Strategies to Prevent Severe Retinopathy of Prematurity: A 2020 Update and Meta-analysis

Talkad S. Raghuveer, MD,* R. Zackula, MA†

*Departments of *Pediatrics and †Research, University of Kansas School of Medicine at Wichita, Wichita, KS*

Practice Gaps

The incidence of retinopathy of prematurity (ROP) and severe ROP continues to be a concern in extremely preterm infants in the United States. It is important to develop strategies to prevent severe ROP based on our understanding of the pathogenesis of ROP and the best available evidence.

Abstract

The incidence of retinopathy of prematurity (ROP) is showing an increasing trend in the United States. This may be because of increasing survival rates among extremely preterm infants (<25 weeks' gestation) and targeting higher oxygen saturation. Five randomized clinical trials of low versus high oxygen saturation target ranges found increased mortality in the low oxygen saturation target group and an increased incidence of ROP in the high oxygen saturation target group. The American Academy of Pediatrics recommends using an oxygen saturation target range of 90% to 95% in extremely low-birthweight infants. The change of practice to target this higher oxygen saturation range, from admission until discharge, may be contributing to the increasing incidence of ROP in extremely preterm infants. To decrease the incidence of ROP without increasing mortality, 2 new cohort trials suggest gradually increasing oxygen saturation targets as preterm infants mature. There is evidence that human milk, vitamin A, and omega-3 fatty acids can help, in addition to continuous oxygen saturation monitoring, to decrease the risk of ROP. We review this literature and provide a meta-analysis to evaluate the evidence.

Objectives After completing this article, readers should be able to:

1. Describe the pathogenesis of the 2 phases of retinopathy of prematurity.
2. Explain the current evidence regarding oxygen saturation targets that can decrease severe retinopathy without increasing mortality in extremely preterm infants.
3. Based on current evidence, summarize therapies and oxygen saturation targets that can help to decrease the risk of retinopathy of prematurity.

AUTHOR DISCLOSURE Dr Raghuveer and Ms Zackula have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

aOR	adjusted odds ratio
BEAT-ROP	Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity
BOOST	Benefits of Oxygen Saturation Targeting
COT	Canadian Oxygen Trial
DHA	docosahexaenoic acid
EPO	erythropoietin
ET-ROP	Early Treatment for Retinopathy of Prematurity
IGF-1	insulinlike growth factor 1
mRNA	messenger RNA
NeOProM	Neonatal Oxygen Prospective Meta-analysis
OIR	oxygen-induced retinopathy
PMA	postmenstrual age
RCT	randomized controlled trial
ROP	retinopathy of prematurity
STOP-ROP	Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity
SUPPORT	Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial
VEGF	vascular endothelial growth factor
VEGFR2	VEGF receptor 2

INTRODUCTION

Retinopathy of prematurity (ROP) is an abnormal development of retinal vessels that occurs in extremely preterm infants. Severe ROP is a leading cause of decreased vision/blindness in children worldwide. (1)(2) The increased survival of extremely preterm infants, especially with birth gestational ages between 22 and 24 weeks, has increased the population of premature infants at risk for ROP/severe ROP. (3)

INCIDENCE OF ROP/SEVERE ROP

Data from the Neonatal Research Network Centers showed that in the 2008–2012 cohort of extremely preterm infants (22–28 weeks' gestation) the incidence of ROP was 56% for all infants evaluated, whereas the incidence of severe ROP (stage ≥3) was 12%. (3) However, for infants with a birth gestational age between 22 and 24 weeks, the incidence of ROP and severe ROP was 90% and 43%, respectively. Thus, there was an inverse relationship between the incidence of ROP and gestational age. (3) A cross-sectional study analyzed the incidence of ROP in the United States by querying the Healthcare Cost and Utilization Project Kids' Inpatient Database. The incidence of ROP showed an increasing trend from 14.7% in 2000 to 19.88% in 2012. (4)

