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High or Low Oxygen Saturation and Severe Retinopathy of Prematurity: A Meta-analysis

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Abstract

CONTEXT—Low oxygen saturation appears to decrease the risk of severe retinopathy of prematurity (ROP) in preterm newborns when administered during the first few weeks after birth. High oxygen saturation seems to reduce the risk at later postmenstrual ages (PMAs). However, previous clinical studies are not conclusive individually.

OBJECTIVE—To perform a systematic review and meta-analysis to report the association between severe ROP incidence of premature infants with high or low target oxygen saturation measured by pulse oximetry.

METHODS—Studies were identified through PubMed and Embase literature searches through May 2009 by using the terms “retinopathy of prematurity and oxygen” or “retinopathy of prematurity and oxygen therapy.” We selected 10 publications addressing the association between severe ROP and target oxygen saturation measured by pulse oximetry. Using a random-effects model we calculated the summary-effect estimate. We visually inspected funnel plots to examine possible publication bias.

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RESULTS—Low oxygen saturation (70%–96%) in the first several postnatal weeks was associated with a reduced risk of severe ROP (risk ratio [RR]: 0.48 [95% confidence interval (CI): 0.31–0.75]). High oxygen saturation (94%–99%) at 32 weeks' PMA was associated with a decreased risk for progression to severe ROP (RR: 0.54 [95% CI: 0.35–0.82]).

CONCLUSIONS—Among preterm infants with a gestational age of 32 weeks, early low and late high oxygen saturation were associated with a reduced risk for severe ROP. We feel that a large randomized clinical trial with long-term developmental follow-up is warranted to confirm this meta-analytic result.

Keywords

oxygen; pulse oximetry; retinopathy of prematurity

Retinopathy of prematurity (ROP) is the second leading cause of blindness in childhood in the United States.¹ The pathogenesis of ROP includes 2 phases. In the first phase, hyperoxia leads to vessel-growth cessation. The second phase, precipitated by the increasing metabolic demand of the developing retina with a compromised vascular supply is characterized by relative hypoxia, which leads to pathologic neovascularization that extends into the vitreous.^{2,3} Although laser treatment of infants at risk for severe ROP decreases retinal detachment and reduces blindness by ~25%,⁴ non-blinding ocular morbidity is not reduced by treatment and makes preventive efforts desirable.

Excessive oxygen in the first few weeks of postnatal life has been known as a major risk factor for ROP for >50 years.^{5–7} The optimal oxygen-saturation targets for preterm newborns are still controversial.^{8,9} A number of relatively small studies have assessed protocols of reduced oxygen saturation for preterm infants with a prominent reduction of severe ROP during the first several weeks of post-natal life,^{10–12} some of which did not achieve statistical significance.^{13,14} Results from another set of studies suggested that higher oxygen saturation at later postmenstrual ages (PMAs) decreases the likelihood of progression to threshold ROP,^{15–17} whereas others were inconclusive.^{18,19} One previous meta-analysis²⁰ included 5 small studies with patient enrollment between 1951 and 1969, a time at which pulse oximetry was not available. New meta-analysis is needed to explore current data to provide clinicians with evidence-based information for practice.

Therefore, we conducted a meta-analysis to evaluate the association between oxygen saturation monitored by pulse oximetry and severe ROP among preterm infants with a gestational age at birth of 32 weeks. In addition to assessing the association between severe ROP and oxygen saturation during each phase (phase 1 and 2) of the disease, we were interested in exploring the optimal oxygen-saturation range for phase 1, which is associated with hyperoxia, and phase 2, which is associated with hypoxia.

METHODS

Data Sources

We identified studies through a Medline and Embase literature search. All articles and abstracts published in English through May 2009 were identified by use of the Medical

Subject Headings (MeSH) terms “retinopathy of prematurity and oxygen” or “retinopathy of prematurity and oxygen therapy” (PubMed) and “retinopathy of prematurity and oxygen” (Embase). Studies with titles or abstracts that discussed oxygen for ROP were retrieved. Studies that included a relative exposure and relative outcomes, gestational age or birth weight of the infants, and oxygen-saturation timing were included for further review. References were examined to supplement articles recovered through the initial search. A relevant exposure included low and high oxygen saturation measured by pulse oximetry. Relevant outcomes included grade 3 or higher ROP as defined by the International Classification of Retinopathy of Prematurity^{21–23} or prethreshold or threshold ROP as defined in the Early Treatment for Retinopathy of Prematurity (ET-ROP),²⁴ Cryotherapy for Retinopathy of Prematurity (CRYO-ROP),²⁵ or Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) studies.¹⁸ Attempts were made to contact authors of the studies if they were unclear. Results of all the identified studies are summarized in Tables 1 and 2 and are discussed below. Only human studies published in English were included.

