AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Retinal and Optic Nerve Hemorrhages in the Newborn Infant

One-Year Results of the Newborn Eye Screen Test Study

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Purpose: To report the birth prevalence, risk factors, characteristics, and location of fundus hemorrhages (FHs) of the retina and optic nerve present in newborns at birth.

Design: Prospective cohort study at Stanford University School of Medicine.

Participants: All infants who were 37 weeks postmenstrual age or older and stable were eligible for screening. Infants with known or suspected infectious conjunctivitis were excluded.

Methods: Infants born at Lucile Packard Children's Hospital (LPCH) from July 25, 2013, through July 25, 2014, were offered universal newborn screening via wide-angle digital retinal photography in the Newborn Eye Screen Test study. Maternal, obstetric, and neonatal factors were obtained from hospital records. The location, retinal layer, and laterality of FH were recorded by 1 pediatric vitreoretinal specialist.

Main Outcome Measures: Birth prevalence of FH. Secondary outcomes included rate of adverse events, risk factors for FH, hemorrhage characteristics, and adverse events.

Results: The birth prevalence of FH in this study was 20.3% (41/202 infants). Ninety-five percent of FHs involved the periphery, 83% involved the macula, and 71% involved multiple layers of the retina. The fovea was involved in 15% of FH cases (birth prevalence, 3.0%). No cases of bilateral foveal hemorrhage were found. Fundus hemorrhages were more common in the left eye than the right. Fundus hemorrhages were most commonly optic nerve flame hemorrhages (48%) and white-centered retinal hemorrhages (30%). Retinal hemorrhages were found most frequently in all 4 quadrants (35%) and more often were multiple than solitary. Macular hemorrhages most often were intraretinal (40%). Among the risk factors examined in this study, vaginal delivery compared with cesarean section (odds ratio [OR], 9.34; 95% confidence interval [CI], 2.57–33.97) showed the greatest level of association with FH. Self-identified ethnicity as Hispanic or Latino showed a protective effect (OR, 0.43; 95% CI, 0.20–0.94). Other study factors were not significant.

Conclusions: Fundus hemorrhages are common among newborns. They often involve multiple areas and layers of the retina. Vaginal delivery was associated with a significantly increased risk of FH, whereas self-identified Hispanic or Latino ethnicity was protective against FH in this study. The long-term consequences of FH on visual development remain unknown. *Ophthalmology 2016;123:1043-1052 © 2016 by the American Academy of Ophthalmology.*

Studies conducted outside of the United States on ethnically homogenous populations report the incidence of birth-related fundus hemorrhages (FHs) to be between 2.6% and 50%.[1–4] The mechanism of increased risk of FH during a vaginal delivery is hypothesized as follows: passage of the head through the canal can cause an acute rise in intracranial pressure that causes stasis of blood flow in the central retinal vein, which then turns into an acute change in pressure of the central retinal artery, and thus may precipitate a hemorrhage.[5,6] Still, not all infants born via vaginal delivery have FH. Therefore, there must be maternal or neonatal factors that remain poorly understood that influence the development of FH at birth.

Little is known about FH at birth because evidence is limited and prospective studies are usually conducted in select populations.[2,7] The studies that have examined FH at birth report that FH are not uncommon at birth, are more frequent among infants delivered via vaginal delivery, and at times can take up to 58 days to resolve completely.[8] No study has performed universal retinal examination on a diverse group of infants such as the United States population. Herein, we present the results of a universal newborn ocular screening initiative conducted in the United States. The study aimed to determine the birth prevalence of FH, to describe risk factors for FH, and to describe the retinal layer, location, characteristics, and laterality of FH. We hypothesized that FH is present in a large proportion of otherwise healthy newborns and that vaginal delivery increased the odds of FH.

Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ophtha.2016.01.004
ISSN 0161-6420/16

Methods

Study Design

The Newborn Eye Screen Testing (NEST) study was a prospective institutional cohort study conducted at Lucile Packard Children's Hospital (LPCH) at Stanford University School of Medicine. It was designed to determine the birth prevalence of ophthalmic disease and the long-term vision outcomes of newborns with ocular abnormalities identified at birth. Universal newborn screening with retinal image photography was offered to all infants born at LPCH who do not undergo retinopathy of prematurity (ROP) screening. A pediatric vitreoretinal specialist (D.M.M.) reviewed images sent to the Byers Eye Institute telemedicine reading center. Parents were notified within 48 hours of any abnormal screenings. Baseline demographic, maternal, obstetric, delivery, and newborn characteristics were recorded for each subject. In this article, we report the 1-year birth prevalence, characteristics, and associated risk factors for FH among newborns screened in the NEST study during the first year of enrollment.

Ethical Considerations

The Institutional Review Board and Ethics Committee at Stanford University School of Medicine prospectively approved this study (Institutional Review Board no. 25098). Informed consent was obtained from all subjects participating in NEST screening, and the study was conducted in a Health Insurance Portability and Accountability Act (HIPAA)-compliant fashion. All research adhered to the tenets of the Declaration of Helsinki.

Operational Logistics

Lucile Packard Children's Hospital is one of only a few hospitals offering quaternary care in Northern California. It captures an ethnically, geographically, culturally, and socioeconomically diverse patient population. The hospital has 3 levels of newborn care: the well-baby nursery, the intermediate care nursery, and the neonatal intensive care unit. All infants who did not qualify for ROP examination were considered eligible for screening.