Two single-center cohort studies, one in Canada and the other in the United States, also reported an increasing incidence of ROP and severe ROP. (5)(6) The Canadian study showed that the incidence of ROP was 40.4% in the years between 2006 and 2010 and 67.1% between 2010 and 2016; severe ROP increased from 9.2% to 14.3% during these periods. (5) The authors attributed the increased incidence of ROP to the higher number of infants born at less than or equal to 24 weeks' gestation in the later cohort (15.7%) compared with the early cohort (8.7%). In the US study (2010–2015), the incidence of ROP and treated ROP in preterm infants of less than 28 weeks' gestation at birth was high, at 67% and 29.7%, respectively. The incidence of treated ROP (9.9%) was also high in infants born between 28 and 34 weeks' gestation. (6) Thus, the trend shows increasing incidence of ROP and severe ROP at many centers. This trend is concerning because severe ROP can have a negative impact on long-term visual and neurodevelopmental outcomes in extremely premature infants. In addition, there are significant side effects from treatment (laser surgery, vascular endothelial growth factor [VEGF] inhibitors or a combination of the two) of severe ROP.

SEVERE ROP AND LONG-TERM NEURODEVELOPMENTAL OUTCOME

Severe ROP is a predictor of functional disability in multiple domains in childhood (7). Infants with severe ROP, compared with infants without severe ROP, showed significant maturational delay of the optic radiation, posterior limb of internal capsule, external capsule, and posterior white matter that was associated with poorer cognitive and motor outcomes at 18 months' corrected age. (8) After adjusting for perinatal risk factors, Molloy et al reported that children with severe ROP, compared with those without severe ROP, had a significantly lower longitudinal IQ from 2 to 18 years of age. (9)

Studies have compared neurodevelopmental outcomes based on type of treatment for severe ROP: VEGF inhibitor versus laser surgery. In the Morin et al study, infants treated with the VEGF inhibitor bevacizumab had higher odds of severe neurodevelopmental disability (adjusted odds ratio [aOR]=3.1, 95% confidence interval [CI]=1.2–8.4) compared with the infants in the laser therapy group. (10) In the Natarajan et al study, the odds of death (aOR=2.54, 95% CI=1.42–4.55; *P*=.002) and cognitive score less than 85 (aOR=1.78, 95% CI=1.09–2.91; *P*=.02) were significantly higher in the infants treated with bevacizumab compared with laser surgery, but the odds of severe neurodevelopmental impairment did not differ between the groups (aOR=1.14, 95% CI=0.76–1.70). (11) Both of these reports were observational studies and there was no information regarding why one mode of treatment was chosen over the other to treat severe ROP. However, in the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) randomized controlled trial (RCT), which compared VEGF inhibitor treatment to laser therapy to treat severe ROP, no difference was found in neurodevelopmental outcomes in infants treated with bevacizumab versus laser surgery. (12)

ROP AND VISUAL OUTCOMES

Visual Acuity

Premature infants with advanced stages of ROP are at the highest risk for severe visual impairment or blindness. (13) In the Natarajan et al study of preterm infants treated for severe ROP (laser surgery, bevacizumab, or both), 6.3% (23/362) developed bilateral blindness, 4.7% (17/362) developed blindness in one eye with some function in at least one eye, and 3.9% (14/362) developed blindness in at least one eye. (11)

Refractive Errors

In the Early Treatment for Retinopathy of Prematurity (ET-ROP) trial, infants with severe ROP who were treated with laser therapy had a higher prevalence of myopia and high myopia (<−8 to −5 diopters [D]) than infants with ROP who experienced spontaneous regression. (14) In the BEAT-ROP RCT, infants treated with bevacizumab had significantly lower rates of myopia, particularly high myopia (zone 1: 3.8% vs 51.4%, zone 2: posterior: 1.7% vs 36.4% in the VEGF inhibitor vs laser ablation groups, respectively) at 2.5 years of age. However, treatment of recurrent ROP resulted in higher rates of high myopia (76.5% in those patients treated with laser vs 25% in patients treated with bevacizumab). (15) The prevalence of high myopia (defined as spherical equivalent ≥−5 D) was 8% to 35% with bevacizumab, (16) and in a small study (n=37 infants, 72 eyes) high myopia was 0% with the VEGF inhibitor ranibizumab compared with 14.6% with bevacizumab. (17)

