

Natural History of Retinopathy of Prematurity in Infants Born Before 27 Weeks' Gestation in Sweden

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Objective: To investigate the natural history of retinopathy of prematurity (ROP) in 506 extremely preterm infants born before 27 weeks' gestation in Sweden during a 3-year period.

Methods: A national population-based study was performed in Sweden from April 1, 2004, to March 31, 2007. According to the study protocol, initial eye examinations were to be performed at postnatal week 5, and examinations were repeated until the retina was completely vascularized or until criteria for treatment were met. The examinations were to be performed weekly, enabling study of the course and severity of ROP. In infants without ROP or with mild ROP without progression during the latest examinations, further examinations were performed weekly or every other week from postmenstrual age 35 weeks.

Results: During the study, 368 infants (72.7%) developed ROP. Postmenstrual age at onset of ROP was significantly related to severity of ROP, even when controlling for gestational age (ie, the earlier the onset of ROP, the higher the risk of developing severe ROP). Site of onset of ROP was significantly related to gestational age at birth. The risk of nasal onset was almost doubled for every week of decrease in gestational age at birth. Nasal onset was associated with severe ROP, even after adjusting for gestational age at birth.

Conclusion: This population-based study confirms results of the Cryotherapy for Retinopathy of Prematurity study and shows new correlations regarding time and site of onset of ROP, both of which are associated with disease severity.

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THE NATURAL HISTORY OF retinopathy of prematurity (ROP) was studied in the 1980s among preterm infants.¹⁻⁶ Results regarding the onset and course of the disease^{2,6,7} became the basis for new treatment recommendations.⁸ In the Early Treatment for Retinopathy of Prematurity (ETROP) study⁹ a multiple logistic risk model was used that integrated risk factors from the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study such as the rate of progression to unfavorable outcome in eyes that had reached prethreshold ROP. Improvements in neonatal care have resulted in increased survival of extremely preterm infants. Although the natural history of ROP has been studied during the last decade,¹⁰⁻¹³ more current information is needed in this preterm population.

In Sweden, a recent national study¹⁴ reported 70% survival among infants born before 27 weeks' gestation. This population had a high incidence of ROP and a high frequency of infants needing treatment.^{15,16} The present study was designed to investigate the natural history of ROP in this population of extremely preterm infants. Beginning examinations at postnatal week 5 and performing weekly follow-up examinations in the infants,

the study focused on time and site of onset of ROP and on progression of the disease.

METHODS

A prospective population-based study¹⁴ of extremely preterm infants was performed in Sweden from April 1, 2004, to March 31, 2007. All infants having gestational age (GA) younger than 27 weeks at birth and surviving at least until the first eye examination were included in this national study.

A network of pediatric ophthalmologists directing ROP examinations in their hospitals across Sweden was organized to continuously collect and record data from ROP screening. The ophthalmologists were informed about the study, procedures, and protocols. Information and recommendations were given at yearly meetings of the Swedish Ophthalmologic Society and the Swedish Society of Medicine, as well as at regional ophthalmologic meetings. The principal ophthalmologists from 7 regions in Sweden met regularly during the study period to assure quality of the study.

According to the study protocol, initial eye examinations were to be performed at postnatal week 5, and examinations of the infants were repeated weekly, enabling study of the course and severity of ROP. In infants without ROP or with mild ROP (stage 1 or 2) without progression during the latest examinations, further examinations were performed weekly or every other week from postmenstrual age (PMA) 35 weeks.