At Stanford, a telemedicine infrastructure is in place for the Stanford University Network for the Diagnosis of Retinopathy of Prematurity initiative that screens premature infants for ROP. The NEST study used the same network with a separate database routed to a central reading center at Byers Eye Institute. Infants who did not require ROP screening were offered screening with the NEST study. For those who agreed to participate, images were obtained, stored electronically, and forwarded via a HIPAA-compliant, encrypted, secure image server to the reading center. One pediatric vitreoretinal specialist (D.M.M.) then interpreted these images. Parents were contacted within 48 hours of screening if the examination warranted ophthalmic referral.

Patients and Study Population

Selection of subjects for the study aimed to maximize the study's external and internal validity by using a large, tertiary referral center drawing from an ethnically, racial, and socioeconomically diverse patient population. The target population was all newborns in the United States who were 37 weeks' postmenstrual age or older. The source population was all infants born at LPCH. The eligible population was all infants born at LPCH weekdays excluding holidays who were deemed stable for retinal image photography examination by their attending pediatrician at morning rounds. The study sample represented subjects whose parent and pediatrician consented to the study and who completed the screening procedure.

Inclusion criteria were all live infants born at LPCH who were 37 weeks' postmenstrual age or older from July 25, 2013, through July 25, 2014. Exclusion criteria were patients who were bilaterally anophthalmic, patients whose images or medical charts were not available for review, patients with infectious conjunctivitis (risk of transmission via camera contact lens), and patients deemed too unstable for examination by their attending pediatrician. Informed consent and HIPAA forms included risks, benefits, and alternatives, which were discussed thoroughly with parents before obtaining consent for screening. The consent process was conducted in the parent's preferred language using translators when necessary. The screening was offered free of charge to all parents. For subjects who declined screening, a brief questionnaire about their demographics, delivery method, and reasons for not participating was administered. No standard treatment was withheld or delayed for the purposes of this study.

Photography Protocol

The RetCam III (Clarity Medical Systems, Pleasanton, CA) was used to obtain wide-angle images of all infants enrolled in the NEST study. A neonatal intensive care unit−certified nurse was trained before initiating screening. First, Clarity Medical Systems provided RetCam III training by a certified ophthalmic photographer using both mannequins and live infants. There the nurse was observed and corrected on technique for capturing high-quality images and managing potential adverse outcomes. Second, the nurse was trained by the overseeing vitreoretinal specialist (D.M.M.) to obtain photographs of adequate quality and proper retinal views for physician reading.

Parents and nursing staff assisted in positioning the newborn during screening. Parents were encouraged to swaddle infants and to offer nonnutritive sucking during the examination, and if necessary, nursing staff provided oral sucrose solution to agitated infants before the examination. These interventions have been shown to reduce infant pain profiles during ophthalmic screening.[9,10] Subjects' eyes were dilated with 2.5% phenylephrine and 1% tropicamide 30 to 60 minutes before examination. Feedings were discontinued 2 hours before and after examination, in keeping with aspiration precaution guidelines. Infants were evaluated continuously during the examination for signs of apnea or distress. A topical anesthetic 0.5% proparacaine was administered in each eye before examination. A sterile lid speculum was used to open the eye and provide adequate exposure for photography. To couple the digital camera lens to the infant's cornea, 2.5% hydroxypropyl methylcellulose was used. Digital images were obtained by the nurse and were stored on the RetCam III computer hard drive as well as input into the NEST study telemedicine database management system via automated, HIPAA-compliant synchronization.

The goal was to obtain at least 6 clearly focused images in each eye and 1 external image of the face using the 130° lens (Fig 1A): (1) iris image, (2) optic nerve centered, (3) optic nerve superior, (4) optic nerve inferior, (5) optic nerve nasal, and (6) optic nerve temporal. After screening, the infant was observed by the neonatal intensive care unit nurse for any adverse outcomes. In accordance with the current standard for red reflex screening, all screenings were performed before hospital discharge (mean, 45.0 hours; range, 11.6−103.3 hours). In general at LPCH, newborns are hospitalized for 48 hours after vaginal birth and 72 hours after cesarean section. Therefore, an effort was made to screen newborns within 48 hours after vaginal delivery and within 72 hours after cesarean delivery. The nursing staff did not obtain images during weekends.

Data Collection and Management

Retinal images were reviewed at the Byers Eye Institute telemedicine reading center, and a pediatric vitreoretinal specialist (D.M.M.)