In the ET-ROP study, the incidence of strabismus was 44% at 6 years of age. (18)

SIDE EFFECTS OF ROP TREATMENT

Currently 2 treatment options are available for severe ROP: laser therapy and/or VEGF inhibitors. Many side effects occur with both modalities of treatment. Laser therapy increases the risk of loss of peripheral vision, myopia, cataract, and pthisis bulbi (shrunken, nonfunctional eye). (14)(19) A meta-analysis found that laser therapy was associated with a decreased spherical equivalent, a shallower anterior chamber, and an increased incidence of astigmatism and myopia. (20) In addition, there are potential side effects from intubation and anesthesia, which are often needed for laser therapy.

Bevacizumab is a humanized monoclonal antibody to VEGF that is used primarily as a chemotherapy agent with no pharmacologic formulation for premature infants. (21) Bevacizumab can be detected in the serum 1 to 2 days after ROP treatment and persists in the serum for 2 months. (22). Serum VEGF decreases slowly after laser surgery but falls rapidly after bevacizumab treatment. The serum VEGF levels have been found to be 50% lower in infants treated with bevacizumab compared with laser surgery. (22) After treatment with a VEGF inhibitor, serum VEGF was suppressed for 1 (ranibizumab) to 8 weeks (bevacizumab). (22)(23)(24) The clinical significance of prolonged low levels of serum VEGF levels, after treatment with a VEGF inhibitor, on the angiogenesis in the lungs, kidneys, and brain of premature infants is unknown.

Recurrence can occur after treatment with either laser surgery or VEGF inhibitors. Infants with zone 1 disease treated with VEGF inhibitors may not develop adequate retinal vessels and are at risk for recurrence and retreatment as late as 55 weeks' postmenstrual age (PMA). (25) Therefore, infants treated with VEGF inhibitors need prolonged follow-up.

IMPORTANCE OF PREVENTING SEVERE ROP

Pathogenesis of ROP

To develop strategies to prevent ROP, it is important to understand a) the normal retinal vascular development in utero, and b) the altered retinal vascular development after premature birth.

Normal Retinal Vascular Development. In the human fetus, the retinal vasculature develops by vasculogenesis (de novo synthesis of blood vessels) and angiogenesis (formation of blood vessels from preexisting vessels). Vasculogenesis starts at approximately 12 weeks' gestation as vascular precursor cells start to grow from the hyaloid artery and migrate toward the periphery to form future retinal arcades and mesenchymal cells aggregate to form vascular cords. Retinal vasculogenesis is complete by 21 to 22 weeks' gestation. Retinal angiogenesis starts at 17 to 18 weeks' gestation and leads to the development of new vessels from existing vessels: perifoveal vessels, peripheral vessels, deep plexus vessels, and the capillary system in the fetal retina. Retinal angiogenesis is complete when superficial and deep retinal vessels reach the ora serrata between 36 and 40 weeks' gestation. (26)

VEGF is necessary for retinal vasculogenesis. The developing retinal tissues have an increased demand for oxygen, which leads to localized hypoxia; in response, the expression of local VEGF is increased. Retinal blood vessels grow by following a wave of physiologic hypoxia in the retina. Vessels grow toward the VEGF stimulus with formation of new vessels and continue to progress toward the adjacent stimulus of VEGF triggered by a distant area of hypoxia (27)(28).