Data Extraction

According to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting meta-analyses of observational studies,²⁶ information from individual studies was extracted by using standardized forms by 2 independent reviewers (Drs Chen and Guo). Discrepancies were resolved by referencing the original articles and discussions. The following data were abstracted onto standardized forms: author, publication year, study type, recruitment period, gestational age, birth weight, sample size, oxygen timing and duration, target oxygen saturation, severe ROP incidences, and outcomes. Raw (grouped) data and risk-ratio (RR) estimates for each study are available from the corresponding author (Dr Chen). A meta-analysis that combines published studies faces the challenge that different studies on the same topic might provide different comparisons; for example, cutoff points to define oxygen-saturation categories might be chosen differently. To make comparisons possible, we combined groups of similar oxygen-saturation levels to 2 groups for comparison if there were more than 2 oxygen-saturation groups in a study.

Study Eligibility for Analysis

We included cohort studies and randomized clinical trials (RCTs). The following inclusion criteria were applied:

- oxygen-saturation level measured by pulse oximetry;
- cohort study or RCT design;
- raw (grouped) data to calculate estimate;
- gestational age of ≥ 32 weeks at birth; and
- timing of oxygen saturation for ROP supplied to distinguish 2 different phases for ROP.

We excluded animal studies, case reports, review articles, and studies without oxygen-saturation level measured by pulse oximetry, gestational age of infants, oxygen-saturation

timing, or raw (grouped) data to calculate RRs. We performed meta-analyses by using 10 of 15 initially identified publications that addressed the association between early or late oxygen saturation and severe ROP.

Early oxygen was defined as oxygen saturation from birth to the first several (up to ~8) weeks of age. If a study started monitoring oxygen saturation at birth and continued through a PMA of 32 weeks, it was still considered early oxygen. Late oxygen was defined as oxygen saturation monitored at a PMA of ≥ 32 weeks.

Statistical Analysis

We used Stata 8 software (Stata Corp, College Station, TX) using a random-effects model to calculate the summary-effect estimates. The random-effects model provides a more conservative estimate by incorporating both within- and between-study variation. We calculated summary RR estimates by taking a weighted average of individual study results. The weight for each study was the inverse of the sum of 2 terms: the study variance and a term that accounted for between-study variability. We measured statistical heterogeneity by using the χ^2 test. Because this test has limited power to detect heterogeneity, we also calculated the I^2 statistic (Q statistic minus degrees of freedom, divided by Q statistic) as a quantitative measure of the extent of heterogeneity across studies, which does not depend on the number of studies (an I^2 value of 0% indicates no observed between-study heterogeneity, and large values show increasing between-study heterogeneity).²⁷ Low oxygen-saturation ranges of 70% to 96% were compared with high oxygen-saturation ranges from 85% to 100% during the first up to ~8 weeks of neonatal life for studies of infants born at a gestational age of ≥ 30 weeks. High oxygen-saturation low limits of >94% to 99% were compared with low oxygen saturation of <96% after 32 weeks' PMA. We are aware of the potential overlap between these 2 time frames for some infants, but high variation among studies did not allow for a better distinction between early and late epochs of oxygen exposure. Effect-modification tests were performed by stratification factors pertaining to study design, oxygen-saturation level, oxygen timing, and duration. Finally, potential publication bias was assessed by Begg's funnel plot and Egger's test.²⁸ All P values of <.05 were considered statistically significant.

RESULTS

Description of Studies

We identified 459 potential studies through Medline (1966 to May 2009) and 619 through Embase (1966 to May 2009), of which 1063 met the exclusion criteria. Fifteen potentially appropriate studies underwent further evaluation, of which 5 were finally excluded because they turned out to meet our exclusion criteria. Ten studies were eventually included in our meta-analysis.