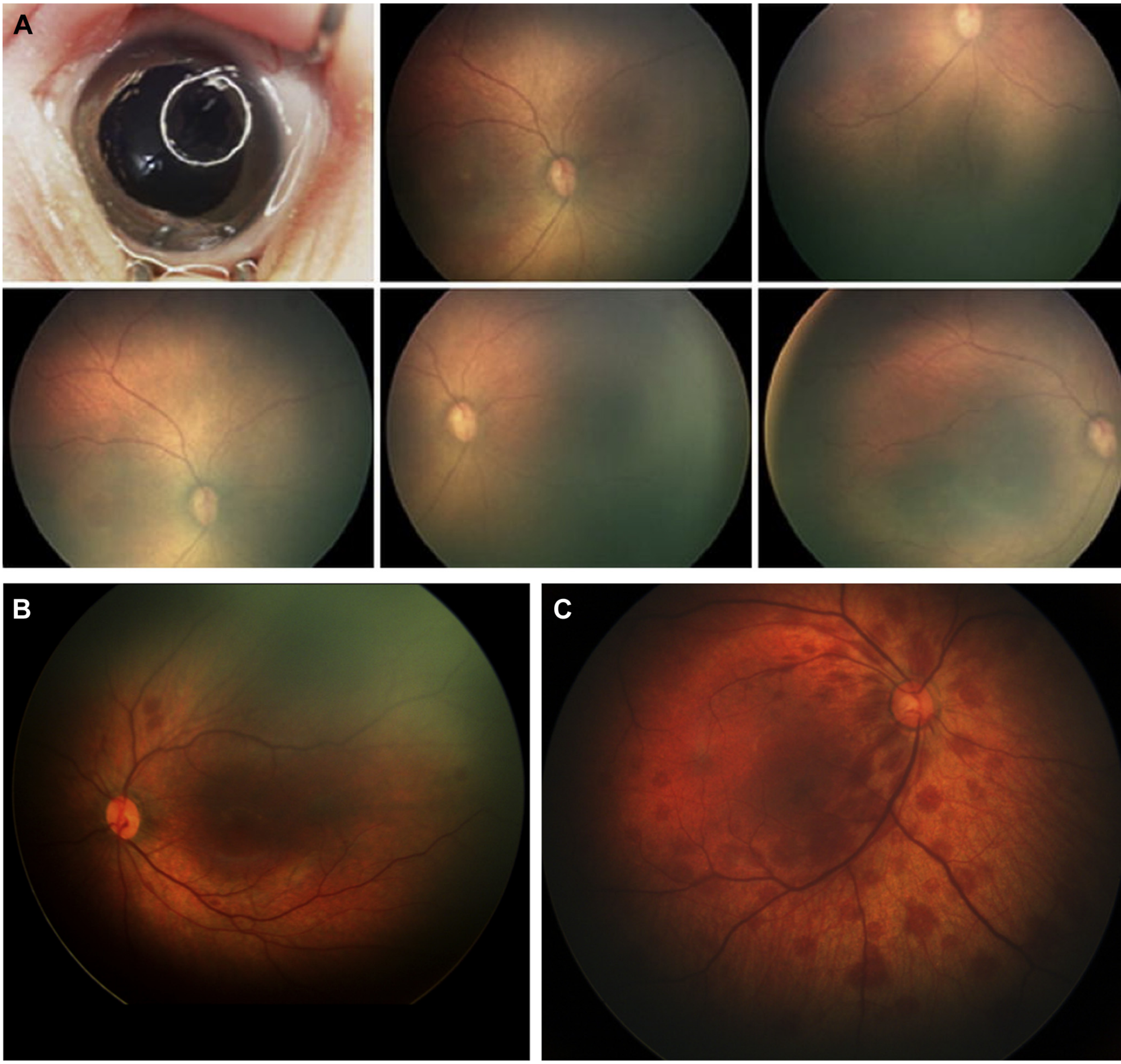

Figure 1. Images showing normal and pathologic examination results. **A**, Normal results: (1) iris image, (2) optic nerve centered, (3) optic nerve superior, (4) optic nerve inferior, (5) optic nerve nasal, and (6) optic nerve temporal. **B**, Macular and extra macular hemorrhages sparing the fovea. **C**, Extensive bilateral retinal hemorrhages.

recorded data in the HIPAA-compliant, encrypted, REDCap server.[11] Image review included ascertainment of external (facies) structures in addition to the standard ophthalmic examination that included eyelids, orbit, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens, vitreous, macula, retina and vessels, and the optic nerve, as they are seen on retinal image photography. Attempts to contact the parents via secure healthcare messaging, phone call, or both about any abnormalities requiring ophthalmic referral were performed within 48 hours of screening.

The examiner collected the following information: gender, self-identified ethnicity (Hispanic or Latino vs. not), and recruitment in English (yes vs. no). The following factors were collected via chart review of hospital notes after subject enrollment and were unknown to the examiner: mother's first baby (yes vs. no), parity (number), age at screening (hours), maternal age (years), birth weight (grams), delivery method (vaginal vs. cesarean section), instrumentation (any forceps or vacuum assist during vaginal delivery), gestational age, Apgar score, and time of rupture of membranes (minutes). Maternal age was classified as advanced when the mother was 35 years of age or older, and birth weight was low when the infant weighed less than 2500 g. Early screening was defined as screening before 48 hours of age. Instrumentation was any use of forceps or vacuum during delivery.

Outcomes

The primary outcome in this study was the birth prevalence of FH. Fundus hemorrhage included hemorrhages in the retina, macula, fovea, or optic nerve. Birth prevalence was calculated as the number of cases at birth over the number of subjects screened during the study period. Secondary aims were to assess the rate of adverse events in the study; to determine the maternal, obstetric, and neonatal risk factors for FH in the study population; and to describe the location, laterality, and morphologic features of FH. Fundus hemorrhage characteristics were reported by pathologic features noted (not by subject), including layer, solitary versus multiple, description (i.e., white-centered), and location.

Statistical Analysis

All data were analyzed using Statistical Analysis Software Enterprise Guide version 6.1 (SAS Institute, Cary, North Carolina). Variables were tested for normality with the Kolmogorov-Smirnov test to assess for outliers and to determine the appropriate statistical test. Crude bivariate (unadjusted) testing was used to compare the cohort with and without FH. Exposure variables were excluded if they were missing and missing variables comprised less than 10% of the sample. There were no missing outcome data.