Abnormal Retinal Vascular Development Leading to ROP. In 1954, Ashton et al showed that high oxygen concentration in kittens led to obliteration of growing retinal complexes (vaso-obliteritative phase). Later, when these kittens were exposed to room air, there was profuse growth of vessels into the retina and into the vitreous (vasoproliferative phase). (29) Extremely preterm infants are at risk for a delay/decrease in physiologic retinal vascular development (phase 1) with subsequent vasoproliferation (phase 2). (30) Two rodent models, the Smith mouse model and the Penn rat model, of oxygen-induced retinopathy (OIR) have been used to study the pathogenesis of ROP. (31) The changes in retinal

vasculature in the OIR model resemble changes seen in preterm infants with ROP. In the following section, we describe the evidence for the pathogenesis of ROP based on rodent models of OIR and clinical studies in premature infants.

PHASE 1 ROP

Hyperoxia Causes Reduced/Altered Physiologic Retinal Vascular Development

VEGF facilitates the development of retinal vessels during normal angiogenesis. In the mouse model of OIR, hyperoxia results in reduced VEGF messenger RNA (mRNA) and protein with decreased retinal vessel growth; exogenous VEGF has been found to stop this vaso-obliteration. (32)

Erythropoietin (EPO) is expressed locally during retinal hypoxia and has been shown to be an important angiogenic factor. (33) In the OIR mouse model, EPO protein and receptor are present in retinal vessels and the EPO mRNA expression is reduced with hyperoxia. (34) By increasing the local expression of EPO, retinal vaso-obliteration was prevented. (34)

Human preterm birth leads to an immediate increase in oxygen tension (an increase from the intrauterine partial pressure of oxygen of 50 mm Hg to the ambient air postdelivery partial pressure of oxygen of 160 mm Hg, which is even higher with supplemental oxygen). Increased oxygen tension in the retina can lead to suppression of retinal VEGF and EPO, as seen in the animal models of OIR, leading to arrest/decrease of retinal vessel growth.

Normal retinal vessel development is decreased in insulin-like growth factor 1 (IGF-1) knockout mice, and low IGF-1 suppresses VEGF survival signaling in the retinal endothelial cells. (35) Low IGF-1 levels or lack of IGF-1, in the mouse model, prevents normal retinal vessel development despite the presence of normal levels of VEGF. (35) In many premature infants, serum IGF-1 levels fall shortly after birth. (36)

In the OIR mouse model, an increase in dietary omega-3 fatty acids leads to an increase in retinal omega-3, increased retinal vessel regrowth, and decreased avascular retina in phase 1 ROP. (37) Extremely preterm infants have lower serum omega-3 fatty acid levels, which may contribute to phase 1 ROP. (38)

Thus, retinal hyperoxia leads to a decrease in retinal VEGF and EPO, and a decreased amount of growth factors (IGF-1 and omega-3 fatty acid) in the serum increases the risk of phase 1 ROP.

PHASE 2 ROP

Hypoxia from an Avascular Peripheral Retina Causes Vasoproliferation (ie, Neovascularization)

The metabolic activity in the retina increases as preterm infants mature. However, infants with phase 1 ROP are at risk for retinal hypoxia because of the avascular peripheral retina. These infants can progress to phase 2 ROP starting at 30 to 32 weeks' PMA, with peak phase 2 ROP occurring at approximately 36 to 38 weeks' PMA. (39) In very immature infants born at less than or equal to 24 weeks' gestation, stage 3 ROP may develop by 31 weeks' PMA. (40)

In the OIR rodent model, exposure to high or fluctuating amounts of supplemental oxygen led to vaso-obliteration of retinal vessels (phase 1 ROP, hypoxic inner retina) and subsequent exposure to room air led to elevation of VEGF mRNA and protein levels, resulting in neovascularization (phase 2 ROP). (41)(42) In a murine model, the inhibition of VEGF by VEGF-receptor chimeric proteins decreased neovascularization by 56%. (43) In the rat OIR model, subretinal injections of lentiviral vectors with endothelial cell-specific VEGF receptor 2 (VEGFR2) short hairpin RNA inhibited vasoproliferation and improved physiologic retinal vascular development. Excessive stimulation of VEGFR2 from hypoxia and disruption of endothelial cell function in the retina may be an important mechanism for abnormal physiologic vascular development and severe ROP found in premature infants. (44)

In addition to elevated VEGF, increased levels of retinal EPO may play a role in the pathogenesis of phase 2 ROP. EPO (in addition to VEGF) was significantly elevated in the vitreous of eyes of preterm infants with ROP compared with infants without ROP. (45) Based on this evidence, it may be prudent to avoid EPO in patients with phase 2 ROP.