The characteristics of the included studies are listed in Tables 1 and 2. The studies were published between 1997 and 2007 and included a total of 3088 infants. Five cohort studies with 1446 infants compared low oxygen-saturation range (70%–96%) with a higher oxygen-saturation range (85%–100%) during the first several weeks after birth (Table 1). Five other

cohort or randomized, controlled trials compared lower oxygen (<89%–96%) to high oxygen (>94%–99%) at a PMA of 32 weeks, which included 1642 infants (Table 2).

Figure 1 shows the association between low oxygen saturation and risk of severe ROP in the first several weeks of neonatal life in 5 individual studies,^{10–14} with RRs ranging from 0.17 to 0.76. Two of these 5 studies yielded no significant association.^{13,14} The pooled estimate suggests a significantly decreased risk of severe ROP (RR: 0.48 [95% confidence interval (CI): 0.31–0.75]).

Figure 2 shows the individual and joint results from 5 studies that evaluated the association between high oxygen saturation and severe ROP at a PMA of 32 weeks^{15–19}; 2 studies reported no significant association.^{18,19} The pooled estimate here showed a statistically significant risk reduction (RR: 0.54 [95% CI: 0.35–0.82]).

Stratified Analysis

In Table 3 we list results from stratified analyses performed to explore possible sources of heterogeneity among studies. In early-oxygen studies, a low-oxygen lowest limit of >83% and 83% resulted in significant summary RRs, but a stronger effect was seen in studies that used 83% (RR: 0.34 [95% CI: 0.18–0.65]). In 3 studies with duration of oxygen use for the first 4 postnatal weeks, the protective effect was significant (RR: 0.49 [95% CI: 0.28–0.88]). The 2 studies without specification of oxygen-use duration showed a similar strong risk reduction but did not achieve formal significance (RR: 0.42 [95% CI: 0.17–1.03]).

Among studies of late high oxygen, a lower limit of 98% revealed a more prominent risk reduction for severe ROP (RR: 0.27 [95% CI: 0.14–0.50]) than a lower limit of <98% (RR: 0.72 [95% CI: 0.54–0.96]). This effect modification is highly significant ($P=.005$). The reduction of severe ROP by high oxygen saturation is less prominent than the overall pooled effect at a mean PMA of 32 to 35 weeks (RR: 0.63 [95% CI: 0.34–1.16]) and even more prominent after a mean PMA of 36 weeks (RR: 0.38 [95% CI: 0.17–0.84]). This effect modification did not yield statistical significance ($P = .31$).

When studies were sorted according to study design, the 2 RCTs without statistical significance pooled together exhibited a significant reduction of severe ROP risk (RR: 0.84 [95% CI: 0.71–0.99]). As expected, the 3 cohort studies remained statistically significant when pooled together (RR: 0.46 [95% CI: 0.35–0.61]).

Sensitivity Analysis

We examined the influence of individual studies by omitting 1 study at a time from each of the 2 separate analyses depicted in Figs 1 and 2. None of the studies, when omitted, changed the respective pooled RR dramatically.

Publication Bias

Meta-analysis is subject to potential publication bias (ie, selective nonpublication of studies that show no association between exposure and outcome, nonsignificant associations, or

both). Neither our early ($P = .483$) nor the late ($P = .394$) oxygen analysis seems to have been affected by publication bias.

DISCUSSION

Results of our meta-analysis on the association between oxygen saturation measured by pulse oximetry and risk of severe ROP indicate a statistically significant risk reduction of 52% by low oxygen saturation (70%–96%) in the first postnatal weeks and of 46% by high oxygen saturation (>94%–99%) at a PMA of 32 weeks. To our knowledge, this is the first meta-analysis to show that oxygen-saturation levels seem to reduce the risk of severe ROP, which supports the notion that high oxygen saturation has different effects at postnatal time points that roughly correspond to the first and second phases of ROP.