Multivariate logistic regression modeling was performed to calculate the odds ratio (OR) and 95% confidence interval (CI) as measures of the association between FH and each potential risk factor. Because the OR is less intuitive and can exaggerate the effect of an association, a previously published conversion formula was used to calculate the relative risk.[12] All FHs in modeling were reported according to newborn (i.e., whether the subject had any FH in either eye) unless otherwise noted. Those undergoing cesarean section served as the reference category for all comparisons related to delivery method. We considered screening before 2 days of age, self-identified ethnicity, low birth weight, parity, and maternal age as potential confounders based on literature review and our crude bivariate comparisons. The final model contained terms for delivery method, self-identified ethnicity, screening before 2 days of age, and low birth weight. All statistical tests had a 2-tailed α of 0.05.

Results

Eligible Study Population

During the 1-year study period, 830 newborns who met inclusion criteria for NEST study participation were approached. The approached study population was 53.7% male and included 33 sets of twins and 3 sets of triplets. Thirty-one percent of approached mothers self-identified as Hispanic or Latino, and self-identified race was reported as 52.2% white or Caucasian, 41.0% Asian, 4.3% Native Hawaiian or other Pacific Islander, and 2.6% African American or black. Study recruitment was performed in English 88.0% of the time. Other languages included Spanish, Arabic, French, Mandarin, and Portuguese. The newborn was the mother's first baby 45.9% of the time, and the delivery method was cesarean section 41.6% of the time.

Screened Population

Two hundred two subjects (403 eyes; 1 eye was not visualized) participated in the NEST study screening, for a participation rate of 24.3%. Overall, the screened population had an average birth weight of 3318 g (range, 2010−4510 g) that included 6.4% of infants who qualify as being of low birth weight (<2500 g). One hundred thirty-one infants were screened less than 48 hours after birth and 71 infants were screened 48 hours or more after birth. Maternal age ranged from 16 to 48 years of age, with a median of 32.0 years at delivery. The most common indications for cesarean section were repeat cesarean delivery (22.4%), elective (18.4%), and arrested labor (17.1%).

Screened vs. Unscreened Cohort

The screened cohort was 47.5% female (difference between 2 cohorts by gender, $P = 0.79$), 50% of those screened were the mother's first baby ($P = 0.18$), and there was no significant difference in the percentage of recruitment that was carried out in English between the 2 cohorts (87.6% screened in English vs. 88.2% declined screening in English, $P = 0.80$). There was no statistically significant difference in delivery method (vaginal vs. cesarean section) between the 2 cohorts, with 61.9% of screened participants having a normal spontaneous vaginal delivery and 57.3% of unscreened individuals with a normal spontaneous vaginal delivery ($P = 0.25$). There was a statistically significant difference ($P = 0.0001$) in the ethnic composition of the screened and unscreened cohorts, with significantly more families who self-identified as Hispanic or Latino participating in screening (117/451; 32.9%) compared with those who self-identified as not being Hispanic or Latino (84/255; 20.1%) There was also a significant difference in screening among families with multiple births, specifically triplets, because the parents of all 3 sets of triplets consented to screening, whereas none of the parents declined. There was no significant difference in screening rates among single and twin births.

The most common reasons why individuals chose not to participate in screening were: "Don't want to bother baby," "Believe it is not necessary for the child," and "Concern about adverse effects." Other less common reasons for declining screening included "Do not want to wait for screening" and "Mom too tired."

Fundus Hemorrhages

Among the 202 subjects screened during the 1-year study period, 41 subjects had an FH; thus, the birth prevalence of FH was 20.3%. Table 1 compares baseline characteristics and previously reported risk factors for FH between the cohorts with and without any FH. There was no statistically significant difference in the gender, recruitment language, mother's parity, advanced maternal age (>35 years), birth weight (low birth weight binary and continuous), or location (neonatal intensive care unit vs. well-baby nursery) between the screened and unscreened cohorts, all with P values of more than 0.10. There was a significant difference in the rate of FH by delivery method. Among infants delivered by vaginal delivery, 29.6% (37/125) had FH versus 5.2% (4/77) among those born via cesarean section (OR, 7.67; 95% CI, 2.61−22.53; $P < 0.0001$). When evaluating vaginal delivery forms (normal spontaneous vaginal delivery, forceps, vacuum), there was a very small sample size; however, there were increased odds of FH that was statistically significant among those delivered via instrumentation (forceps or vacuum assisted) when compared with subjects delivered via normal spontaneous vaginal birth ($P = 0.01$). Age at time of screening (in hours) was statistically significant ($P = 0.04$ when continuous, $P = 0.02$ when binary). Of the total reported, 80.5% (33/41) of FH were among infants screened within the first 2 days of life. Finally, self-identified ethnicity approached statistical significance, where 29.3% (12/41) of infants with FH had parents who identified as Hispanic or Latino as opposed to 45.0% (72/160) among the cohort who did not have FH ($P = 0.07$).