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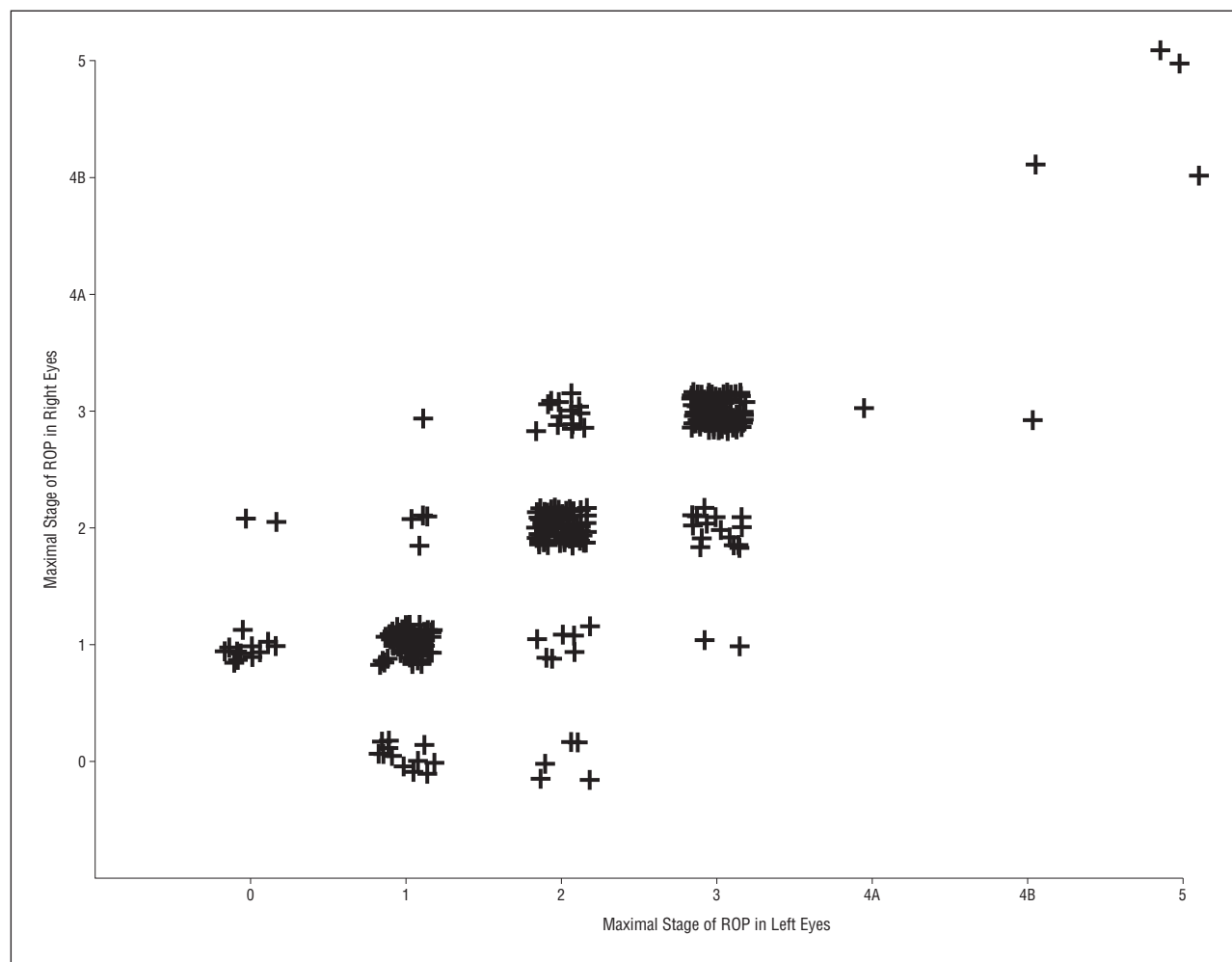


Figure 1. Symmetry of the maximal stages of retinopathy of prematurity (ROP) in right eyes and left eyes.

Indirect ophthalmoscopy was performed after dilatation of the pupils with cyclopentolate hydrochloride (0.5%) and phenylephrine hydrochloride (0.5%) and with topical anesthesia if needed. A lid speculum and scleral indentation were used to visualize the border between vascularized and nonvascularized retina. If the infant did not tolerate eye screening as scheduled, the examination was performed as soon as permitted by the neonatologist.

Analyses of postnatal age (PNA) and PMA at first detection of ROP included only infants with initially normal results on ophthalmic examination. When analyzing the onset of various stages of ROP, eyes were excluded that had the studied stage of ROP at the initial screening examination.

This natural history study was designed to include data on ROP screening until criteria for treatment were met (ie, type 1 ROP according to the ETROP recommendations⁸) or until the retina was completely vascularized. Retinopathy of prematurity was categorized according to the revised International Classification of Retinopathy of Prematurity.¹⁷ Stages 1 and 2 were defined as mild ROP and stages 3 to 5 as severe ROP.