The beneficial effect of low and high oxygen saturation on severe ROP can be explained by the 2 sequential phases of ROP pathogenesis.^{7,29} The first vaso-obliterative phase of ROP is triggered by hyperoxia between birth and ~30 to 32 weeks' PMA.³⁰ Supplemental oxygen suppresses vascular endothelial growth factor (VEGF), which results in the cessation of normal vessel growth and regression of existing vessels.³¹ The second proliferative phase begins around 32 to 34 weeks' gestation³⁰ and is associated with an increased VEGF expression in the retina caused by relative hypoxia, which results in pathologic neovascularization.^{31,32} Thus, it has been suggested that supplemental oxygen might be used therapeutically at appropriate time points to downregulate VEGF expression and to limit the neovascular complications of ROP.³³ Experiments with animal models,^{34–36} transgenic mouse models,³⁷ and nonhuman primates³⁸ have indeed confirmed that VEGF is instrumental in the development of abnormal retinal vasculature. Elevated levels of VEGF are present in the vitreous of humans with ROP³⁹ and in the subretinal fluid of eyes affected by active stage 4 (but not stage 5) ROP.⁴⁰ It is elevated in the vitreous of adult and neonatal patients with retinal neovascularization.^{41–43}

When displayed according to postnatal age, the cumulative proportion of patients with vessels reaching zone 3 at any given postnatal age is highest for infants at 1000 to 1250 g birth weight and lowest for infants at <750 g ($P < .001$).²⁵ However, when analyzed according to PMA, essentially a single pattern emerges that applies to the entire range of birth weights.²⁵ Thus, PMA seems to be more tightly linked to ROP development than chronological age.

The use of pulse oximetry has facilitated oxygen-fluctuation monitoring in newborns.^{44–46} Optimal oxygen saturations for low birth weight premature infants have not been well established.⁹ Normal fetal retinal hypoxia is termed “physiologic hypoxia.”⁴⁷ Along these lines, results of our meta-analysis suggest that oxygen-saturation lower limits at 70% to 83% during the first several postnatal weeks showed stronger protection than 85% to 90% among newborns with a gestational age of 28 weeks. The results of a previous study further support our findings; the researchers compared 4 different oxygen-saturation groups with regard to severe ROP risk.¹⁰ The infants who received oxygen saturations of 70% to 90% had the lowest incidence of threshold ROP (6%), whereas those in the 88% to 98% group

had the highest incidence (28%); 84% to 94% oxygen saturations yielded a 14% risk, and 85% to 95% oxygen saturations yielded a 16% risk.

However, there is currently no published evidence to indicate that high oxygen saturations increase ROP risk after 32 weeks' PMA. Indeed, when infants with ROP were older than 32 weeks' PMA, an oxygen-saturation lower limit of 98% was associated with a more prominent protection than <98% oxygen saturation (Table 3). Still, previous clinical trials on late high oxygen-saturation levels and severe ROP were inconclusive. The Benefits of Oxygen Saturation Targeting (BOOST) multicenter double-blind, randomized, controlled trial revealed a nonsignificant risk reduction of severe ROP after a PMA of 32 weeks (odds ratio: 0.78 [95% CI: 0.46–1.31]).¹⁹ The STOP-ROP multicenter study group also reported a nonsignificant reduced risk of ROP progression with higher oxygen-saturation levels (96%–99%) (odds ratio: 0.72 [95% CI: 0.52–1.01]).¹⁸ It is unfortunate that the STOP-ROP multicenter group started oxygen administration at a mean of 35.4 ± 2.5 weeks' PMA. Because infants' PMA ranged from 30 to 48 weeks at randomization, some might still have been in phase 1, whereas others might have already been far into phase 2 of the disease. Thus, the high supplemental oxygen may have started too early for some infants to exhibit its protective effect during phase 1. For some others, the high oxygen might have come too late in the second stage of ROP. Also, because the trial failed to enroll the prespecified number of infants, the study result did not achieve statistical significance because of a subsequent decrease in statistical power (from 90% to ~80%),⁴⁸ which explains why the 16% reduction of severe ROP risk after pooling these 2 RCTs now achieves statistical significance.

