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Changes in Course of Retinopathy of Prematurity from 1986 to 2013

Comparison of Three Studies in the United States

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Purpose: To compare infant and retinopathy of prematurity (ROP) characteristics from 3 clinical studies conducted over a 27-year period in the United States.

Design: Secondary analysis of results of 3 clinical studies.

Participants: Infants with birth weight (BW) <1251 g.

Methods: Analysis of data from the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and Early Treatment for Retinopathy of Prematurity (ETROP) trials and the primary data from the Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity (e-ROP) study.

Main Outcome Measures: Infant characteristics and onset, severity, and time course of ROP.

Results: Across the 3 studies, mean (standard deviation) BW and mean gestational age (GA) decreased over time from CRYO-ROP (954 g [185 g], 27.9 weeks [2.2 weeks]) to ETROP (907 g [205 g], 27.4 weeks [2.2 weeks]) to e-ROP (864 g [212 g], 27.0 weeks [2.2 weeks]), with an increase in the percentage of infants enrolled weighing <750 g (15.8% CRYO, 24.9% ETROP, 33.4% e-ROP; $P<0.0001$). The percentage of infants who developed ROP varied only minimally (65.8% CRYO, 68.0% ETROP, 63.7% e-ROP; $P = 0.003$). Moderately severe ROP (defined as prethreshold or referral warranted) varied (17.8% CRYO, 12.3% ETROP, 19.4% e-ROP; $P<0.0001$), whereas the time of onset of any ROP did not vary (34.3 weeks CRYO, 34.1 weeks ETROP, 34.8 weeks e-ROP).

Conclusions: The BW and GA of infants enrolled in ROP studies in the United States have decreased over the past 27 years, whereas ROP prevalence and onset of disease are stable. *Ophthalmology 2016;123:1595-1600 © 2016 by the American Academy of Ophthalmology.*

Retinopathy of prematurity (ROP) is a disease seen almost exclusively in premature infants, although the incidence varies widely across the world.[1,2] Less than 10% of those infants who develop ROP will develop severe enough ROP to require treatment, although, even with treatment, ROP can lead to visual impairment and blindness.[3] In countries with well-developed neonatal intensive care units (NICUs), the proportion of smaller birth weight (BW) and lower gestational age (GA) infants who survive to discharge is increasing, although there is variation when individual institutions are compared in terms of treatment given and outcome.[4–8] Among large, multicenter ROP clinical studies conducted in the United States over the past few decades, 3 studies shared many of the participating centers and in total enrolled more than 12 000 premature infants with BW <1251 g. These studies reported the incidence and course of acute-phase ROP. The Cryotherapy for ROP (CRYO-ROP) study enrolled 4099 babies from January 1986 to November 1987[9,10]; the Early Treatment for ROP (ETROP) study screened 6998 babies and enrolled 2320 babies with ROP from October 1, 2000, to September 30, 2002[3,11]; and the Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity (e-ROP) study enrolled 1284 babies from May 2011 to October 2013.[12]

The purpose of this report is to examine the demographic characteristics and the onset, severity, and time course of acute-phase ROP among the infants in these studies.

Methods

The 3 studies were conducted with cooperative agreements with the National Eye Institute of the National Institutes of Health. Each was approved by the institutional review board at the study headquarters and at all clinical centers. In each study, detailed information was collected on infant demographics and the natural history of ROP found during the eye examinations conducted during the at-risk period for ROP by study-certified ophthalmologists. The timing of initial and subsequent examinations for acute-phase ROP was based on clinical guidelines in place at the time and was essentially the same for the 3 studies. In each study, the International Classification for ROP[13,14] was used by study-certified ophthalmologists for documenting the presence and severity of ROP.

Most of the data evaluated for this report were in the same format. For some of the analyses, the data required adjustment to allow comparison. The CRYO-ROP Study[10] and the ETROP[3] trial

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used the same definition of "threshold" and "prethreshold" ROP. Threshold ROP was defined as zone I or II, 5 contiguous or 8 composite hours of stage 3 ROP, with plus disease. Prethreshold ROP was defined as zone I, any ROP; zone II, stage 2 ROP with plus disease; zone II, any amount of stage 3 ROP and no plus disease; or zone II, stage 3 ROP with plus disease but less than required threshold clock hours. In 2003, the ETROP trial established a new treatment level for severe ROP, termed "type 1 ROP," defined as zone I ROP any stage with plus disease; zone I, stage 3 ROP; or zone II, stage 2 or 3 ROP with plus disease, as well as less severe ROP that requires increased surveillance, termed "type 2 ROP," defined as zone I, stage 1 or 2 without plus, or zone II, stage 3 without plus.