In the mouse OIR model, a diet rich in omega-3 fatty acids led to decreased neovascularization in phase 2 ROP because of a decrease in retinal tumor necrosis factor α levels. (37) In addition, omega-3 fatty acids have a direct inhibitory effect on neovascularization via the peroxisome proliferator-activated receptor γ pathway. This study found a reduction in neovascularization by 40% without altering the normal growth of retinal vessels; this decreased neovascularization was independent of the VEGF pathway. (46)

STRATEGIES TO DECREASE ROP

Several strategies have been shown to decrease ROP and severe ROP (Fig 1). In this section, we provide the

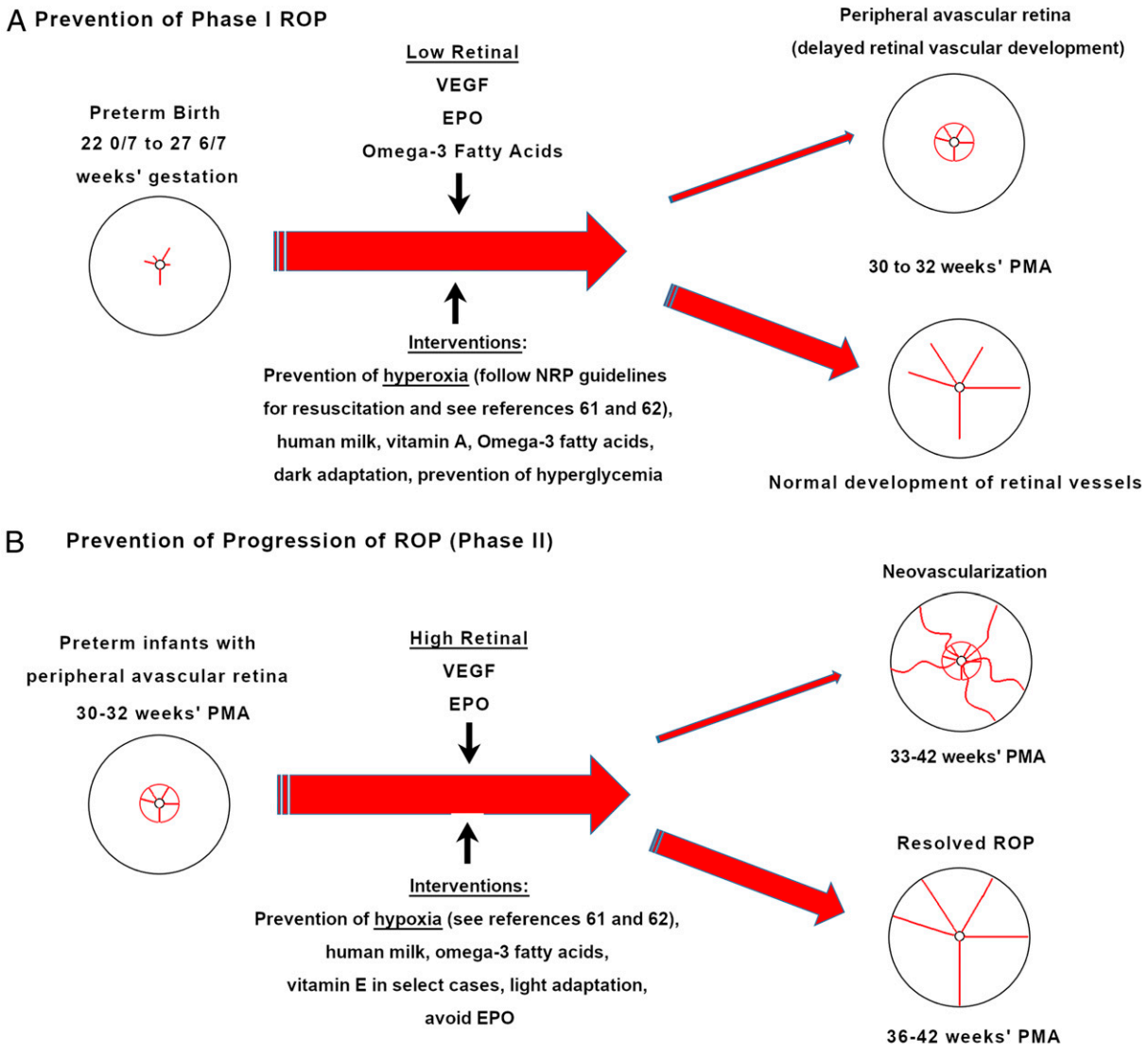

Figure 1. Phase 1 retinopathy of prematurity (ROP). There is risk of exposure to retinal hyperoxia and significant decrease in the retinal levels of vascular endothelial growth factor (VEGF) and erythropoietin (EPO; compared to in utero levels) after preterm birth. Retinal levels of nutrients such as omega-3 fatty acids also fall after preterm birth. These factors may delay the retinal vascular development in a significant number of extremely premature infants born between 22 0/7 and 27 6/7 weeks' gestation. Interventions suggested in A can improve the chances of normal retinal vascular development (no ROP). However, many extremely preterm infants may develop ROP (delayed development of retinal vascular development) by 30 to 32 weeks' postmenstrual age (PMA) despite these interventions. B. Phase 2 ROP. In premature infants with delayed development of retinal vascular development (phase 1 ROP), there is a risk of retinal hypoxia leading to significant increase in retinal levels of VEGF and EPO at or after 30 to 32 weeks' PMA. Interventions suggested in B can improve the chances of regression of ROP and allow for normal retinal vascular development. Some extremely preterm infants may progress to neovascularization (severe ROP), despite the suggested interventions, and may need treatment (laser or VEGF inhibitor or both).