Another reason why the STOP-ROP and BOOST trials did not yield stronger effects might be that their target oxygen-saturation levels were not high enough. STOP-ROP investigators used 96% to 99% and BOOST trialists used 95% to 98%, which are lower than the oxygen-saturation target levels used in other studies (>98%).^{15,16} Gaynon et al¹⁵ discovered that when they abandoned the 99% target oxygen-saturation level (which decreased progression to threshold ROP to 7%) and entered the STOP-ROP study with its 96% to 99% saturation target, they observed a threshold ROP rate increase to 33% to 44%. The results of our stratified analysis support the notion that a stronger protective effect is seen with high-oxygen lower limits of 98% than with 89% to 96%.

Duration of oxygen supplementation has been suggested to be related to ROP severity.^{7,49,50} Our stratified analyses remain inconclusive, because not all studies specified duration of oxygen exposure.

Is oxygen concentration more important than timing of oxygen saturation? The results of our meta-analysis suggest that both timing and oxygen-saturation level are important for severe ROP risk reduction. Early and late high oxygen-saturation levels seem to have different effects on severe ROP. Results of a recent survey of neonatal pulse-oximetry practices in infants born weighing <1500 g support our results of the beneficial effect of early low oxygen saturation on ROP. The authors reported a significantly reduced rate of stage 3 ROP when maximum pulse oxygen saturation (SpO_2) was <92% after the first 2 weeks of postnatal life.⁵¹ We were unable to include this survey study because no raw data were

supplied to calculate RRs. Two other important studies were excluded because the timing of oxygen-saturation monitoring was not specified.^{52,53} In our stratified analysis, higher oxygen-saturation levels (>94%–99%) exhibited stronger protection on threshold ROP at 36 weeks' PMA than at 32 to 35 weeks' PMA, although results of the effect-modification test were not statistically significant.

We speculate that if oxygen saturations were controlled in both phases of ROP, the expected protection effect on severe ROP should be greater than that with early low or late oxygen-saturation schemes alone. Results from 2 studies that examined low oxygen saturation early and high oxygen late support this notion. The first study initiated a clinical oxygen-practice change in 1998 based on 2 phases of ROP pathogenesis (ie, SpO₂ from 85% to 95% for infants >32 weeks' gestation and 85% to 93% for those 32 weeks' gestation during the first 2–8 postnatal weeks). The authors observed a fivefold decrease of severe ROP from 12.5% in 1997 to 2.5% in 2001. The need for ROP laser treatment decreased from 4.5% in 1997 to 0% in the period after the practice change between 1999 and 2001.⁵⁴ It is worth noting that the difference between policies in target oxygen ranges was very small. This study was not included in our meta-analysis because no raw (grouped) data were provided.

Another recent nonrandomized study with results that support our speculation strictly monitored oxygen among infants with a gestational age of <36 weeks at birth (mean: 28 weeks) with target oxygen saturation set at 85% to 92% (limits: 80%–95%) before 34 weeks' PMA and 92% to 97% (limits: 85%–100%) after 34 weeks' PMA.⁵⁵ This setup was compared with a previous standard oxygen-supplementation protocol with saturation targets set at 95% to 100%. Although the historical controls had 35% ROP incidence, it decreased to 13% after switching to an early low-oxygen and late high-oxygen policy. The incidence of stage 3 ROP decreased from 11% to 2% ($P = .021$), and the incidence of threshold ROP decreased from 7% to 1% ($P = .001$). We did not include this study, because early and late phases of ROP in the affected infants were not distinguished.

Mortality and chronic lung disease are of concern with lower oxygen saturation for preterm infants.⁵⁶ Among the studies eligible for meta-analysis, 3 early-oxygen^{10,12,14} and 2 late-oxygen^{18,19} studies did not reveal a difference in mortality rate, whereas the remaining studies did not report on mortality (Tables 4 and 5). Indeed, neonatal resuscitation with room air seems to be as effective as 100% oxygen and may even be associated with reduced mortality rates.^{57,58} Regarding pulmonary outcomes, the authors of 2 early-oxygen studies reported a reduced risk of chronic lung disease with low oxygen saturations,^{10,14} a finding that was confirmed by a cohort study on bronchopulmonary dysplasia.⁵⁹

