The impact of the COVID-19 lockdown on retinopathy of prematurity screening and management in the United States: a multicenter study

Shefali Sood, MD,[a] Mina M. Naguib, MD,[a] David S. Portney, MD,[b] Cagri G. Besirli, MD, PhD,[b] Cole A. Martin, BS,[c] C. Armitage Harper III, MD,[c,d,e] Maria P. Fernandez, MD,[f] Audina M. Berrocal, MD,[f] Polly A. Quiram, MD, PhD,[g] Peter Belin, MD,[g] Noreen Clarke, DNP, DN,[h] Aaron Nagiel, MD, PhD,[h,i] Melissa Chandler, BS,[j] Christopher Bair, MD,[j] M. Elizabeth Harnett, MD,[j] and Vaidehi S. Dedania, MD[a]

PURPOSE To study the effect of the pandemic-related lockdown (physical distance measures and movement restrictions) on the characteristics and management of retinopathy of prematurity (ROP).

METHODS In this controlled, multicenter cohort study, the medical records of patients born prematurely and screened for ROP in the neonatal intensive care unit during four time periods were reviewed retrospectively: (1) November 1, 2018, to March 15, 2019; (2) March 16, 2019, to August 2, 2019 (lockdown control period); (3) November 1, 2019, to March 15, 2020; and (4) March 16, 2020-August 2, 2020.

RESULTS A total of 1,645 patients met inclusion criteria. Among the 1,633 patients with complete data, mean gestational age (GA) at birth was 28.2, 28.4, 28.0, and 28.3 weeks across time periods 1 to 4, respectively ($P = 0.16$). The mean birth weight of all patients was 1079.1 ± 378.60 g, with no significant variation across time periods ($P = 0.08$). There were fewer patients screened during the lockdown period (n = 411) compared with the period immediately before (n = 491) and the same period in the prior year (n = 533). Significantly more patients were screened using indirect ophthalmoscopy, compared to digital imaging (telemedicine), during the lockdown ($P < 0.01$). There were 11.7%, 7.7%, 9.0%, and 8.8% of patients requiring treatment in each time period, respectively ($P = 0.42$), with a median postmenstrual age at initial treatment of 37.2, 36.45, 37.1, and 36.3 weeks, respectively ($P = 0.32$).

CONCLUSIONS We recorded a decrease in the number of infants meeting criteria for ROP screening during the lockdown. The GA at birth and birth weight did not differ. Significantly more infants were screened with indirect ophthalmoscopy, compared to digital imaging, during the lockdown. (J AAPOS 2023;27:137.e1-6)

The coronavirus disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), beginning in January 2020, presented a unique cultural shift in which strict social distancing and government-mandated lockdowns (physical distance measures and movement

Author affiliations: [a]Department of Ophthalmology, Grossman School of Medicine NYU Langone Health, New York University, New York; [b]Department of Ophthalmology and Visual Sciences, University of Michigan Kellogg Eye Center, Ann Arbor, Michigan; [c]Department of Ophthalmology, Dell Medical School, University of Texas at Austin; [d]Department of Ophthalmology, University of Texas Health, San Antonio, Texas; [e]Austin Retina Associates, Austin, Texas; [f]Department of Ophthalmology/Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami, Florida; [g]VitreoRetinal Surgery, PLLC, Retina Consultants of America,Minneapolis, Minnesota; [h]The Vision Center, Department of Surgery, Children's Hospital Los Angeles, Los Angeles, California; [i]Roski Eye Institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California; [j]Moran Eye Center, University of Utah, Salt Lake City, Utah.

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Correspondence: Vaidehi S. Dedania, MD, Department of Ophthalmology, NYU Langone Health, 222 E 41st Street, 3rd Floor, New York, NY 10017 (email: vaidehi.dedania@nyulangone.org).