The e-ROP study did not specifically use the terms "threshold" or "prethreshold." Rather, the e-ROP study used the term "referral-warranted ROP" (RW-ROP)[15] to designate those eyes that needed to be evaluated by an ophthalmologist to consider treatment. Referral-warranted ROP was defined as an eye having any ROP in zone I, stage 3 ROP or worse, or plus disease. Therefore, RW-ROP is consistent with ROP defined in CRYO-ROP and ETROP as at least prethreshold ROP severity. One key difference between e-ROP and the previous studies is that plus disease alone was considered RW-ROP, whereas in the CRYO-ROP and ETROP treatment studies, peripheral changes of ROP also were required. This would bias toward slightly greater severity in the e-ROP study period.

In addition, for the ETROP study that screened 6998 infants and enrolled 2320 infants, the incidence of ROP was estimated by the investigators on the basis of "the data for infants who were monitored and whose ROP status was known" ("ROP observed, or mature") to provide an estimate that was then applied to all 6998 infants in the study to establish the rate of ROP.[11] On the basis of the available data set and using multivariate logistic regression to include all patients in the ETROP study, we were able to estimate the percentage of infants in ETROP who develop prethreshold or worse ROP and plus disease. In this report, "moderately severe or worse ROP" is used to indicate prethreshold ROP or worse using the CRYO-ROP and ETROP terminology and to indicate RW-ROP in e-ROP.

Because our main purpose is to describe the baseline infant and ROP characteristics from 3 large ROP studies, we do not make frequent use of formal statistical comparisons across these 3 studies; the large sample sizes can lead to very high statistical power to detect small, but not clinically meaningful, differences.

Results

Over the 27-year period from 1986 to 2013, there were more than 12 000 infants with BW <1251 g enrolled or screened in 3 ROP studies (Table 1). The mean BW of these infants decreased over time across the 3 studies, from 954 g (standard deviation [SD], 185 g) in CRYO-ROP to 907 g (SD, 205 g) in ETROP to 864 g (SD, 212 g) in e-ROP. The mean GA also decreased by approximately 1 week on average (from 27.9 weeks in CRYO-ROP to 27.0 weeks in e-ROP) during this period.

The percentage of infants with BW <750 g increased over time from CRYO-ROP to ETROP to e-ROP (15.8% to 24.9% to 33.4%, respectively). Likewise, the percentage of infants with GAs ≤27 weeks increased from 43.8% to 47.2% to 68.1%.

The majority of infants in all 3 studies were inborn (infants born at the enrollment site) but there were more outborn infants (not born at enrollment site) in e-ROP (37%). The number of multiple births increased from 18.6% to 26.2% to 29.8% from CRYO-ROP to ETROP to e-ROP, respectively.

Table 1. Characteristics of Study Infants

	CRYO-ROP (N = 4099), January 1986 to November 1987	ETROP (N = 6998), October 2000 to September 2002	e-ROP (N = 1257), May 2011 to October 2013
BW (g), mean (SD)	954 (185)	907 (205)	864 (212)
GA (wks), mean (SD)	27.9 (2.2)	27.4 (2.2)	27.0 (2.2)
Race, n (%)			
Black	1583 (38.6)	2114 (30.2)	31 (29.5)
Non-black	2516 (61.4)	4884 (69.8)	763 (60.7)
Unable to answer			123 (9.8)
Gender: n (%)			
Male	1970 (48.1)	3585 (51.2)	638 (50.8)
Female	2129 (51.9)	3413 (48.8)	619 (49.2)
BW, n (%)			
<750 g	647 (15.8)	1745 (24.9)	420 (33.4)
750–999 g	1590 (38.8)	2640 (37.7)	444 (35.3)
1000–1250 g	1862 (45.4)	2613 (37.2)	393 (31.3)
GA, wks			
≤27	1794 (43.8)	3305 (47.2)	856 (68.1)
>27–31	2027 (49.5)	3454 (49.4)	370 (29.4)
≥32	278 (6.8)	239 (3.4)	31 (2.5)
Born at enrolling site, n (%)			
Inborn	3353 (81.8)	5887 (84.1)	792 (63.0)
Outborn	746 (18.2)	1111 (15.9)	465 (37.0)
Multiple birth, n (%)			
Single birth	3335 (81.4)	5162 (73.8)	882 (70.2)
Multiple birth	764 (18.6)	1836 (26.2)	375 (29.8)