background, summarize the results of our meta-analysis, and discuss the evidence for each strategy.

Supplemental Oxygen and Oxygen Saturation Target Ranges and ROP

Background. Limiting supplemental oxygen based on an oxygen saturation target range is by far the most important factor (via the VEGF pathway), *but not the only factor*, to decrease ROP. An abbreviated history of monitoring oxygen therapy is described here; other reviews provide more details. (47)

In 1951, Campbell discovered that "intensive" oxygen therapy was a cause for retrolental fibroplasia (previous term for ROP). (48) A subsequent multicenter cooperative

study in preterm infants (birthweight ≤1,500 g, N=786) found that a higher concentration of supplemental oxygen caused significantly more ROP compared with restricting supplemental oxygen to 40% or less. The mortality was 10% higher in the oxygen-restricted group. (49) As a result, the clinical practice changed to restricting oxygen supplementation to 40% and may have contributed to an increase in mortality in low birthweight infants (1,000–1,499 g) from 42% in the 1944–1948 cohort to 58% in the 1954–1958 cohort. (50) A study by Flynn et al in 1992 showed that the duration of having a transcutaneous oxygen tension of 80 mm Hg or higher in the first 4 weeks after birth was associated with an increased incidence of ROP/severe ROP in preterm infants weighing less than or equal to 1,300 g. (51)

The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial (52) included preterm infants with confirmed prethreshold ROP in at least 1 eye and oxygen saturation less than 94% who were randomized to an oxygen saturation range of either 89% to 94% (conventional oxygen arm) or 96% to 99% (supplemental oxygen arm). The primary outcome was progression to threshold ROP needing treatment (laser or cryotherapy). The study saturation targets were implemented for a minimum of 2 weeks. The preterm infants in this study were born at 25.4±1.5 weeks' gestation but were not included in the study until 35.4±2.5 weeks' PMA when phase 2 ROP was already well-established.