Gestational age denotes time from the last menstrual period to birth, estimated by ultrasonographic examination at 17 to 18 postmenstrual weeks.¹⁴ Postmenstrual age was calculated as the sum of GA at birth plus PNA (ie, the number of weeks and days after birth). Further details about examination techniques, logistics, and survival are available in publications of earlier results of this study.¹⁴⁻¹⁶

The study was approved by the ethics committee of the Faculty of Medicine, Lund University, Lund, Sweden. It was consid-

ered a quality assurance project, and no informed consent was needed.

The incidence of ROP by PMA was determined by standard Kaplan-Meier survival analysis. Spearman rank correlation (ρ) was computed to estimate the degree of ROP stage symmetry in right eyes and left eyes. The associations of age at onset and site of onset with severe ROP (ie, stage ≥ 3) as a dichotomous outcome variable were investigated using simple logistic regression analyses or using multiple logistic regression analyses adjusting for GA at birth as a continuous linear variable. Age at onset (PNA and PMA) relative to severity of ROP (stage 1, 2, or 3) and GA at birth were investigated using multivariate analysis of variance. The rates of progression from onset of ROP to stage 3 over GA at birth strata were compared using Kruskal-Wallis nonparametric test.

All statistical analyses were performed using commercially available software (Gauss version 6.0; Aptech Systems Inc, Black Diamond, Washington). All testing was 2-sided, and $P < .05$ was considered statistically significant.

RESULTS

As reported previously, 72.7% (368 of 506) of infants in the total study cohort developed ROP.¹⁶ The mean and median GAs at birth and birth weights of the infants with ROP were 25.2 and 25.3 (range, 22.1-26.9) weeks and 754.2 and

Table 1. Postnatal Age and Postmenstrual Age at Onset of Different Stages of Retinopathy of Prematurity (ROP) and of Plus Disease in 352 Right Eyes^a

Variable	No. of Eyes		Median (Range) [5th-95th Percentiles]	
	Excluded	Included	Postnatal Age, wk	Postmenstrual Age, wk
ROP stage				
1	26	179	8.6 (5.7-16.4) [6.3-13.1]	34.1 (30.3-42.0) [31.3-38.3]
2	9	229	9.4 (5.9-19.4) [6.9-14.4]	34.6 (29.9-44.3) [31.9-39.6]
3	3	157	11.1 (6.6-24.7) [7.7-19.1]	35.9 (31.6-50.6) [32.6-43.3]
Plus disease	0	82	11.3 (7.4-29.3) [8.4-17.7]	35.9 (31.7-54.1) [32.7-41.6]

^aWhen analyzing each stage of ROP, eyes were excluded that had the studied stage of ROP at the initial screening examination.

748.5 (range, 348-1315) g, respectively. Some stage of ROP was noted in at least 1 eye at the first screening examination in 8.3% (42 of 506) of infants. Twenty-nine infants had ROP stage 1, 10 had stage 2, and 3 had stage 3 at the first examination. In the 3 infants with ROP stage 3, the first examinations had been delayed to postmenstrual weeks 32 (+4), 33 (+1), and 34 (+6). In the remaining 326 infants with ROP, the mean and median PNAs and PMAs at onset of ROP were 8.9 and 8.6 (range, 4.7-16.3) weeks and 34.0 and 33.6 (range, 29.9-41.7) weeks, respectively.

Symmetrical stages of ROP in right eyes and left eyes were found in 424 of 506 infants (83.8%). There was a difference of 1 stage between right eyes and left eyes in 72 infants (14.2%) and a difference of 2 stages in 10 infants (2.0%). There was significant correlation between right eyes and left eyes for maximal stage of ROP ($P < .001$) (**Figure 1**); therefore, subsequent analyses were performed among right eyes only. Among the population of 506 infants, ROP developed in 352 right eyes.

Site of onset of ROP was recorded in 308 of 352 right eyes. Retinopathy of prematurity was first localized in the nasal retina in 85 eyes (27.6%), both nasally and temporally in 73 eyes (23.7%), and temporally in 150 eyes (48.7%). Site of onset of ROP was significantly related to GA at birth ($P < .001$). The risk of nasal onset was almost doubled for every week of decrease in GA at birth (odds ratio, 1.8; 95% confidence interval, 2.3-1.5). Nasal onset was associated with severe ROP, even after adjusting for GA at birth ($P < .001$).