BW = birth weight; CRYO-ROP = Cryotherapy for Retinopathy of Prematurity; ETROP = Early Treatment for Retinopathy of Prematurity; e-ROP = Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity; GA = gestational age; SD = standard deviation.

The overall incidence of ROP across the time period of the 3 studies was similar, with approximately two thirds of the infants <1251 g developing some stage of acute ROP (Table 2). There was a decrease in the incidence of ROP between the ETROP and e-ROP studies among the >750-g BW infants (61.3%, 59.8%, and 51.4% for CRYO, ETROP, and e-ROP, respectively; $P<0.0001$) and among the >27 weeks' GA infants (52.1%, 50.2%, and 33.9% for CRYO, ETROP, and e-ROP, respectively; $P<0.0001$).

It is more difficult to interpret change in incidence. The overall incidence of prethreshold or worse ROP across the 3 studies varied minimally (Table 3). The percentage of prethreshold or worse ROP decreased among larger BW (1000–1250 g) infants, from 7.3% in CRYO-ROP to 3.9% in ETROP and 3.8% in e-ROP. Among infants with BW between 750 and 999 g, the percentage decreased from 21.4% in CRYO-ROP to 13.2% in ETROP, but was up slightly to 14.9% in e-ROP. Among the most at-risk group of infants with BW <750 g, the percentage of prethreshold or worse ROP decreased from 39.4% in CRYO to 31.5% in ETROP, but then rebounded to 38.8% in e-ROP. There was no change by race or sex.

There was little difference in the overall percentage of infants with plus disease across the 3 studies (11.0% for CRYO-ROP, 9.3% for ETROP, and 10.7% for e-ROP). However, plus disease was more commonly observed in non-black infants in all 3 studies, and among infants with GA >32 weeks, the incidence of plus

Table 2. Number and Percentage of Infants with Retinopathy of Prematurity of any Stage

	CRYO-ROP (N = 4099) n/N (%)	ETROP* (N = 6998) n/N (%)	e-ROP (N = 1257) n/N (%)
Black	1000/1583 (63.2%)	1429/2144 (67.6%)	218/371 (58.8%)
Non-black	1699/2516 (67.5%)	3331/4884 (68.2%)	510/763 (66.8)
Unable to answer			73/123 (59.4)
Male	1309/1970 (66.4%)	2429/3583 (67.8%)	413/638 (64.7)
Female	1300/2129 (65.3%)	233/3415 (68.3%)	388/619 (62.7)
<750 g	582/647 (90.0%)	1618/1745 (92.7%)	371/420 (88.3)
750–999 g	1243/1590 (78.2%)	2001/2640 (75.8%)	283/444 (63.7)
1000–1250 g	874/1862 (46.9%)	1142/2613 (43.7%)	147/393 (37.4)
≤27 wks	1497/1794 (83.4%)	2941/3305 (89.0%)	665/856 (77.7)
>27–31 wks	1120/2027 (55.3%)	1820/3454 (52.7%)	131/370 (35.4)
≥32 wks	82/278 (29.5%)	34/239 (14.2%)	5/31 (16.1)
Inborn	2155/3353 (64.3%)	3944/5887 (67.0%)	459/792 (58.0)
Outborn	544/746 (72.9%)	815/1111 (73.4%)	342/465 (73.6)
Single birth	2202/3335 (66.0%)	3510/5162 (68.0%)	562/882 (63.7)
Multiple birth	497/764 (65.1%)	1248/1836 (68.0%)	239/375 (63.7)
Total	2699/4099 (65.8%)	4759/6998 (68.0%)	801/1257 (63.7)

CRYO-ROP = Cryotherapy for Retinopathy of Prematurity; ETROP = Early Treatment for Retinopathy of Prematurity; e-ROP = Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity.
*Estimated with a multivariate logistic-regression equation to include all patients screened for retinopathy of prematurity in the ETROP study.

disease decreased from 2.9% (8/278) in CRYO to 0% (0/31) in e-ROP (Table 4).