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restrictions) were enforced to prevent disease spread. Researchers in Denmark first demonstrated that the rate of premature births decreased significantly during the COVID-19 lockdown as compared to similar time periods in the 5 years prior.[1] This result was corroborated by researchers in Tennessee, who observed lower odds of preterm birth in 2020 during the stay-at-home order.[2] Investigators have offered many possible quarantine-related contributing factors for the decline in premature births, including decreased mobility, increased sleep, more family support, decreased exposure to infectious pathogens, and increased intrauterine fetal demise among others.[2,3] However, other studies in the United States and other countries have reported increases in preterm birth rates associated with lockdown periods.[4,5]

The degree of prematurity and frequency of retinopathy of prematurity (ROP) are directly related, and variations in premature birth rates may affect the incidence or the severity of ROP. In addition, the COVID-19 pandemic significantly affected how providers delivered care for patients in inpatient and outpatient settings.[6] The primary objective of this study was to determine whether the clinical characteristics of patients who met criteria for screening changed during lockdown. Our secondary objective was to characterize the effect of the COVID-19 pandemic on practice patterns of ophthalmologists caring for infants at risk of or diagnosed with ROP.

Subjects and Methods

This is a multicenter, retrospective, observational, cohort study. The approval of the Institutional Review Boards at all participating institutions was obtained prior to the commencement of the study, which was conducted in accordance with the US Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki. This study included infants admitted to the neonatal intensive care unit who were eligible for ROP screening at 7 major academic institutions during the following time periods: (1) November 1, 2018, to March 15, 2019; (2) March 16, 2019, to August 2, 2019 (lockdown control period); (3) November 1, 2019, to March 15, 2020; and (4) March 16, 2020, to August 2, 2020. Time period 4 was selected to represent the beginning of the COVID-19 pandemic and government-mandated lockdown in the United States, when physical distancing, self-isolation, and measures to protect those at high risk (closing schools, many in-person workplaces, and avoiding gatherings of more than 10 people) were instituted. These measures also included avoiding physical contact between physicians and patients, including limiting the frequency and length of contact. Time period 3 was the 5 months immediately prior to the lockdown, and time periods 1 and 2 correspond to time periods 3 and 4, respectively, as controls in the year before, to account for seasonal variation in births. Treatment for ROP was at the treating physician's discretion, and was based on results of the Early Treatment of Retinopathy of Prematurity clinical trial.[7] Data were obtained from the electronic medical record at each institution.

Patient Characteristics

Patients eligible for ROP screening during the specified time periods were included in the study. Criteria for screening included birth before or at 30 weeks' gestational age (GA) or a birthweight ≤1500 g or with an unstable clinical course. ROP screening began for infants at 4-6 weeks after birth or between 31-33 weeks' GA, whichever was later. We collected information on sex, date of birth, GA at birth, birth weight, postmenstrual age (PMA) at the first screen, and screening method (indirect ophthalmoscopy versus digital imaging [this terms is used interchangeably with telemedicine]). For patients requiring treatment, modality of the treatment, severity of ROP at treatment, presence of plus disease and/or aggressive retinopathy, and interval between diagnosis and treatment were included.

Data Analysis

All statistical analyses were conducted using SSPS version 24 (IBM Corp, Armonk, NY). Categorical variables were evaluated using a χ^2 test, and Pearson χ^2 P values were reported. Analysis of variance was performed utilizing a Tukey-Kramer post hoc correction for GA, birthweight, PMA at screen, PMA at first treatment, interval from diagnosis to treatment, and PMA at subsequent treatments. Analyses was performed across all time periods, between each time period, and for institutions providing data for time period 1 (comparison to time period 1 was only performed for the 4 institutions for which data was included, not across all institutions).

Results

A total of 1,645 patients met inclusion criteria. Twelve patients were excluded due to incomplete data. Of the 1,633 remaining patients, 411 patients were screened for ROP from March 16 to August 2, 2020, during the initial months of the COVID pandemic/government shutdown, compared with 491 patients in the immediately preceding months (November 1, 2019, to March 15, 2020), and 533 patients in the corresponding months the previous year (March 16 to August 2, 2019). Data were available for four of the seven sites from November 1, 2018, to March 15, 2019, in which 198 patients were screened.