The PNAs and PMAs at onset of different stages of ROP and of plus disease in right eyes ($n=352$) are summarized in **Table 1**. The onset of ROP was also calculated taking into account the interval between examinations. For this purpose, another 18 eyes with a mean interval of more than 14 days between examinations were excluded. In the remaining eyes, no differences in the mean or median PNAs or PMAs at the onset of ROP were found compared with results for the total population of right eyes. Therefore, subsequent analyses were performed among the total population of right eyes.

The onset of ROP in right eyes relative to GA at birth is summarized in **Table 2** and in **Figure 2**. Postnatal age at onset of ROP was significantly older in the most immature infants ($P < .05$), while PMA at onset of ROP was significantly younger in the most immature infants ($P < .001$).

Postmenstrual age at onset of ROP stages 1, 2, and 3 and of plus disease in right eyes was significantly younger

Table 2. Onset of Retinopathy of Prematurity (ROP) in 314 Right Eyes Relative to Gestational Age (GA) at Birth^a

GA at Birth, wk	Mean (Median) [Range]	
	Postnatal Age, wk	Postmenstrual Age, wk
22 (n=5)	8.9 (8.4) [8.0-10.4]	31.5 (31.3) [30.7-32.6]
23 (n=45)	9.6 (9.6) [6.6-15.6]	33.1 (32.9) [29.9-38.6]
24 (n=74)	9.4 (9.1) [6.1-16.3]	33.8 (33.5) [30.3-40.7]
25 (n=111)	9.0 (8.6) [5.9-17.0]	34.4 (34.1) [31.0-42.1]
26 (n=79)	8.6 (8.1) [5.7-15.6]	35.0 (34.7) [31.9-41.7]

^aThirty-eight right eyes with ROP at the initial screening examination were excluded.

in the most immature infants ($P < .05$). No correlation with PNA was found. Postmenstrual age at onset of ROP stage 3 in right eyes relative to GA at birth is summarized in **Figure 3**.

Postmenstrual age at onset of ROP was significantly related to severity of ROP ($P < .001$) (ie, the younger the PMA, the more severe the final stage of ROP). This relationship remained after adjustment for GA at birth ($P < .05$).

Time from onset of ROP to stage 3 was significantly shorter in infants who met criteria for treatment (median, 14 days) compared with those who did not (median, 20.5 days) ($P < .05$). No correlation was found between GA at birth and the rate of progression from onset of ROP to stage 3. The proportion of regression and progression of ROP for various stages present at some point in time in right eyes are summarized in **Table 3**.

COMMENT

This national study of infants born before 27 weeks' gestation with high survival of the most immature¹⁴ provides us with information about the natural history of ROP in this population. The course of ROP was similar to that of previous studies¹⁻⁵ reporting on more mature infants, but new information is presented herein about the importance of time and site of onset.

Postmenstrual age at onset of ROP ranged between 29.9 and 41.7 weeks, which is a narrower range than that found in earlier population-based studies.^{1,3,5} This is not surprising, as the infants in our population were born within a narrower range of gestational weeks. However, be-