With respect to the timing of the onset of the stages of acute ROP, plus disease, and prethreshold or worse ROP, there was no clinically significant change identified over this period (Table 5).

The data were available to allow us to compare of rate of prethreshold ROP among infants in the 2000–2002 ETROP study and 2011–2013 e-ROP study in terms of BW and GA. Figure 1 shows that the differences in the rate of prethreshold ROP vary with BW and GA. In the lowest BW and least mature infants (BW <1000 g and GA ≤27 weeks), the prethreshold ROP rate was higher in e-ROP than ETROP (30.6% vs. 22.0%; $P<0.0001$), whereas in the most mature infants (GA ≥28 weeks or BW ≥1000 g), the rate of the prethreshold ROP was similar (4.1% vs. 2.9%; $P = 0.13$).

Table 3. Prethreshold Retinopathy of Prematurity Worse in Cryotherapy for Retinopathy of Prematurity Study or Early Treatment for Retinopathy of Prematurity and Referral-Warranted Retinopathy of Prematurity in Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity

	CRYO-ROP (N = 4099)	ETROP (N = 6998)*	e-ROP (N = 1257)
Black	208/1583 (13.1%)	233/2114 (11.0%)	51/371 (13.8%)
Non-black	523/2516 (20.8%)	768/4884 (15.7%)	162/763 (21.2%)
Unable to answer			31/123 (25.2%)
Male	367/1970 (18.8%)	543/3585 (15.2%)	136/638 (21.3%)
Female	364/2129 (17.1%)	457/3413 (13.4%)	108/619 (17.5%)
<750 g	255/647 (39.4%)	550/1745 (31.5%)	163/420 (38.8%)
750–999 g	341/1590 (21.4%)	349/2640 (13.2%)	66/444 (14.9%)
1000–1250 g	135/1862 (7.3%)	102/2613 (3.89%)	15/393 (3.82%)
≤27 wks	519/1794 (28.9%)	893/4172 (21.4%)	232/856 (27.1%)
>27–31 wks	204/2027 (10.1%)	105/2587 (4.07%)	11/370 (2.97%)
≥32 wks	8/278 (2.9%)	2/239 (2.34%)	1/31 (3.23%)
Inborn	551/3353 (16.4%)	821/5887 (13.9%)	102/792 (12.9%)
Outborn	180/746 (24.1%)	180/1111 (16.2%)	142/465 (30.5%)
Single birth	573/3335 (17.2%)	703/5162 (13.6%)	169/882 (19.2%)
Multiple birth	158/764 (20.7%)	298/1836 (16.2%)	75/375 (20.0%)
Total	731/4099 (17.8%)	1001/6998 (14.3%)	244/1257 (19.4%)

CRYO-ROP = Cryotherapy for Retinopathy of Prematurity; ETROP = Early Treatment for Retinopathy of Prematurity; e-ROP = Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity.
*Estimated from multivariate logistic regression equation to include all patients screened for retinopathy of prematurity in the ETROP Study.

Table 4. Number and Percentage of Infants with Plus Disease

	CRYO-ROP (N = 4099)	ETROP (N = 6998)*	e-ROP (N = 1257)
Black	107/1583 (6.8%)	109/2114 (5.17%)	22/371 (5.93%)
Non-black	343/2516 (13.6%)	540/4884 (11.0%)	96/763 (12.6%)
Unable to answer			17/123 (13.8%)
Male	229/1970 (11.6%)	350/3585 (9.77%)	76/638 (11.9%)
Female	221/2129 (10.4%)	298/3413 (8.74%)	59/619 (9.53%)
<750 g	159/647 (24.6%)	364/1745 (20.9%)	92/420 (21.9%)
750–999 g	204/1590 (12.8%)	221/2640 (8.36%)	37/444 (8.33%)
1000–1250 g	87/1862 (4.7%)	64/2613 (2.45%)	6/393 (1.53%)
≤27 wks	319/1794 (17.8%)	582/4172 (14.0%)	130/856 (15.2%)
>27–31 wks	123/2027 (6.1%)	65/2587 (2.51%)	5/370 (1.35%)
≥32 wks	8/278 (2.9%)	2/239 (0.61%)	0/31 (0.00%)
Inborn	338/3353 (10.1%)	527/5887 (8.95%)	54/792 (6.82%)
Outborn	112/746 (15.0%)	122/1111 (11.0%)	81/465 (17.4%)
Single birth	350/3335 (10.5%)	452/5162 (8.75%)	98/882 (11.1%)
Multiple birth	100/764 (13.1%)	197/1836 (10.7%)	37/375 (9.87%)
Total	450/4099 (11.0%)	649/6998 (9.27%)	135/1257 (10.7%)

