOL, the PMA to worst ROP is similar across birth weight tertiles: for the highest birth weight tertile the median PMA at worst examination was 36.1 weeks (range, 32.9–46.3 weeks); for the middle tertile, 37 weeks (range, 32.3–44.7 weeks); for the smallest tertile, 35.5 weeks (range, 33.1–40.6 weeks).

DOL at laser was earlier in lower GA infants. The cumulative probability of receiving laser therapy was near 46% when GA was 22 or 23 weeks, 30% when GA was 24 weeks, and

18% when GA was 25 weeks. Risk of laser was reduced by 44% (subhazard ratio [SHR] = 0.56; $P = 0.007$) with each week of advancing GA.

A total of 21 infants had documented plus disease. The risk of plus disease was significantly decreased by 51% with each week of advancing GA (SHR = 0.49, $P = 0.001$). When broken down into GA tertiles, the cumulative probability of plus disease was near 53% when GA was 22 or 23 weeks, 31% when GA was 24 weeks, and 17% when GA was 25 weeks.

Discussion

The clinical course of ROP reported here indicates that current ROP screening guidelines are appropriate for extremely premature infants of 22–25 weeks' GA. The earliest type 1 disease in our cohort was treated at 33 weeks PMA. This study confirms current screening guidelines are correct even for infants of 22 and 23 weeks' GA when ROP screening begins at PMA 31 weeks.

Of particular note, 40% of infants needing laser presented with AP-ROP. Laser for APROP was required at a median PMA of 34.5 weeks, 2 weeks earlier than infants without APROP who were treated. The youngest case was the ischemic twin in a case of twin–twin transfusion who presented with AP-ROP in just 1/3 of zone 1 at exactly PMA 33 weeks. Our data suggests that ROP screening should begin no later than 31 weeks' PMA for infants of 22–25 weeks' GA.

The probability of laser treatment was high in infants of 22–23 weeks' GA. The cumulative probability of receiving laser therapy was near 46% when GA was 22 or 23 weeks; 30% when GA was 24 weeks, 18% when GA was 25 weeks. Interestingly, 4 of 20 infants developed type 1 ROP after PMA of 40 weeks. Our data suggests that extremely low GA infants are at risk of type 1 ROP for a 10-week interval from 33 to 43 weeks' PMA.

We investigated the time to ROP events in terms of DOL rather than PMA. This approach allowed evaluation of factors that affect ROP evolution after birth. An unexpected finding of our paper was related to higher birth weight in this extremely small, premature cohort. Earlier progression to the worst ROP examination was found in higher birth weight infants. Birth weight (high or low) did not predict time to type 1 ROP disease within this cohort. The relation between birth weight and the evolution of ROP requires more study in the extremely low birth weight cohort.

The present study is limited by its retrospective nature and all the biases inherent in a retrospective study design. A single pediatric ophthalmologist performed all the screening examinations, which might induce bias for diagnosis such as plus, while several pediatric retinal surgeons were involved in treating the patients, thereby potentially introducing variability in interpretation of ROP severity. In addition, due to the rarity of extremely premature infants, our sample size was small. Despite these weaknesses, this study offers valuable insights on ROP in extremely premature infants and further validates current guidelines on ROP screening in this growing patient population.

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Table 1

Descriptive statistics

Variables	No.	Median
Gestational age (week, N = 78)		24
22–23	23	23
24	39	24
25	16	25
Birth weight, g (N = 78)		623.5
464–585	26	529
586–655	26	623.5
660–1120	26	716
Transfer admission diagnosis (N = 76)		
Patent ductus arteriosus	26	34.2
Respiratory distress syndrome ^a	13	17.1
Bowel perforation	9	11.8
Necrotizing enterocolitis	6	7.9
Other	22	29.0

^aLife-threatening respiratory distress that could not be managed at the birth hospital.

Table 2

Descriptive statistics of time to events^a

Time to events	No.	Statistics	Events	No events	Mortality
Time to initial ROP	65	N (%)	34 (52)	14 (22)	17 (26)
		Days of life	65	106.5	30
		Median (min–max)	(48–103)	(84–297)	(2–306)
Time to worst exam	64	N (%)	51 (80)	0 (0)	13 (20)
		Days of life	87		26
		Median (min–max)	(58–149)		(2–108)
Time to laser	65	N (%)	20 (31)	28 (44)	17 (26)
		Days of life	89	155	30
		Median (min–max)	(63–131)	(86–846)	(2–306)
Time to AP-ROP	20	N (%)	8 (40)	11 (55)	1 (5)
		Days of life	80	118	100
		Median (min–max)	(63–103)	(84–374)	
Time to plus	65	N (%)	21 (32)	27 (42)	17 (26)
		Days of life	91	149	30
		Median (min–max)	(58–138)	(86–846)	(2–306)

AP-ROP, aggressive posterior ROP; ROP, retinopathy of prematurity.

^aInitial ROP examination date and worst ROP examination date were not available on all infants.

Table 3

Results of Competing-risks Regression in the presence of possible mortality

Outcomes	Predictors	SHR (95% CI)	P value ^b
Time to ROP	GA, weeks	1.22 (0.77–1.94)	0.393
	BW, 100 g	1.09 (0.83–1.44)	0.536
	Admission diagnosis ^a		
	=1	3.03 (0.80–11.48)	0.103
	=0 (reference)	—	—
Time to worst exam	GA, weeks	1.09 (0.77–1.54)	0.626
	BW, 100 g	1.27 (1.01–1.60)	0.044
	Admission diagnosis ^a		
	=1	0.98 (0.39–2.48)	0.964
	=0 (reference)	—	—
Time to laser	GA, weeks	0.56 (0.37–0.85)	0.007
	BW, 100 g	0.67 (0.37–1.20)	0.176
	Admission diagnosis ^a		
	=1	0.67 (0.19–2.35)	0.527
	=0 (reference)	—	—
Time to AP-ROP	GA, weeks	0.66 (0.37–1.18)	0.162
	BW, 100 g	1.70 (0.86–3.35)	0.129
	Admission diagnosis ^a		
	=1	0.48 (0.11–2.18)	0.342
	=0 (reference)	—	—
Time to plus disease	GA, weeks	0.49 (0.32–0.73)	0.001
	BW, 100 g	0.73 (0.44–1.21)	0.222
	Admission diagnosis ^a		
	=1	0.78 (0.24–2.53)	0.674
	=0 (reference)	—	—

BW, birth weight; CI, confidence interval; GA, gestational age; SHR, subhazard ratio.

^a Transfer admission diagnosis is 1 when a patient had any of patent ductus arteriosus, respiratory distress syndrome, necrotizing enterocolitis, or bowel perforation; is 0 otherwise.

^b Significance of the effect of a predictor.