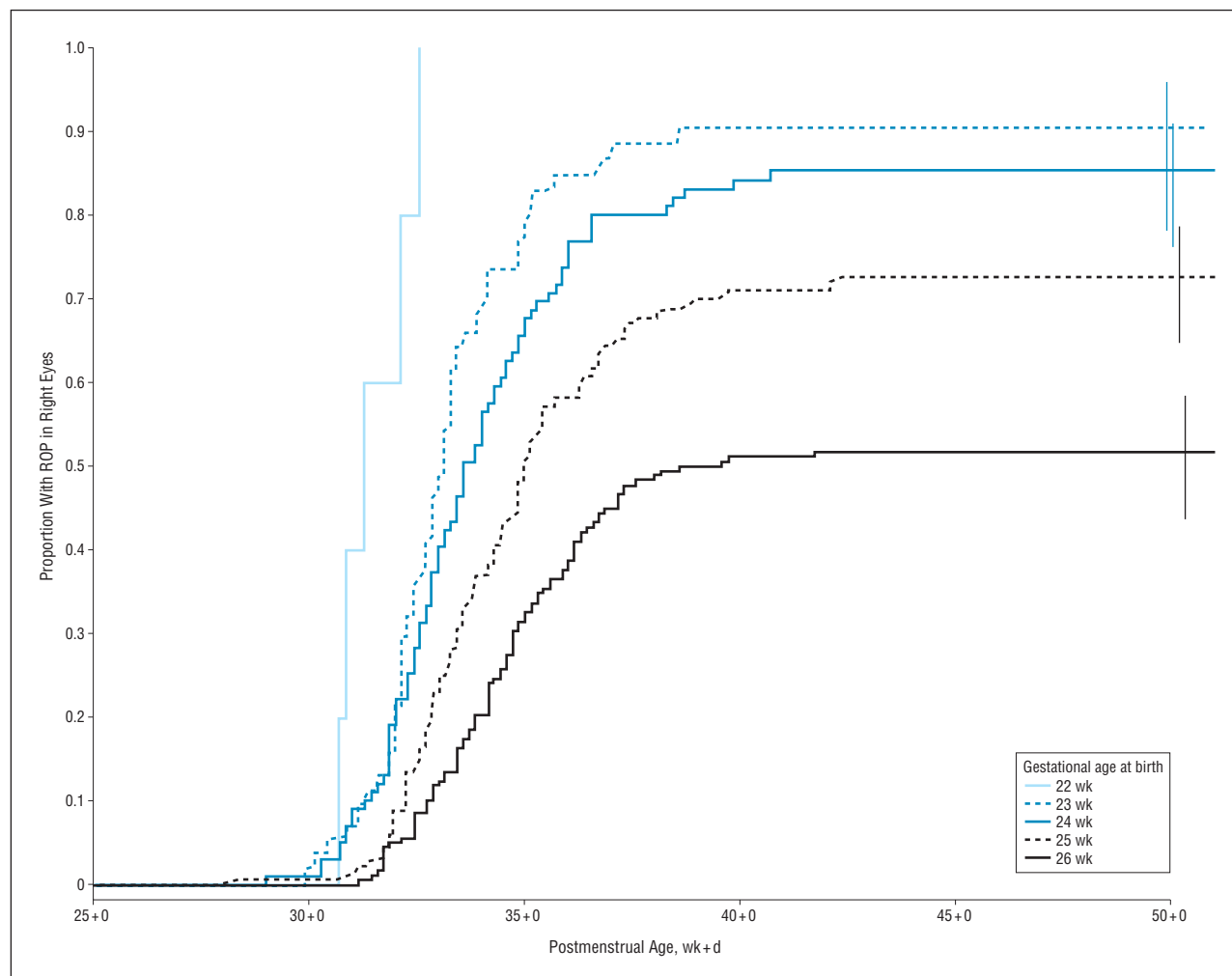


Figure 2. Onset of retinopathy of prematurity (ROP) in right eyes relative to gestational age at birth (with 95% confidence intervals at 50 weeks as vertical bars).

cause 8.3% of infants in our study group had ROP at the first screening examination, we cannot exclude that the PNAs and PMAs given for the onset of ROP and for different ROP stages may be overestimates. Most important, in 3 infants with ROP stage 3 at the first screening, this examination was performed within sufficient time for successful treatment.

Postmenstrual age at onset of ROP was closely related to GA at birth, with the most immature infants developing ROP at an earlier PMA than the more mature ones (eg, infants with GA at birth of 23 weeks would develop ROP a mean of 2 weeks earlier than infants with GA at birth of 26 weeks). This corresponds with findings of earlier natural history studies^{1,2,4,5} based on more mature infants born about 20 years ago and is integrated in the first risk model based on CRYO-ROP study⁷ data.

As expected, PMA at onset of different stages of ROP increased with increasing stage of ROP. Compared with the American multicenter studies CRYO-ROP² and ETROP,¹¹ we found similar age at onset of ROP stages and of plus disease (**Table 4**). However, ROP stage 2 and stage 3 had a slightly earlier onset in the present study, which can be explained by the shorter examination interval in the present study or by the fact that the popu-

lation comprised more preterm infants. Retinopathy of prematurity stage 3 developed before PMA 43.3 weeks in 150 infants (95th percentile), while stage 3 was first seen at PMA 43.3 weeks or older in 7 infants (fifth percentile). Two of these 7 infants were severely diseased and unstable and, therefore, had an interval of several weeks between eye examinations. Five of 7 infants, 2 of whom were treated, had late onset of local proliferations at the border between zone II and zone III.