In the STOP-ROP trial, infants in the supplemental-oxygen group had a slightly higher incidence (12%) of pneumonia/chronic lung disease–related events than those in the conventional group (8%), but no differences in growth or neuromotor development were present between groups. However, infants in the supplemental-oxygen-saturation group had more severe lung disease at baseline.¹⁸ In the BOOST trial, children in the high-oxygen group had a higher risk of oxygen dependence at 36 weeks' PMA.^{18,19} However, their saturation threshold for discontinuation of oxygen was higher per study design. Still, some of these oxygen-related pulmonary effects might also be true aberrations of lung

development (eg, caused by impaired lung VEGF).⁶⁰ In the reports from 3 early-oxygen and 3 late-oxygen studies, chronic lung disease was not mentioned. Authors of recent reviews on oxygen-saturation monitoring for the preterm infant proposed SpO₂ targets of 85% to 93% for preterm infants; however, the effects of oxygen saturation on the 2 phases of ROP were not taken into consideration.^{61,62}

Some might consider early low oxygen-saturation levels potentially harmful for the developing brain. However, oxygen saturation in the 70% to 90% target range was not associated with an increased risk for cerebral palsy compared with those in higher oxygen groups in 1 study.¹⁰ In another study, intraventricular hemorrhage and white-matter damage risks were not different between those in low versus high oxygen-saturation groups.¹⁴

Some limitations of this meta-analysis should be considered. Study designs and related factors were highly heterogeneous. We included both RCTs and cohort studies. Because of the obvious deleterious effects of high early oxygen on the early phase of ROP,^{49,63,64} such treatment cannot be included in an RCT. Thus, we had to include observational studies, even with historical controls.^{13,16} It is obvious that the data quality from clinical trials (eg, because of blinding of investigators and nursing staff) differs appreciably from unblinded observational studies. For example, the authors of 4 early-oxygen and 3 late-oxygen studies reported baseline characteristics incompletely or not at all, and those of 3 early-oxygen and 3 late-oxygen studies did not report developmental outcomes (Tables 4 and 5).

Among the studies we used in this meta-analysis, some used different denominators for reporting threshold ROP incidence, which may have led to selection bias. Confounders could not be adjusted for in our meta-analyses, because not all study authors reported on confounders. One study did not provide a high oxygen-saturation starting point by reference to PMA but did provide one to ROP stage 3 instead.¹⁶ On the basis of the PMA ranges at ROP stage 3 occurrence as reported in previous studies,^{24,25} we assumed that infants received supplemental oxygen between ~33 and 42 weeks' PMA if they were reported to have received oxygen at the time of ROP stage 3 diagnosis.

We are aware of the potentially large overlap between "low" and "high" oxygen-saturation targets when studies are combined. Only 1 of the 5 early-oxygen studies (Table 1) had no overlap in low versus high target ranges, whereas the same was true for at least 4 of 5 late-oxygen studies. However, this potential problem is inherent to the original studies we analyzed and cannot be corrected in meta-analyses.

Another source of variability among studies is the known difficulty in adhering to oxygen-saturation target policies.⁶⁵ In all 5 early-oxygen studies, clinical staff were educated and trained to minimize fluctuations in SpO₂.^{10–14} Of the 5 late-oxygen studies, how compliance to oxygen-saturation policy was assessed was not reported for 3 of them.^{15–17} The STOP-ROP investigators used pulse oximetry and laptop computers to monitor, record, and report the oxygen-saturation range so that adjustments could be made to maximize the time spent in the target range.¹⁸ In the BOOST trial, compliance with the target oxygen-saturation range of 93% to 96% was assessed with the use of twice-weekly downloading of each infant's oxygen-saturation data.¹⁹ Despite the heterogeneity of the studies, sensitivity

analyses revealed that no single study significantly changed the overall estimate of the reduced severe ROP risk.

CONCLUSIONS

A sufficiently powered RCT on optimal oxygen delivery in the early and late stages of ROP is needed that also ensures long-term visual, pulmonary, and neurodevelopment follow-up. Moreover, we suggest that the PMA concept be embraced in such studies, because it is unclear currently whether clinical trials that investigate different lower oxygen-saturation protocols in very preterm infants have done this.^{66–68} We speculate that low oxygen saturation in the first phase combined with high oxygen in the second phase of ROP pathogenesis might achieve greater protection than low oxygen alone.