Fundus Hemorrhage Characteristics

A matrix of the retinal layer (or optic nerve) characteristics of all FH is shown in Table 2. Fundus hemorrhages most often were optic nerve flame hemorrhages (48.3%; 98/203), followed by

Table 1. Birth Prevalence of Fundus Hemorrhages (by Subject) by Baseline Characteristics in the Newborn Eye Screen Testing Study

Characteristic	No Fundus Hemorrhage (79.7%; n = 161)	Fundus Hemorrhage (20.3%; n = 41)	Odds Ratio (95% Confidence Interval)	Unadjusted *P* Value
Gender, % (no.)				0.22
Male	50 (81)	61 (25)	0.65 (0.32–1.30)	
Female	50 (80)	39 (16)	1.0	
Self-identified ethnicity, % (no.)				0.07
Hispanic or Latino	45 (72)	29 (12)	0.51 (0.24–1.06)	
Not Hispanic or Latino	55 (88)	71 (29)	1.0	
Recruitment in English, % (no.)				0.79
Yes	87 (139)	90 (37)	1.40 (0.52–4.32)	
No	13 (21)	10 (4)	1.0	
Mother's first baby, % (no.)				0.12
Yes	47 (76)	61 (25)	1.75 (0.87–3.52)	
No	53 (85)	39 (16)	1.0	
Age at screening (hrs), mean (SD)	46.3 (20)	39.7 (11)	0.98 (0.96–1.00)	0.17
Screening before 2 days of age (hrs)				0.02
<48	61 (98)	80 (33)	2.65 (1.15–6.11)	
48+	39 (63)	20 (8)	1.0	
Advanced maternal age (≥35 yrs)				0.77
Yes	29 (47)	27 (11)	0.89 (0.41–1.92)	
No	71 (114)	73 (30)	1.0	
Low birth weight (<2500 g), % (no.)				0.73
Yes	6 (10)	7 (3)	1.19 (0.31–4.55)	
No	94 (151)	93 (38)	1.0	
Delivery method, % (no.)				<0.001
Vaginal	55 (88)	90 (37)	7.67 (2.61–22.53)	
Cesarean section	45 (73)	10 (4)	1.0	
Vaginal delivery only, % (no.)				0.01†
Instrumentation	6 (5)	16 (6)	5.35 (1.54–18.52)*	
Forceps	1 (1)	0 (0)	N/A	
Vacuum assisted	5 (4)	16 (6)	6.69 (1.79–24.96)	
Normal spontaneous	94 (83)	84 (31)	1.0	

SD = standard deviation.
Fundus hemorrhage is reported by participant (i.e., a retinal hemorrhage in 1 or both eyes qualifies a newborn has having a retinal hemorrhage). Fundus hemorrhages included hemorrhages of the retina, macula, fovea, and optic nerve. Newborns who met retinopathy of prematurity screening criteria were excluded from the Newborn Eye Screen Testing study because they were screened by another telemedicine initiative targeting retinopathy of prematurity detection. Forceps delivery was not included in a separate analysis because there was only 1 subject delivered this way. Percentages may not add up to 100 because of rounding.
*Normal spontaneous vaginal delivery was used as a reference in determining the odds ratio for instrumentation (forceps and vacuum assisted combined) as well as forceps and vacuum-assisted deliveries individually.
†Instrumentation versus normal spontaneous vaginal delivery.

white centered (30.0%; 61/203). By location, retinal hemorrhages were distributed throughout the eye most often in all 4 quadrants (35.2%; 37/105). By location, optic nerve flame hemorrhages were detected most often temporally (34%; 33/98) and nasally (32%; 31/98). There were no vitreous hemorrhages found during screening.

Macular and Foveal Hemorrhages

Macular hemorrhages are reported by layer of retina and whether they affect the fovea. A matrix of macular hemorrhage characteristics by retinal layer, solitary versus multiple, and foveal versus extrafoveal is shown in Table 3. A total of 34 of 202 subjects (16.7%) had a macular hemorrhage (82.9% of all FH) in at least 1 eye, with 11 subjects having a left macular hemorrhage and 5 with a right macular hemorrhage. Eighteen subjects had bilateral macular hemorrhages. Most macular hemorrhages detected at birth were intraretinal (40.0%; 38/95), extrafoveal (93.7%; 89/95), and multiple (85.4%; 76/89). Overall birth prevalence of foveal hemorrhage was 3.0% (6/202).

Laterality and Location of Fundus Hemorrhage

Figure 2 summarizes the laterality and location of FH detected during the 1-year study period in the NEST study. Of the 41 newborns found to have any hemorrhages, 70.7% (29/41) were found to have multilaminar hemorrhages, 41% (12/29) of which were bilateral. Furthermore, 95.1% (39/41) of hemorrhages included the peripheral retina and 82.9% (34/41) affected the macula. Only 14.6% (6/41) of hemorrhages affected the fovea, and overall, FH affected the left fovea (5/6) more often than the right fovea (1/6). There were no bilateral cases of foveal hemorrhage.

Logistic Regression Modeling

Based on crude bivariate analyses and review of the available literature, the following variables were assessed as possible risk factors in regression modeling: delivery method, screening before 48 hours after birth, self-identified ethnicity, low birth weight, parity, and maternal age. The final multivariate model is shown in

Table 2. A: Location and Layer of All Retinal Hemorrhages Detected in 41 Newborns with Unilateral or Bilateral Retinal Hemorrhages

All Retinal Hemorrhages (n = 105)*	Inferior (19%; n = 20)	Nasal (22%; n = 23)	Superior (22%; n = 23)	Temporal (2%; n = 2)	360° (35%; n = 37)
Preretinal (3%; n = 3)	1 solitary, 0 multiple	1 solitary, 0 multiple	0	0	0 solitary, 1 multiple
Intraretinal (10%; n = 11)	2 solitary, 2 multiple	2 solitary, 1 multiple	3 solitary, 1 multiple	0	0
Subretinal (29%; n = 30)	1 solitary, 3 multiple	4 solitary, 1 multiple	4 solitary, 4 multiple	1 solitary, 0 multiple	0 solitary, 12 multiple
White centered (58%; n = 61)	4 solitary, 7 multiple	7 solitary, 7 multiple	3 solitary, 8 multiple	1 solitary, 0 multiple	0 solitary, 24 multiple