Analyses of age at onset of ROP as a risk factor for progression to severe ROP revealed new findings. Postmenstrual age at onset of ROP was significantly related to severity of ROP, even when controlling for GA at birth (ie, the earlier the onset of ROP, the higher the risk of developing severe ROP). This finding contradicts results of the CRYO-ROP study^{6,9} and might be explained by several factors. First, the study designs differed, with the CRYO-ROP study¹⁴ being hospital-based in contrast to our national population-based Extremely Preterm Infants Study in Sweden (EXPRESS). Second, and more likely, are the advances in neonatal care during the last decades, providing us with a population of preterm infants at the limit of viability¹⁸ and a shift in infants susceptible to ROP from more mature preterm infants toward extremely preterm infants.^{19,20}

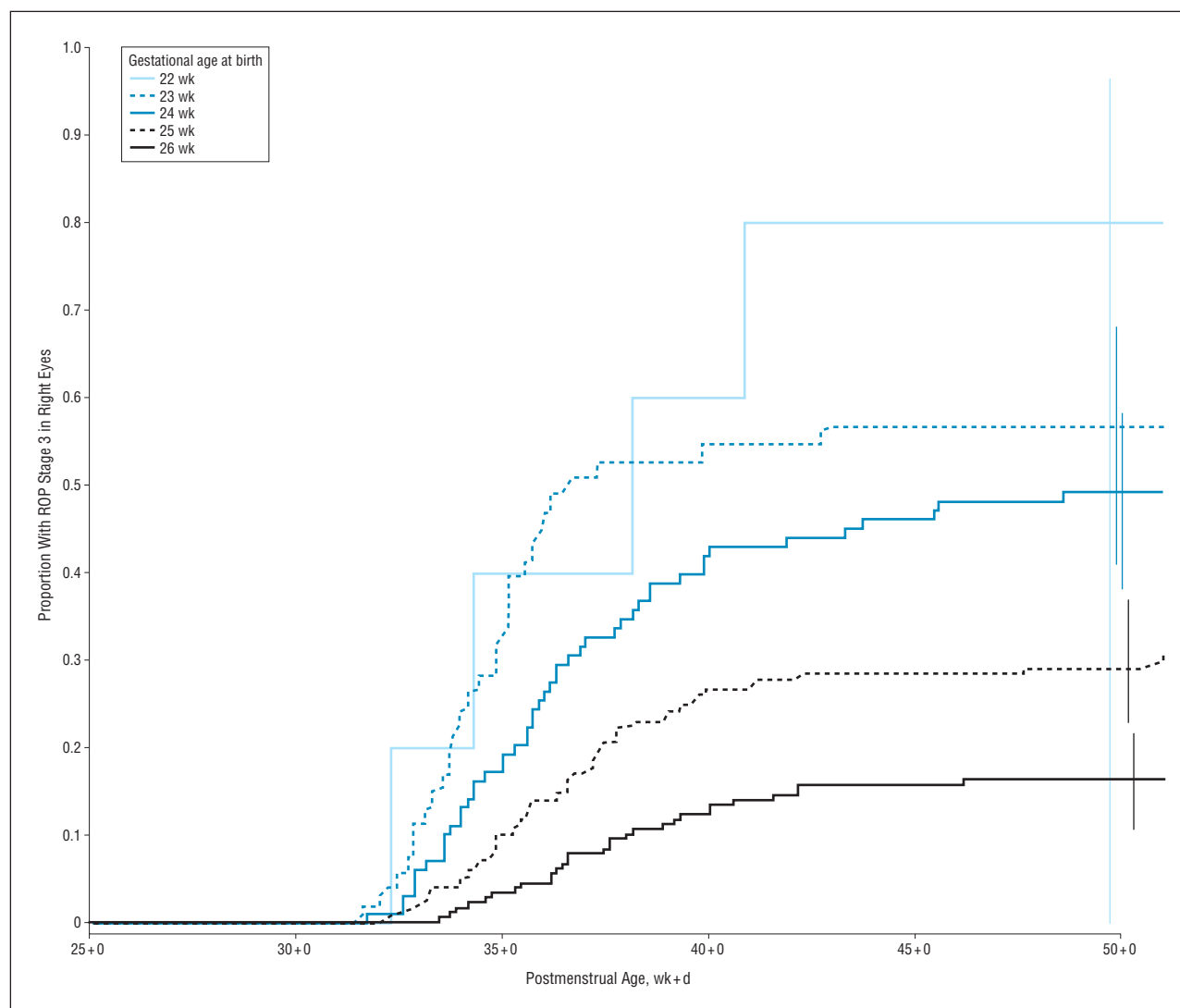


Figure 3. Onset of retinopathy of prematurity (ROP) stage 3 in right eyes relative to gestational age at birth (with 95% confidence intervals at 50 weeks as vertical bars).

Table 3. Regression and Progression of Retinopathy of Prematurity (ROP) in 352 Right Eyes^a

ROP Stage	Regression, No. (%)	Progression, No. (%)	Dead
1 (n=179)	57 (31.8)	120 (67.0)	2
2 (n=229)	116 (50.7)	112 (48.9)	1
3 (n=157)	63 (40.1)	94 (59.9) ^b	0

^aThirty-eight right eyes with ROP at the initial screening examination were excluded.

^bProgression to criteria for treatment.

In the natural history cohort of the CRYO-ROP study,⁶ there was a higher risk of unfavorable macular outcome among infants with a rapid rate of ROP progression to pre-threshold disease. Furthermore, in the multiple logistic risk model for prethreshold ROP by Hardy et al,⁹ the interval of ROP progression from onset to prethreshold level correlated with prognosis, being most favorable for eyes with an interval of more than 3 weeks. Our results are in accord with these findings, revealing a mean progression time of 2 weeks between the onset of ROP to stage 3 among

