• Brief Report •

Retina status at first ROP exam and the subsequent development of type 1 ROP

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Abstract

● **AIM:** To evaluate the association between findings at the first retinopathy of prematurity (ROP) exam and the subsequent development of type 1 ROP in a large registry of infants.

● **METHODS:** A retrospective cohort study of the records of infants (*n*=1582) screened for ROP (2013–2022) was conducted using an ROP registry. Logistic regression using generalized estimating equations was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of developing type 1 ROP following any ROP at initial exam, or for infants who required a one-week follow-up exam following initial exam.

● **RESULTS:** Gestational age at delivery of 1582 infants (834 males) were 28.8±2.5wk. Infants with any ROP noted at initial exam had increased odds of developing type 1 ROP [OR=3.64, 95%CI (1.93, 6.88), *P*<0.001] compared to infants without any ROP noted at initial exam. Infants who required a one-week follow-up exam for any reason after initial ROP exam had even higher odds of developing type 1 ROP [OR=9.31, 95%CI (5.63, 15.4), *P*<0.001] compared to infants who did not require a one-week follow-up exam.

● **CONCLUSION:** Infants with ROP noted at initial exam and infants requiring a one-week follow-up exam are significantly more likely to develop type 1 ROP. When signs of ROP or concern for ROP are noted by the ophthalmologist at the first ROP exam, there is a significant increase in the likelihood of developing type 1 ROP. These data will assist ophthalmologists in informing families and neonatologists of the risk of ROP from the onset of ROP exams.

● **KEYWORDS:** retinopathy of prematurity; type 1 retinopathy of prematurity; first retinopathy of prematurity exam

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INTRODUCTION

Low birth weight and prematurity, specifically for infants born at the lower extreme of prematurity and birth weight[1-2], are major risk factors for the development of retinopathy of prematurity (ROP), a disorder of the developing retinal blood vessels. Other ROP risk factors include postnatal fluctuating oxygen levels, low postnatal weight gain, and loss of the maternal-fetal interaction[3-5]. One area of research not previously investigated to predict the development of type 1 ROP is the utility of the findings from the first ROP examination. The purpose of this study was to determine whether the presence of ROP (presence of stage 1 or higher in any zone[6-7]) at the first screening exam, or the need for a one-week follow-up after that exam, is associated with the subsequent development of type 1 ROP.

PARTICIPANTS AND METHODS

Ethical Approval The Colorado Multiple Institutional Review Board approved the study (COMIRB #14-1480). The tenets of the Declaration of Helsinki and the requirements set by the US Health Insurance Portability and Accountability Act of 1996 have been adhered to.

A retrospective cohort study was conducted using records from an ROP registry[8] developed by the University of Colorado School of Medicine, Department of Ophthalmology. The study was conducted between January 2013 and December 2022 and included all infants born at both University of Colorado Hospital and Children's Hospital Colorado. The registry contains detailed information on maternal risk factors, perinatal events, and the results of ROP examinations. Information was collected by a team of research assistants

Table 1 Characteristics of the preterm cohort stratified by observation of ROP at initial examination (*n*=1582)

Infant characteristics	Overall (*n*=1582)	ROP at initial examination		
		No (*n*=1493)	Yes (*n*=89)	*P*[b]
Gestational age at delivery, wk				<0.001
Mean±SD	28.8±2.5	29.0±2.5	26.3±2.3	
Range	22.1–36.9	22.3–36.9	22.1–31.9	
Birth weight, g				<0.001
Mean±SD	1110.6±341.6	1123.5±339.5	896.5±304.8	
Range	365.0–2560.0	365.0–2560.0	440.0–1925.0	
Sex, *n* (%)				0.585
Female	748 (47.0)	703 (47.0)	45 (51.0)	
Male	834 (53.0)	790 (53.0)	44 (49.0)	
Race/ethnicity, *n* (%)				0.004
Non-Hispanic White	806 (50.8)	777 (52.0)	29 (32.6)	
Hispanic	455 (28.8)	416 (28.0)	39 (43.8)	
African American	172 (10.9)	160 (10.7)	12 (13.5)	
Asian	42 (2.7)	41 (2.7)	1 (1.1)	
Other	107 (6.8)	99 (6.6)	8 (9.0)	

[b]*P*-values were derived from *t*-tests for continuous variables and Fisher's exact test for categorical variables. ROP: Retinopathy of prematurity; SD: Standard deviation.

trained in perinatal data abstraction. All infants in the registry fulfilled the American Academy of Pediatrics 2013 screening criteria for ROP and were examined according to the schedule recommended by the American Academy of Pediatrics with the first exam occurring at 4 weeks of age or postmenstrual age of 31wk, whichever occurred later[9]. The main outcome of the study was the development of type 1 ROP, and the primary exposures were the presence of ROP at the first ROP exam, or requirement for a one-week follow-up examination following the first ROP exam. Type 1 ROP was defined as zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 with plus disease[6-7].