CRYO-ROP = Cryotherapy for Retinopathy of Prematurity; ETROP = Early Treatment for Retinopathy of Prematurity; e-ROP = Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity.
*Estimated from multivariate logistic regression equation to include all patients screened for retinopathy of prematurity in the ETROP Study.

Discussion

Over the past 3 decades, the incidence of ROP among infants with BW <1251 g has remained relatively stable in large clinical centers in the United States. When comparing the CRYO-ROP, ETROP, and e-ROP studies, overall approximately 65% of infants developed some stage of ROP and approximately 1 in 6 infants developed more serious disease. This was observed despite the fact that the infants most at risk were found in increasing numbers. The mean BW decreased from 954 g in CRYO-ROP to 864 g 25 years later in e-ROP. Likewise, the mean GA of infants in the CRYO-ROP study was 28 weeks, with 44% of infants born earlier than 27 weeks; in the e-ROP study, the mean GA was 27 weeks, with 68% born earlier than 27 weeks. Thus, the population of infants in the <1251 g BW group has shifted to smaller, less mature infants, but despite this increased survival of the most at-risk population, the overall proportion of infants who develop ROP has varied little. The most plausible explanation for this observation is the care that premature infants receive has improved since infants were enrolled in the CRYO-ROP study. The numerous innovations have included advances in obstetrical care, including the use of antenatal steroids, expectant delivery protocols, and close monitoring of preterm labor. In the NICU itself, there has been improved care provided with better oxygen monitoring and ventilator support, increased awareness of the importance of nutritional support including human breast milk, and increased awareness of the environment for the infants, including reducing stress when possible.[16] Of note, the use of surfactant became routine in the early 1990s.[17] It is of interest that in the clinical centers represented in this study, the percentage of infants who were not born in the center doubled over the 27-year period, perhaps reflecting that there is an increased likelihood of referral of the sicker, more critically ill infants with severe respiratory failure or surgical necrotizing enterocolitis for neonatal intensive care or even referral for ROP care. It is also important to note that some of the clinical centers in these studies increased capacity for referrals during the intervening years.

These improvements in survival of at-risk infants have not had an effect on the onset of ROP and progression to more serious disease[13] (Table 5). An effect would not be

Table 5. Onset of Different Retinopathy of Prematurity Status by Postmenstrual Age (Median, 5th and 95th Percentiles)

	CRYO-ROP (N = 4099)	ETROP (N = 6998)	e-ROP (N = 1257)
Stage 1 ROP	34.3 (–, 39.1)	34.1 (–, 38.9)	34.8 (32.3, 39.4)
Stage 2 ROP	35.4 (32.0, 40.7)	35.1 (32.4, 40.1)	35.0 (32.7, 39.4)
Stage 3 ROP	36.6 (32.9, 42.4)	36.6 (33.4, 41.6)	36.3 (33.0, 40.7)
Plus disease	36.3 (32.6, 42.9)	36.0 (33.0, 41.4)	36.8 (33.0, 41.1)
Prethreshold/threshold ROP – RW-ROP	36.1 (32.4, 41.5)	36.1 (32.1, 42.1)	36.1 (32.5, 40.4)

CRYO-ROP = Cryotherapy for Retinopathy of Prematurity; ETROP = Early Treatment for Retinopathy of Prematurity; e-ROP = Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity; ROP = retinopathy of prematurity; RW-ROP = referral-warranted retinopathy of prematurity.