Table 4. Postmenstrual Age at Onset of Different Stages of Retinopathy of Prematurity (ROP) and of Plus Disease in the Present Study vs the ETROP¹¹ and CRYO-ROP² Studies

Variable	Postmenstrual Age, Median (5th-95th Percentiles), wk		
	Present Study	ETROP	CRYO-ROP
ROP stage			
1	34.1 (31.3-38.3)	34.1 (ND-38.9)	34.3 (ND-39.1)
2	34.6 (31.9-39.6)	35.1 (32.4-40.1)	35.4 (32.0-40.7)
3	35.9 (32.6-43.3)	36.6 (33.4-41.6)	36.6 (32.9-42.4)
Plus disease	35.9 (32.7-41.6)	36.0 (33.0-41.4)	36.3 (32.6-42.9)

Abbreviations: CRYO-ROP, Cryotherapy for Retinopathy of Prematurity; ETROP, Early Treatment for Retinopathy of Prematurity; ND, not determined.

infants who met criteria for treatment compared with 3 weeks among those who did not. Although the studies and criteria for treatment differ and the population of infants meeting criteria for treatment has changed during the last 20 years, we conclude that the speed of progression still predicts risk. In our population, only 4 of 99 infants meet-

ing criteria for treatment had aggressive posterior ROP, and 9 had zone I disease, which are comparable to results of the CRYO-ROP study^{6,21} but much fewer than were found in the ETROP study.⁸

Nasal onset significantly correlated with the youngest GAs at birth in our cohort of extremely immature infants. In addition, nasal onset was related to severe ROP, even after adjusting for GA at birth. These findings confirm previous observations by Fielder et al.^{3,22} Site of onset of ROP was not included in the risk model on which the ETROP study⁹ was based nor in the subsequent current treatment recommendations. According to our results, site of onset is an additional risk factor for clinicians to consider.

In conclusion, we confirm results of previous studies reporting earlier, more frequent, and more severe ROP in the youngest infants born before 27 weeks' gestation. To our knowledge, this is the first report that PMA at onset and nasal onset of ROP are correlated with severity of ROP. Therefore, examiners should be aware of the time and site of onset of ROP, as these are related to the severity of disease.

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