Frequencies and percentages of select characteristics of infants were stratified by presence of ROP at the first exam and requirement for a one-week follow-up examination at the first exam. Logistic regression using generalized estimating equations was used to assess differences in characteristics between groups. Odd ratios (OR) and 95% confidence intervals (CI) were estimated for infants developing type 1 ROP following the observation of ROP at initial exam and for infants who required a one-week follow-up exam following initial exam, with and without adjusting for exclusively gestational age (GA) at birth.

RESULTS

The clinical characteristics of the entire cohort and between infants who did and did not have ROP at the first ROP examination are shown in Table 1. The average postmenstrual age at the first ROP examination was 33.4±29.9d. Infants with ROP at the initial examination were significantly more likely to have both lower GA at delivery and lower birth weight. The average GA for an infant with ROP at the initial exam was 26.3±2.3wk, while the average birth weight for infants noted to have ROP at the initial exam was 896.5±304.8 g. Hispanic infants had significantly increased odds of having ROP at the first ROP screening examination compared with non-Hispanic White infants. The findings in Table 1 were similar when the cohort was stratified by those infants requiring one-week follow-up examination following the initial ROP examination.

We demonstrate in Table 2 that infants with stage 1 or higher ROP noted at the initial exam had significantly increased odds of developing type 1 ROP [OR=3.64, 95%CI (1.93, 6.88), *P*<0.001] compared to infants without ROP noted at the initial exam. Infants who required a one-week follow-up exam following the initial ROP exam also had a significantly increased odds of developing type 1 ROP [OR=9.31, 95%CI (5.63, 15.4), *P*<0.001]. Following adjustment for GA, the association between a one-week follow-up exam and the development of type 1 ROP was attenuated but remained significant [OR=2.31, 95%CI (1.24, 4.28), *P*=0.008].

DISCUSSION

We were interested to see where the first ROP screening examination fit into the natural history of ROP and importantly if the first ROP examination had any association with the development of type 1 ROP. As presented, infants with ROP at the first screening examination had an increased odds of developing type 1 ROP compared with infants without ROP at the first examination. The odds were even greater if the infant required a one-week follow-up examination. These data suggest that the ophthalmologist's clinical concern on the first exam is associated with a higher risk of type 1 ROP.

It is not surprising that there was a higher rate of developing type 1 ROP in patients with early signs of disease. The more compelling finding was that the clinician's initial concern correlated with the need for treatment. The most common

Table 2 Type 1 ROP after ROP at initial exam or one-week follow-up subsequent to initial examination

Findings	Overall (*n*=1582)	Type 1 ROP following initial visit		Logistic regression[c]	
		No (*n*=1502)	Yes (*n*=80)	OR (95%CI)	*P*
ROP at initial exam, *n* (%)	89 (5.6)	76 (5.1)	13 (16.0)	3.64 (1.93 to 6.88)	<0.001
One-week follow-up exam, *n* (%)	171 (11.0)	133 (8.9)	38 (48.0)	9.31 (5.63 to 15.4)	<0.001

[c]Generalized estimating equations. OR: Odds ratio; CI: Confidence interval; ROP: Retinopathy of prematurity.

reasons for scheduling a one-week follow-up included very posterior (zone 1) stage 0 disease and poor view to the retina due to hazy media. Unfortunately, not all the reasons for scheduling a one-week follow-up were documented. Nevertheless, the results suggest that there are some key findings observed by the providers as early as the first exam that predict future risk. Further research may be able to elucidate which factors present on the first examination explain the risk of progression.

The results of this study were based on data from a cohort of carefully characterized infants who were delivered at an academic institution where there was a standard approach to the care of preterm infants and of ROP screening. These results may not necessarily be extrapolated to other cohorts with different underlying clinical and demographic characteristics. Additionally, while "poor view" and posterior stage 0 were described as indications for one-week follow-up examinations, these reasons were not systematically documented in all cases, which may have introduced potential classification bias in the assignment of follow-up intervals.

Here we demonstrate that infants with ROP noted at the initial exam and infants requiring a one-week follow-up exam are significantly more likely to develop type 1 ROP. Our findings could potentially be integrated into ROP examination frequency decision making by the examining ophthalmologists. Additionally, these findings can aid clinicians examining babies to counsel families on the importance of frequent follow-up exams and provide guidance regarding the risk of needing treatment in the future.

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Data Availability Statement: The data underlying this study are derived from patient medical records and are not publicly available due to patient privacy and institutional restrictions. Requests for access to deidentified data may be considered on a case-by-case basis, subject to Institutional Review Board approval, institutional policies, and applicable data-use requirements.

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