There was no significant difference in the number of infants who progressed to threshold ROP (48.5% vs 40.9%). Subgroup analysis showed that infants without plus disease at randomization progressed to the threshold significantly less frequently in the supplemental oxygen arm (32%) compared with the conventional oxygen arm (46%). In addition, subjects with zone II ROP progressed less frequently with supplemental oxygen (37%) compared with the conventional oxygen group (46%). Oxygen requirement increased by 5% to 9% after randomization to the supplemental oxygen group, and at 50 weeks' PMA, significantly more infants in the supplemental oxygen group than in the conventional oxygen group continued to need supplemental oxygen (46.8% vs 37%, *P*=.002).

In the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) study (53), premature infants (born at 24 weeks to 27 weeks and 6 days' gestational age) were randomized to either a low oxygen saturation range (85%–89%) or a high oxygen saturation range (91%–95%). The oxygen saturation targets were started shortly after birth and continued until discharge (or death). The primary outcome was a composite of severe ROP (threshold ROP, need for treatment), death before discharge, or both. The composite primary outcome was similar between the groups. Although an increased incidence of severe ROP was observed in the higher oxygen saturation group (17.9% vs 8.6%), the infants with a low oxygen saturation range (85%–89%) compared with a high oxygen saturation range (91%–95%) had an increased mortality (19.9% vs 16.2%).

In a study of premature infants of less than 29 weeks' gestation, the partial pressure of oxygen in arterial blood was significantly lower with an oxygen saturation range of 85% to 89% compared with an oxygen saturation range of 90% to 95% (~28.5–53.6 vs ~34.5–66 mm Hg, respectively). (54)

The SUPPORT study was 1 of 5 randomized trials with similar protocols. The others were the Benefits of Oxygen Saturation Targeting (BOOST) II trials in the United Kingdom (UK), Australia, and New Zealand (55) and the Canadian Oxygen Trial (COT) (56). In these trials, the subjects were of less than 28 weeks' gestation, and the primary outcome was to evaluate the effects of oxygen saturation target ranges of 85% to 89% compared with 91% to 95% on survival and neurodevelopmental outcomes at 18 to 24 months of age. Halfway through the study, the calibration algorithm in the study pulse oximeters were changed in the UK and Australia, and it is not known if this change had any impact on the results. The recruitment to BOOST II in the UK and Australia was closed prematurely when interim analysis showed that infants in the low oxygen saturation group (85%–89%) had a higher mortality at 36 weeks' PMA (21.8%) compared with those in the high oxygen saturation group (91%–95%) with a mortality of 13.3%.

The data from 4,965 infants enrolled in the aforementioned 5 trials were combined as a part of the Neonatal Oxygen Prospective Meta-analysis (NeOProM) collaboration. A meta-analysis (57) showed that the infants in the lower oxygen saturation group (85%–89%), compared with those in the higher oxygen saturation group (91%–95%), had a significantly increased incidence of death at 18 to 24 months' corrected age (19.9%, 484/2,433 vs 17.1%, 418/2,440, risk ratio [RR]=1.16) and a decreased incidence of severe ROP/ROP requiring treatment (10.6%, 214/2,022 vs 14.8%, 305/2,067, RR=0.72).

Meta-analysis of Oxygen Saturation and ROP (Fig 2, Fig 3). Results from our meta-analysis of trials of oxygen saturation monitoring and ROP (52)(53)(55)(56) showed a significant increased risk of death (Fig 2) in the lower oxygen saturation group (85%–89%) compared with the higher oxygen saturation group (91%–95%): RR=1.16, 95% CI=1.03–1.31, *P*=.02; risk difference (RD)=0.03, 95% CI=0.00–0.05. The risk for severe ROP (Fig 3) was significantly reduced in infants in the lower oxygen saturation