B: Location of All Optic Nerve Flame Hemorrhages Detected in 28 Newborns with Unilateral or Bilateral Optic Nerve Flame Hemorrhages

	Inferior	Nasal	Superior	Temporal
Optic nerve flame hemorrhage (n = 98)	14% (n = 14)	32% (n = 31)	20% (n = 20)	34% (n = 33)

*Forty-one infants were noted on universal newborn screening with wide-angle digital photography to have retinal hemorrhages on image review. Findings from all reported types of hemorrhages in either eye are included in this total. Infants can have multiple pathologic features reported per eye.

Table 4. Vaginal delivery significantly increased the odds of FH (OR, 9.34; 95% CI, 2.5−33.97). Screening before 48 hours after birth and low birth weight were not significant in the model. Parity and maternal age were not significant and were not included in the model. Self-identified ethnicity as Hispanic or Latino was protective against FH (OR, 0.428; 95% CI, 0.2−0.94). The OR also was converted to the more intuitive risk ratio using the previously published methodology for this conversion based on the prevalence of the disease among the reference cohort for each variable.[12]

Adverse Outcomes

There were no episodes of clinically significant bradycardia, allergic reactions to drops, or corneal abrasions evident after screening or reported to the study team at discharge. No infants in the 1-year cohort have returned to the LPCH Department of Pediatric Ophthalmology for evaluation of possible corneal abrasion or any other screening-related issue after NEST study participation.

Table 3. Characteristics Matrix of All Macular Hemorrhages Detected in 34 Infants in the Newborn Eye Screening Test Study during the First Year of Screening

Retinal Layer in the Macula	Location and Distribution of Hemorrhage in the Macula (Total n = 95)	
	Extrafoveal (n = 89)	*Foveal (n = 6)*
Preretinal (0.02%; n = 2)	0.1% (0 solitary, 1 multiple)	17% (1)
Intraretinal (40%; n = 38)	38% (5 solitary, 29 multiple)	66% (4)
Subretinal (28%; n = 27)	29% (5 solitary, 21 multiple)	17% (1)
White centered (29%; n = 28)	31% (3 solitary, 25 multiple)	0% (0)

Thirty-four infants were noted on universal newborn screening with RetCam III wide-angle digital photography to have macular hemorrhages on image review. Findings from all reported locations of macular hemorrhages in either eye are reported above. Infants may have multiple pathologic features reported per eye.
Percentages may not add up to 100 due to rounding.

Discussion

This article presents the 1-year results of the first universal retinal image screening performed in healthy term infants in the United States. The birth prevalence of FH among the newborns screened during the first year of enrollment in the NEST study at LPCH at Stanford University was 20.3% (41/202). The birth prevalence of multilaminar hemorrhages was 14.4% (29/202), and the birth prevalence of foveal hemorrhages was 3.0% (6/202). The rate of FH reported in this study is similar to that reported in studies conducted in other populations.[1−4,8,13,14] However, the presence of multilaminar and white-centered retinal hemorrhages in otherwise healthy term newborns is novel.

Secondary aims of this study were to compare the cohort with and without FH on maternal, obstetric, and neonatal characteristics to understand better the risk factors for FH at birth. Furthermore, we aimed to enrich our understanding of the characteristics, laterality, and descriptive appearance of birth-related FH. Hemorrhages found in healthy term newborns varied from isolated optic nerve hemorrhages to hemorrhages involving the macula (Fig 1B), to extensive FH bilaterally (Fig 1C). When comparing the cohorts on previously reported risk factors, we found an unadjusted difference in the frequency of FH by delivery method ($P < 0.0001$) and by whether instrumentation was used during a vaginal delivery ($P = 0.01$). We also found that early screening was significant ($P = 0.02$) and that self-identified Hispanic or Latino ethnicity approached significance ($P = 0.07$), as shown in Table 1. We used these data and previously described risk factors such as maternal age and low birth weight as possible predictors in a multivariate model.