The mean (with standard deviation) gestational age (GA) at birth of all patients was 28.3 ± 2.87 weeks, which was similar across time periods (P = 0.16). See Table 1. The mean birth weight of all patients was 1079.1 ± 378.60 g, and there was no difference between the time periods (P = 0.08). There were 53.0% male patients, similar across all time periods. The mean birth weight was 1086.5 ± 391.56 g, 1108.0 ± 402.87 g, 1046.4 ± 363.54 g, and 1075.9 ± 354.68 g for time periods 1, 2, 3, and 4, respectively. PMA at time of first screen was 33.5 ± 3.27 weeks, without a difference between any time periods (P = 0.43). See Table 2. Indirect ophthalmoscopy screening by the physician was performed for 85.27% of all patients. The differences in screening modality between time periods 2 and 4 (P < 0.01) and between time periods 3 and 4 were significant (P < 0.01; Table 2), with a larger

Table 1. Baseline characteristics of neonates screened for retinopathy of prematurity in the neonatal intensive care unit across all time periods[a]

Study parameter	All time periods N = 1633	Time period 1[b] n = 198	Time period 2 n = 533	Time period 3 n = 491	Time period 4 n = 411	*P* value[c]
Sex, no. (%)						
Female	761 (47.0)	87 (44.2)	245 (46.9)	218 (44.6)	211 (51.5)	0.17[d]
Male	858 (53.0)	110 (55.8)	278 (53.2)	271 (55.4)	199 (48.4)	
GA, weeks, mean ± SD	28.3 ± 2.87	28.2 ± 3.00	28.4 ± 2.94	28.0 ± 2.75	28.3 ± 2.86	0.16
<28 weeks, no. (%)	701 (42.9)	85 (42.9)	230 (43.2)	221 (45.0)	165 (40.2)	0.54
≥28 weeks, no. (%)	932 (57.1)	113 (57.1)	303 (56.9)	270 (55.0)	246 (59.9)	
<32 weeks, no. (%)	1463 (89.6)	170 (85.9)	470 (88.2)	453 (92.3)	370 (90.0)	0.05
≥32 weeks, no. (%)	170 (10.4)	28 (14.1)	63 (11.8)	38 (7.7)	41 (10.0)	
BW, g, mean ± SD	1079.1 ± 378.60	1086.5 ± 391.56	1108.0 ± 402.87	1046.4 ± 363.54	1075.9 ± 354.68	0.08
<1250 g, no. (%)	1064 (65.2)	130 (65.7)	337 (63.2)	326 (66.4)	271 (65.9)	0.72
≥1250 g, no. (%)	569 (34.8)	68 (34.3)	196 (36.8)	165 (33.6)	140 (34.1)	
<1500 g, no. (%)	1435 (87.9)	175 (88.4)	453 (85.0)	445 (90.6)	362 (88.1)	0.05[e]
≥1500 g, no. (%)	198 (12.1)	23 (11.6)	80 (15.0)	46 (9.4)	49 (11.9)	

BW, birth weight; *GA*, gestational age; *SD*, standard deviation.
[a]Time periods: (1) November 1, 2018, to March 15, 2019; (2) March 16, 2019, to August 2, 2019; (3) November 1, 2019, to March 15, 2020; (4) March 16, 2020, to August 2, 2020 (lockdown period).
[b]Data available for 4/7 institutions.
[c]A *P* value of ≤0.05 was considered significant.
[d]Significant difference between time periods 3 and 4 ($P = 0.04$).
[e]Significant difference between time periods 2 and 3 ($P < 0.01$).

proportion of patients being screened by indirect ophthalmoscopy during the lockdown period. There was no difference between periods 2 and 3.