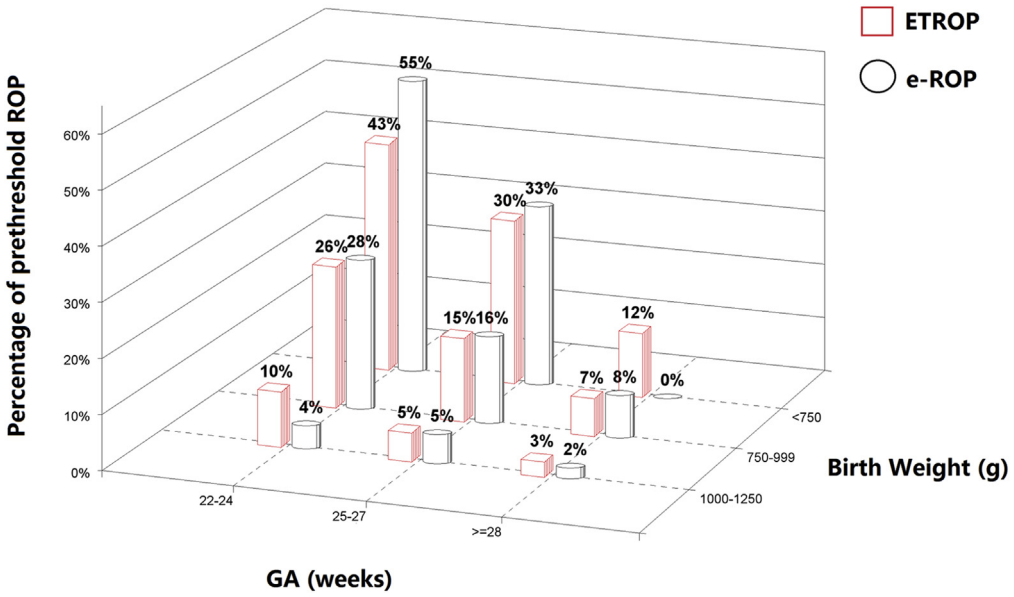

Figure 1. The rate of prethreshold retinopathy of prematurity (ROP) by combination of birth weight and gestational age in the Early Treatment for Retinopathy of Prematurity (ETROP) and Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity (e-ROP) studies.

expected because the development of ROP is tightly correlated with the development of the retina rather than the specific GA or BW of an individual infant.[9]

The results of these comparisons are not necessarily generalizable to all NICU settings, even to all NICUs in the United States, but the results are encouraging. As care of the premature infant improves in middle- and low-income countries and expertise in ROP develops, a decrease in the incidence of ROP and serious ROP in larger and more mature infants likely will be observed.

Study Limitations and Strengths

There are limitations to a study of this type; only a broad overview can be provided because only mean/median and incidence data were available in all 3 studies, and further, values had to be imputed in ETROP for more serious acute-phase ROP. Also, there has likely been an evolution of the definition of plus disease and its clinical diagnosis over the time period covered by these studies. Before the results of the CRYO-ROP study were known, there was likely a bias toward requiring more severe abnormalities of the posterior pole vessels than when the prognostic importance of plus disease became evident in the ETROP study.

Several strengths also are important. Ten clinical centers in the United States participated in each of these 3 studies, with at least 1 investigator participating from 7 of these centers. Furthermore, all of the study ophthalmologists had undergone rigorous certification to be an examiner, thus strengthening the findings of this report. In addition, these 3 studies represent a large sample of the infants born in the United States during each time period, and although individual centers have likely changed practice over this time, the sample is sufficiently large to suggest the findings are representative of practice in the United States.

In summary, the incidence of ROP and serious ROP has remained relatively stable over the past 3 decades in the United States, whereas the percentage of the most at-risk infants has increased over this period. This likely reflects improved neonatal and obstetrical care and is an encouraging sign that ROP remains a risk, but not necessarily an increasing risk for premature infants in the United States.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
BW = birth weight; **CRYO-ROP** = Cryotherapy for Retinopathy of Prematurity; **e-ROP** = Telemedicine Approaches for the Evaluation of Acute-Phase Retinopathy of Prematurity; **ETROP** = Early Treatment for Retinopathy of Prematurity; **GA** = gestational age; **NICU** = neonatal intensive care unit; **RW-ROP** = referral-warranted retinopathy of prematurity; **ROP** = retinopathy of prematurity; **SD** = standard deviation.

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