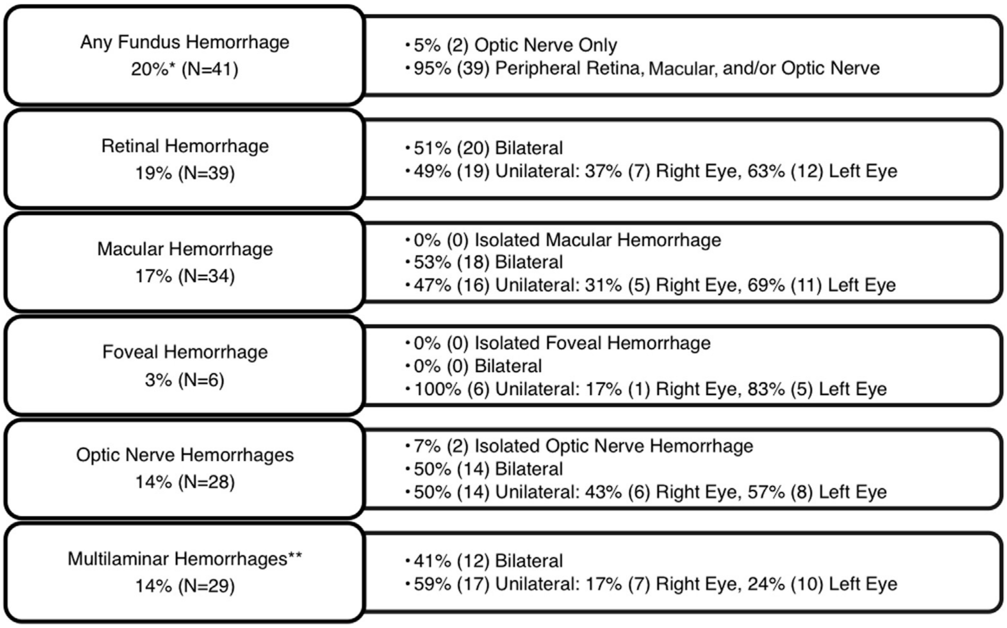

Figure 2. Flow chart showing the laterality and location of fundus hemorrhages noted in the Newborn Eye Screen Testing study at 1 year of enrollment by subject. *Includes optic nerve hemorrhages. **Includes 2 or more of the following: preretinal hemorrhage, intraretinal hemorrhage, subretinal hemorrhage, and optic nerve hemorrhage.

The final multivariate regression model (Table 4) included delivery method, screening before or after 48 hours of age, self-identified ethnicity, and low birth weight. Maternal age and the other study variables were not included because they were not significant in crude comparisons or in other studies.[13,15–18] The model demonstrated a significant increase in the odds (OR, 9.34; 95% CI, 2.57–33.97; $P < 0.001$) of FH among infants delivered via vaginal delivery after controlling for the other variables in the model. After accounting for the underlying prevalence of the condition in the unexposed population, we found that vaginal delivery significantly increased the risk of FH 6.1 fold when compared with newborns delivered by cesarean section. Unfortunately, there were insufficient case counts to include instrumentation in a model; however, we suspect that any instrumentation further increases the odds of FH, given that 72.7% of infants who underwent vaginal delivery with instrumentation had an FH ($P = 0.01$).

A surprising finding in this study was the significant difference in the risk of FH by ethnicity, with self-identified Hispanic or Latino ethnicity conferring a protective effect or a reduction of risk by approximately 56% for FH. This

Table 4. Multivariate Logistic Regression for Retinal Hemorrhage at Birth*

Variable	Odds Ratio*	Risk Ratio†	95% Confidence Interval for Odds Ratio
Delivery method			
Vaginal	9.344	6.075	2.570–33.967
Cesarean section	1.0 (reference)	1.0 (reference)	—
Self-identified ethnicity, % (no.)			
Hispanic or Latino	0.428	0.444	0.195–0.939
Not Hispanic or Latino	1.0 (reference)	1.0 (reference)	—
Screening before 2 days of age (hrs)			
<48	1.001	1.001	0.337–2.971
48+	1.0 (reference)	1.0 (reference)	—
Low birth weight (<2500 g), % (no.)			
Yes	2.237	2.072	0.462–10.837
No	1.0 (reference)	1.0 (reference)	—

— = n/a.
Multivariate logistic modeling based on crude bivariate analysis of baseline maternal, obstetric, and neonatal characteristics. Maternal age and time of rupture of membranes were not significant in initial modeling and were not included in the final multivariate model. Vaginal delivery includes both normal spontaneous delivery and instrumentation because there were too few cases of instrumentation to perform separate modeling.
*All variables adjusted for delivery method, self-identified ethnicity, screening before 2 days of age, and presence of low birth weight.
†Based on a prevalence of 6.5% of retinal hemorrhage among babies delivered by cesarean section who were not low birth weight, not screened before 2 days after birth, and did not identify as Latino or Hispanic. Odds ratio was converted to risk ratio using previously described methodology for cohort studies.

effect held after controlling for the other variables in the model. This finding has never been reported in the literature because no study, to these authors' knowledge, has evaluated ethnicity and its relationship to FH. There may be ethnic factors that affect the maternal pelvic diameter, fetal head circumference, or vessel elasticity that reduce the rate of FH among Hispanic or Latino populations; however, we were unable to discern this information using our current study design. Of note, the distribution of delivery types by ethnicity were similar, with Hispanic or Latino populations undergoing vaginal delivery 67% of the time compared with 59% among non-Hispanic Latinos. Although evaluating for possible effect modification, an interaction term of ethnicity by delivery method was included in a separate model; however, this term was not significant ($P = 0.13$). Thus, there was no evidence of multiplicative interaction. There was a statistically significant difference in the rate of enrollment in the study by ethnicity, with Hispanics and Latinos more commonly being screened. Therefore, there may be selection bias that could be affecting the data. Nevertheless, this finding warrants further investigation.

Importantly, FH in a young infant can be the result of head trauma or could be secondary to birth-related FH. A better understanding of the typical characteristics of both patterns can help the clinician discern the cause of the hemorrhage. Among the 41 infants with FH, most had hemorrhages in multiple parts of their retina, and most retinal hemorrhages were found in all 4 quadrants (35.2% [37/105]; Fig 2). This picture is seen commonly with nonaccidental trauma and Terson syndrome, 2 disease processes commonly associated with intracranial injury.[19−23] This is the first prospective analysis to document the multilaminar hemorrhage nature of FH in a consecutive-term, healthy population. Overall, 70.7% (29/41) of FH involved 2 or more layers of the eye. Approximately half of infants with a retinal or macular hemorrhage had bilateral hemorrhages, consistent with prior studies on birth-related FH.[14] Among infants with unilateral hemorrhage, left-sided hemorrhages were far more common. We suspect this is because the left occiput anterior presentation is the most common, in which the left eye may press against the sacrum during delivery and is most likely to experience rapid pressure changes through the birth canal. For the same reason, the left eye is also the most likely be affected by injury or pressure when instrumentation is used.