There was no significant variation in the proportion of infants requiring treatment, the PMA at first treatment, or the treatment modality employed across all time periods. The median PMA at first treatment was assessed (Table 2), because there were outliers that confounded analysis. The range across all periods was 31.6 weeks to 85.1 weeks. The stage of ROP at first treatment was not significantly different between any of the time periods (Table 3). There was significant variation in zone of ROP at first treatment, presence of aggressive ROP (AROP, previously known as aggressive posterior ROP), and presence of plus disease across the time periods (Table 3). However, subgroup analysis comparing time period 4 with time periods 2 and 3 did not show any significant differences for zone of ROP or presence of AROP. Plus disease among treated patients differed between time periods 3 and 4 but not when comparing time periods 2 and 4 to control for seasonal variation. The mean time between diagnosis and treatment was 1.12 ± 1.82 days and was similar across all time periods (Table 2). Finally, there was no difference in PMA at second treatment or treatment modality employed; however, a majority of the second treatments were laser photocoagulation.

Subgroup analysis by institution yielded similar results with few differences. At one site, there was significant variation in PMA at first screen ($P < 0.001$) and use of digital imaging as a screening method ($P < 0.005$) across time periods. At two other sites, there was significant variation in the first treatment modality ($P < 0.05$) and PMA at first treatment ($P < 0.05$) across time periods.

Discussion

The COVID-19 pandemic significantly altered the delivery of healthcare across the world. In the case of ROP, timely screening and treatment are paramount in reducing ocular morbidity and, unlike some other ophthalmic interventions, cannot be safely delayed.[7,8] In most cases, providers adapted accordingly by observing appropriate infection control practices[9] and possibly utilizing digital imaging which according to some studies was found to be both safe and feasible for ROP screening.[10,11] Other obstacles to ROP evaluation and treatment included parental perception of risk; one study out of India[6] attributed a significant reduction in the number of infants screened and treated during periods of the pandemic to parental fears as well as practical hindrances resulting from mandated shutdowns.

Data from two studies, one out of Denmark[1] and the other out of Tennessee,[2] indicated that the rate of premature births may have actually decreased during the mandated COVID-19 lockdowns. Given that the degree of prematurity and incidence of ROP are directly correlated, the authors of the current study hypothesized that the lockdown may have reduced the number of infants meeting criteria for ROP screening and treatment and by extension the incidence of disease. An initial report (Bazeer S, et al. IOVS 2021;62:1982) out of the United Kingdom that explored this question as a result of provider perceptions that the number of infants being screened had reduced during the pandemic did not yield a statistically significant difference in the severity or prevalence of ROP during the shutdown. The study did find a trend towards fewer infants being born below 32 weeks gestational age or 1500 g birthweight, but perhaps due to a small

Table 2. Retinopathy of prematurity screening and treatment characteristics of neonates across all time periods[a]

Study parameter	All time periods N = 1633	Time period 1[b] n = 198	Time period 2 n = 533	Time period 3 n = 491	Time period 4 n = 411	*P* value[c]
Screening method, no. (%)						
IO	1,392 (85.27)	198 (100)	436 (81.8)	393 (80.0)	365 (88.8)	<0.01[d]
Digital imaging	241 (14.8)	0 (0)	97 (18.2)	98 (20.0)	46 (11.2)	
PMA 1st screen, weeks, mean ± SD	33.5 ± 3.25	33.7 ± 3.13	33.6 ± 3.49	33.3 ± 3.28	33.5 ± 2.93	0.43
Requiring treatment, no. (%)	144 (8.8)	23 (11.7)	41 (7.7)	44 (9.0)	36 (8.8)	0.42
Treatment 1, no. (%)						
PMA at 1st treatment, weeks, median (range)[e]	36.50 (31.6-85.1)	37.2 (33-76)	36.45 (31.6-74)	37.1 (32.2-59.3)	36.3 (31.6-85.1)	0.32
Laser	51 (36.4)	14 (60.9)	12 (30.0)	17 (41.5)	8 (22.2)	0.08
Anti-VEGF injection	73 (52.1)	9 (39.1)	21 (52.5)	20 (48.8)	23 (63.9)	
Laser + Anti-VEGF injection	15 (10.7)	0 (0)	7 (17.5)	4 (9.8)	4 (11.1)	
Surgery	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (2.8)	
Days between DS and treatment, mean ± SD	1.12 ± 1.82	0.84 ± 1.61	1.23 ± 2.07	1.33 ± 1.85	0.88 ± 1.62	0.64
Recurrent disease after treatment, no. (%)	47 (35.6)	5 (29.4)	21 (51.2)	12 (30.8)	9 (25.7)	0.09[f]
Treatment 2, no. (%)						
PMA at 2nd treatment, weeks, mean ± SD	45.9 ± 6.21	44.8 ± 6.19	44.9 ± 5.15	46.0 ± 5.89	48.3 ± 8.60	0.55
Laser	44 (84.6)	4 (66.7)	18 (85.7)	14 (93.3)	8 (80.0)	0.25
Anti-VEGF injection	4 (7.7)	1 (16.7)	3 (14.3)	0 (0)	0 (0)	
Laser + Anti-VEGF injection	2 (3.9)	0 (0)	0 (0)	1 (6.7)	1 (10.0)	
Surgery	2 (3.9)	1 (16.7)	0 (0)	0 (0)	1 (10.0)	