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ABBREVIATIONS

ROP	retinopathy of prematurity
PMA	postmenstrual age
ET-ROP	Early Treatment for Retinopathy of Prematurity
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity
STOP-ROP	Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity
RR	risk ratio
RCT	randomized clinical trials
CI	confidence interval
VEGF	vascular endothelial growth factor
BOOST	Benefits of Oxygen Saturation Targeting
SpO₂	pulse oxygen saturation

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FIGURE 1.

Association between low oxygen saturation (70%–96%) and risk of severe ROP during the first weeks of preterm life. The test for heterogeneity was not significant ($\chi^2 = 5.41$ [degrees of freedom = 4]; $P = .248$; $I^2 = 26\%$). The RR significantly favors low O₂ ($z = 4.17$; $P < .001$). The size of the marker corresponds to the weight of that study, and error bars represent 95% CIs.

FIGURE 2.

Association between high oxygen saturation (94%–99%) and risk of severe ROP at a PMA of 32 weeks. The test for heterogeneity was significant ($\chi^2=19.49$ [degrees of freedom =4]; $P=.001$; $I^2=79\%$). The RR significantly favors high O₂ ($z=5.54$; $P<.001$). The size of the marker corresponds to the weight of that study, and error bars represent 95% CIs.

TABLE 1

Characteristics of Studies of Preterm Infants in Which the Association Between Low Oxygen Saturation and Severe ROP Risk in the First Several Weeks Were Evaluated in the Meta-analysis

Author	Study Type	Recruitment Period	GA, wk	Birth Weight, g	n	Oxygen Timing and Duration	Target Oxygen Saturation (%)	Severe ROP, %	Severe ROP Outcome
Wright et al ¹² (2006)	Prospective cohort	1998–2002	<30	500–1500	350	Immediate postgestation life	Low (83–93) vs high (89–95)	1.3 vs 7.3	Threshold ROP (CRYO-ROP ²⁵)
Wallace et al ¹³ (2007)	Retrospective cohort	2002–2005	30	<1250	105	First 6 wk	Low (90–96) vs high (98–100)	14 vs 18	Threshold ROP (ET-ROP ²⁴)
Vanderveen et al ¹¹ (2006)	Retrospective cohort	2000–2003	28	<1250	323	First 4 wk	Low (85–93) vs high (87–97)	5.6 vs 17.5	Prethreshold ROP (ET-ROP ²⁴)
Tin et al ¹⁰ (2001)	Prospective cohort	1990–1994	<28	810–1074	295	First 8 wk	Low (70–94) vs high (85–98)	8.8 vs 19.7	Threshold ROP (CRYO-ROP ²⁵)
Deulofeut et al ¹⁴ (2006)	Prospective cohort	2000–2004	26–27 (mean)	<1250	373	Started at birth	Low (85–93) vs high (92–100)	4 vs 7	Stage 3/4 ROP (ICROP ^{21–23})

GA indicates gestational age; ICROP, international classification of retinopathy of prematurity.

TABLE 2

Characteristics of Studies That Evaluated the Association Between High Oxygen Saturation and Severe ROP Risk After a PMA of 32 in Preterm Infants Included in the Meta-analysis

Author	Study Type	Recruitment Period	GA, wk	Birth Weight, g	n	Oxygen Timing or Duration, wk	Target Oxygen Saturation (%)	Severe ROP, %	Severe ROP Outcome
McGregor et al ¹⁷ (2002)	Prospective cohort	1996–1999	26.2 ± 1.8 (mean)	Unknown	365	36.7 ± 2.5 (mean PMA)	High (>94) vs low (< 94)	25 vs 46	Prethreshold to threshold ROP (STOP-ROP)
STOP-ROP group ¹⁸ (1999)	RCT	1994–1999	25.4 ± 1.5 (mean)	726 ± 160	649	35.4 ± 2 (mean PMA)	High (96–99) vs low (89–94)	41 vs 48	Prethreshold to threshold ROP (STOP-ROP)
Gaynon et al ¹⁵ (1997)	Retrospective cohort	1985–1993	26–27 (mean)	814–986	153	36 to ~38 + 9 to ~10 (mean PMA)	High (99) vs low (92–96)	7 vs 37	Threshold ROP (CRYO-ROP ²⁵)
Askie et al ¹⁹ (2003)	RCT	1996–2000	<30	917	358	32 + 1 to ~10 (PMA)	High (95–98) vs low (91–94)	12 vs 16	Stage 3/4 ROP (ICROP ^{21–23})
Seiberth et al ¹⁶ (1998)	Cohort	1994–1996	24–32	Unknown	117	33–42 (PMA; ROP stage 3)	High (< 98) vs low historic	1.8 vs 4.2	Threshold ROP