When looking at all FH (Table 2A, B), this study found that optic nerve flame hemorrhages (48.3%; 98/203) and white-centered retinal hemorrhages (30.2%; 61/203) were the most common types of FH. Also known as "Roth spots," white-centered hemorrhages were associated first with subacute bacterial endocarditis and infection.[24] However, white-centered hemorrhages also may arise from focal ischemia, an inflammatory infiltrate, or an accumulation of fibrin and platelets or neoplastic cells.[1,25] They have been associated with complicated labor and delivery as well as nonaccidental trauma.[26] Herein we report the presence of white-centered hemorrhages in otherwise healthy term newborns.

Table 3 isolates macular hemorrhages because we suspect these have the greatest potential for obscuring the visual axis and potentially affecting vision later in life. Of subjects with birth-related FH, 82.9% (34/41) had hemorrhage that involved the macula. Among macular hemorrhages, 6 subjects had foveal hemorrhage and no subject had bilateral foveal hemorrhages. Hemorrhages that involved the macula more often were intraretinal (40.0%; 38/95) and most commonly were extrafoveal. Macular hemorrhages were mostly multiple, as opposed to solitary (Fig 1B).

The overarching purpose of the NEST study was to describe the birth prevalence of ocular disease among newborns who otherwise would not have undergone screening by an ophthalmologist until they reached school age. The long-term goals of the study were to determine the incidence and risk factors for amblyopia, a leading cause of monocular vision impairment among children and young adults.[27−30] Vision loss resulting from amblyopia can have long-lasting adverse effects on school performance, social interactions, motor tasks, and confidence.[31−35] Because vision development continues after birth, we hypothesize that any obstruction to the visual axis that persists for a sufficient period can induce amblyopia that is found later in the child's life as either strabismic or idiopathic amblyopia. This is in contrast to published literature reporting that retinal hemorrhages are benign, self-resolving conditions.[1] The studies evaluating the resolution of hemorrhages demonstrate that most resolve within 10 days, but studies also include patients with more severe hemorrhages that persist for many weeks.[8,13] These slow-resolving hemorrhages could obstruct the visual axis during the critical period and ultimately may lead to deprivational amblyopia without ophthalmoscopic findings later deemed idiopathic.

Currently, we are unable to evaluate this hypothesis because we do not have longitudinal data for the subjects in this study. Most patients continue their outpatient well-child and ophthalmic care in other healthcare systems. This represents the greatest limitation of this study. Other limitations include a potential difference in enrollment by ethnicity as discussed previously, and obtaining information from patient records retrospectively. Strengths of this study are that this is the first study in the United States to enroll infants prospectively who otherwise would not have undergone ophthalmic screening. This study is the first to present differences by ethnic composition, to the authors' knowledge. This study also highlights the multilaminar nature of FH in a normal-term population, something previously associated with nonaccidental trauma and Terson syndrome in infants. Furthermore, with the support of our research and hospital team, we were able to use translation services to maximize diverse enrollment. Unlike other studies, we did not exclude infants unless they were potentially infectious, unstable, or anophthalmic. Other studies exclude infants with systemic disease. The NEST study aimed to capture the unscreened newborn population.

The next phase of this study is to determine the long-term vision outcomes of patients with various types of FH and to determine the incidence of amblyopia among those with and without FH at birth. If slow-resolving hemorrhages are obstructing the visual axis during the critical period and causing a deprivational amblyopia, then we could identify them at birth, rather than during school screening.[36]

Although there is no treatment for FH, early intervention for deprivational or strabismic amblyopia detected with patching, cycloplegics, and correcting refractive errors would optimize the child's vision potential, because these interventions have been shown to improve outcomes.[37–39] Thus, early identification of birth-related FH may offer the opportunity to identify potentially modifiable disease that could affect the child's vision potential.

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Footnotes and Financial Disclosures

Originally received: November 10, 2015.
Final revision: January 1, 2016.
Accepted: January 5, 2016.
Available online: February 11, 2016. Manuscript no. 2015-1993.

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Presented at: Association for Research in Vision and Ophthalmology Annual Meeting, May 2015, Denver, Colorado.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by the Giannini Foundation (San Francisco, CA); and the Spectrum TL1 Clinical Research Training Program at Stanford University (Palo Alto, CA); supported by the National Institutes of Health (Bethesda, MD) (grant no.: TL1 TR 001084 [N.F.C., C.A.L.]). The sponsor or funding organization had no role in the design or conduct of this research. The database for the project described was supported by the National Center for Research Resources and the National Center for Advancing Translation Sciences, National Institutes of Health (grant no.: UL1 RR025744). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Abbreviations and Acronyms:
CI = confidence interval; **FH** = fundus hemorrhage; **HIPAA** = Health Insurance Portability and Accountability Act; **LPCH** = Lucile Packard Children's Hospital; **NEST** = Newborn Eye Screen Testing; **OR** = odds ratio; **ROP** = retinopathy of prematurity.

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