DS, diagnosis; *IO*, indirect ophthalmoscopy; *PMA*, postmenstrual age; *SD*, standard deviation; *VEGF*, vascular endothelial growth factor.
[a]Time periods: (1) November 1, 2018, to March 15, 2019; (2) March 16, 2019, to August 2, 2019; (3) November 1, 2019, to March 15, 2020; (4) March 16, 2020, to August 2, 2020 (lockdown period).
[b]Data available for 4/7 institutions.
[c]A *P* value of ≤0.05 was considered significant.
[d]Significant difference between time 2 and 4, and 3 and 4 ($P < 0.01$ for each).
[e]Median values provided because outliers confounded the analysis (range, 31.6-85.1).
[f]Significant difference between time period 2 and 4 ($P = 0.02$).

sample size (n = 113) was unable to demonstrate statistical significance.

In this retrospective, controlled, multicenter, cohort study, we reviewed electronic medical record data from 1,645 infants screened across 7 institutions in the United States. We found a decrease in the number of infants screened during the COVID-19 shutdown period compared with the preceding 5 months and a similar period the previous year. There was no significant variation across time periods for the other patient parameters investigated. There was no significant variation in GA at birth, birth weight, PMA at first screen, proportion of infants requiring treatment, PMA at first treatment, treatment modality employed, or interval between diagnosis and treatment when comparing across all time periods. Similar findings were also noted in the subgroup analysis within each institution. There was a high rate of recurrent disease after treatment in our study (Table 2), although the reason for this is unclear.

There has been speculation regarding the factors contributing to the decrease in premature births during the lockdown, including increased intrauterine fetal demise due to delayed care, risk factor alterations (eg, decreased infectious exposures, modified behaviors—decreased travel, improved nutrition). Our findings suggest that even if the overall number of premature births declined, the distribution of severity of prematurity among those born prematurely enough to require ROP screening did not change substantially, with correspondingly little change in the frequency or severity of treatment-requiring ROP. Another possible explanation for our findings is that large referral centers were included in this study, and while there may have been a decline in the severity of prematurity overall or at certain healthcare systems, large referral centers may have seen no change if additional patients were directed to these institutions who would ordinarily have been cared for elsewhere.