GA indicates gestational age; ICROP, international classification of retinopathy of prematurity.

TABLE 3

Summary Estimates of Early and Late Oxygen Saturation and Severe ROP in Premature Infants, Stratified According to Study Characteristics

Study Characteristic	No. of Studies	No. of Cases	Relative Risk (95% CI)	<i>P</i>
Early oxygen (first several weeks after birth)				
Low-oxygen low limit of 83%	2	645	0.34 (0.18–0.65)	.16
Low-oxygen low limit of >83%	3	801	0.60 (0.38–0.95)	
Duration of oxygen 4 wk	3	723	0.49 (0.28–0.88)	.28
Not specified	2	723	0.42 (0.17–1.03)	
Late oxygen (after a PMA of 32 wk)				
High-oxygen low limit of 98%	2	270	0.27 (0.14–0.50)	.005
High-oxygen low limit of <98%	3	1372	0.72 (0.54–0.96)	
Mean PMA 36 wk	2	518	0.38 (0.17–0.84)	.31
32–35 wk	3	1124	0.63 (0.34–1.16)	
RCTs	2	1007	0.84 (0.71–0.99)	.001
Cohort studies	3	635	0.46 (0.35–0.61)	

TABLE 4
Baseline Characteristics, Developmental Outcomes, and Mortality Rates in the Early Oxygen Studies

	Wright et al ¹²		Wallace et al ¹³		Vandervleen et al ¹¹		Tin et al ¹⁰		Deulofeut et al ¹⁴	
	High O ₂	Low O ₂	High O ₂	Low O ₂	High O ₂	Low O ₂	High O ₂	Low O ₂	High O ₂	Low O ₂
Gender, % male	NA	NA	NA	NA	NA	NA	55	46	48	50
Race, %	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
White	—	—	—	—	—	—	—	—	89	87
Black	—	—	—	—	—	—	—	—	4	4
Asian	—	—	—	—	—	—	—	—	0	1
Developmental outcomes, %	NA	NA	NA	NA	NA	NA	17 (CP)	15 (CP)	3 (PVL)	4 (PVL)
Mortality, %	7.9	9.4	NA	NA	NA	NA	47	48	18	19

NA indicates not applicable; CP, cerebral palsy; PVL, periventricular leukomalacia.

TABLE 5
Baseline Characteristics, Developmental Outcomes, and Mortality Rates in the Late Oxygen Studies

	McGregor et al ¹⁷		STOP-ROP Group ¹⁸		Gaynon et al ¹⁵		Askie et al ¹⁹		Seiberth et al ¹⁶	
	High O ₂	Low O ₂	High O ₂	Low O ₂	High O ₂	Low O ₂	High O ₂	Low O ₂	High O ₂	Low O ₂
Gender, % male	60	62	60.5	53.9	NA	NA	54	52	NA	NA
Race, %										
White	67	68	55	55	—	—	—	—	—	—
Black	21	21	31	28	—	—	—	—	—	—
Other	12	11	14	17	—	—	—	—	—	—
Developmental outcomes, %	NA	NA	3.4 ± 1.4 (R-PDQ) ^a	3.5 ± 1.4 (R-PDQ) ^a	NA	NA	23 (MDA)	24 (MDA)	NA	NA
Mortality, %	NA	NA	2.8	2.2	NA	NA	5	3	NA	NA

R-PDQ indicates Revised Parental Denver Questionnaire for development level; MDA, major developmental abnormalities including blindness, cerebral palsy, or a general quotient on the revised Griffiths Mental Development Scales that was >2 SDs below the mean.

^aMean ± SD.