Our results did demonstrate a significant difference in screening modality employed, with a higher proportion of screenings occurring with indirect ophthalmoscopy during the shutdown. Although the use of digital imaging within ophthalmology as a whole dramatically increased[12] during the pandemic, one possible explanation for the decrease noted in this study is that examiners wanted to limit infant exposure to healthcare workers. Studies have demonstrated that while trained imagers can obtain adequate fundus imaging for the purpose of ROP screening, indirect ophthalmoscopy may still be required due to the varying sensitivity of screening in cases of peripheral disease and media opacities,[7] and for patients

Table 3. Retinopathy of prematurity severity in neonates requiring treatment across all time periods[a]

Study parameter	All time periods N[b] = 144	Time period 1[c] n = 23[b]	Time period 2 n = 41[b]	Time period 3 n = 44[b]	Time period 4 n = 36[b]	*P* value[d]
Zone of ROP at treatment, no. (%)						
1	27 (18.8)	1 (4.4)	14 (34.1)	7 (15.0)	5 (13.9)	0.03
2	95 (66.0)	19 (82.6)	21 (51.2)	27 (61.4)	28 (77.8)	
3	13 (9.0)	3 (13.0)	2 (4.9)	6 (13.6)	2 (5.6)	
Not reported	9 (6.3)	0	4 (9.8)	4 (9.1)	1 (2.8)	
Stage of ROP at treatment, no. (%)						
1	7 (4.9)	1 (4.3)	2 (4.9)	2 (4.5)	2 (5.6)	0.63
2	19 (13.2)	3 (13.0)	2 (4.9)	7 (15.0)	7 (19.4)	
3	99 (68.8)	14 (60.9)	33 (80.5)	28 (63.6)	24 (66.7)	
4	2 (1.4)	1 (4.3	0 (0)	0 (0)	1 (2.8)	
5	1 (0.7)	0 (0)	1 (2.4)	0 (0)	0 (0)	
Not reported	16 (11.1)					
AROP, no. (%)	36 (25)	0 (0)	19 (46.3)	8 (18.2)	9 (25.0)	<0.01[e]
Plus disease, no. (%)	98 (68.1)	12 (52.2)	32 (78.1)	22 (50.0)	32 (88.9)	0.01[f]

AROP, aggressive retinopathy of prematurity; *ROP*, retinopathy of prematurity.
[a]Time periods: (1) November 1, 2018, to March 15, 2019; (2) March 16, 2019, to August 2, 2019; (3) November 1, 2019, to March 15, 2020; (4) March 16, 2020, to August 2, 2020 (lockdown period).
[b]Number of patients
[c]Data available for 4/7 institutions.
[d]A *P* value of $\leq$0.05 was considered significant.
[e]Significant difference between time period 1 and 2 ($P < 0.01$), 1 and 3 ($P = 0.02$), and 1 and 4 ($P < 0.01$)
[f]Significant difference between time period 1 and 2 ($P = 0.03$), 1 and 4 ($P < 0.01$), 2 and 3 ($P = 0.02$), and 3 and 4 ($P < 0.01$).

with more severe disease. Thus, infants screened via digital imaging may end up being exposed to both a trained imager and an examining physician, instead of only an examining physician.

In patients that required treatment, the median interval between diagnosis and treatment varied between 0 and 1 day, which was similar across all time periods. There were 2 outliers in time period 2: 1 patient was treated at 15 days, and 1 at 83 days, for unknown reasons. There were a number of patients without plus disease that underwent treatment. These patients were treated for the following reasons: type 1 ROP (zone 1 with stage 3), incomplete vascularization (at >55-60 weeks PMA per physician discretion), or rapidly worsening ROP (increased ridge height or worsening vascular dilation and tortuosity). Across all time periods, there was no variation in treatment modality employed, with a similar proportion of patients being treated with laser and intravitreal antivascular endothelial growth factor injection before and during the lockdown. Thus, changes in hospital protocols during the COVID-19 shutdowns did not appear to affect the timeliness of the delivery of care, and providers were able to maintain their existing preferred treatments. The strengths of this study include the large sample size and participation of multiple, geographically diverse institutions. Limitations of this study include its retrospective nature. Lockdowns may have been implemented differently and to different degrees across various geographic regions of the United States. Practice patterns may also have varied over time in ways unrelated to the pandemic. There were no differences in the characteristics or prevalence of ROP among screened infants during the COVID-19 lockdown in this study. Of note, our results demonstrated significantly greater utilization of indirect ophthalmoscopy screening compared to digital imaging during lockdown.

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