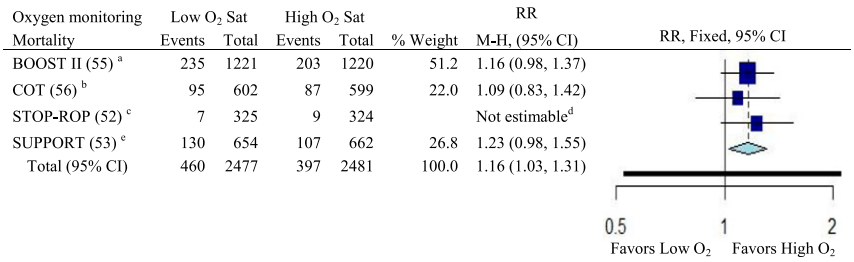

Figure 2. Meta-analysis of mortality risk in infants exposed to low versus high oxygen saturations. Heterogeneity: χ^2=0.47, df=2 (*P*=.79); I^2=0%. Test for overall effect: Z=2.39 (*P*=.02). Statistical method: Mantel-Haenszel, Fixed Effect model. Interpretation: Of the 5 trials evaluated, which included 4,958 infants, the risk of death was observed to be significantly increased for the lower oxygen saturation group (85%-89%) compared with the higher oxygen saturation group (91%-95%) (RR = 1.16, 95% CI=1.03–1.31, *P*=.02; RD=0.03, 95% CI=0.00, 0.05). Note that the intervention for STOP-ROP differed from the other trials (see footnote c) and was deemed not estimable. Differences among trials are reflected in the test for heterogeneity, which were not significant (*P*=.79). In addition, I^2=0% indicates that effect sizes are consistent across studies in the meta-analysis, which is demonstrated in the forest plot as overlapping confidence intervals. Meta-analyses were conducted in Review Manager, version 5.3 with either risk ratios or odds ratios (see Figures 2-7). Forest plots were conducted in R utilizing risk ratios only (see Harrer, M., Cuijpers, P., Furukawa, T.A, & Ebert, D. D. (2019). Doing Meta-Analysis in R: A Hand-on Guide. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/). In addition, treatment arm continuity correction was used in R to adjust for uneven sample sizes between groups. Thus, results may differ slightly on pooled effect sizes. BOOST=Benefits of Oxygen Saturation Targeting; CI=confidence interval; COT=Canadian Oxygen Trial; M-H=Mantel-Haenszel (fixed effect); ROP=retinopathy of prematurity; RR=risk ratio; STOP-ROP=Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity; SUPPORT=Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial.
[a]Death before hospital discharge.
[b]Death before discharge.
[c]Oxygen levels: 96-99% vs 89-95%; all deaths at 3 months' corrected age.
[d]Not estimable if interventions differed, populations differed, events were not directly reported in article, or if conflicting data reported in article.
[e]Death before discharge.

group compared with the higher oxygen saturation group: RR=0.73, 95% CI=0.62–0.87, *P*<.001; RD=−0.04, 95% CI=−0.06 to −0.02.

Discussion of Oxygen Saturation Monitoring and ROP. The rationale for choosing the oxygen saturation ranges in the 5 aforementioned clinical trials (NeOProM) is not clear. The static oxygen saturation targets (both low and high) do not mirror the pathogenesis of ROP. Specifically, the lower oxygen target range (85%–89%) could potentially decrease the risk of retinal hyperoxia in phase 1 ROP but would increase the risk of retinal hypoxia in phase 2 ROP. However, the higher oxygen saturation range (91%–95%) could significantly increase the risk of retinal hyperoxia, especially in premature infants born before 25 weeks' gestation, leading to a larger avascular peripheral retinal region (phase 1 ROP) and increased risk of neovascularization of the retina (phase 2 ROP). This pathophysiology may have contributed to the increased incidence of severe ROP in the higher oxygen saturation group.

The American Academy of Pediatrics Committee on Fetus and Newborn recommends a target oxygen saturation range of 90% to 95% in extremely low-birthweight infants "as it may be safer than 85%–89%." (58) Many centers in the United States and other countries have adopted this recommendation. A study from Australia found an increased incidence of ROP and severe ROP after changing the oxygen saturation target range from 88%–92% to 91%–95%. (59) A US study also found an increased incidence of any ROP,

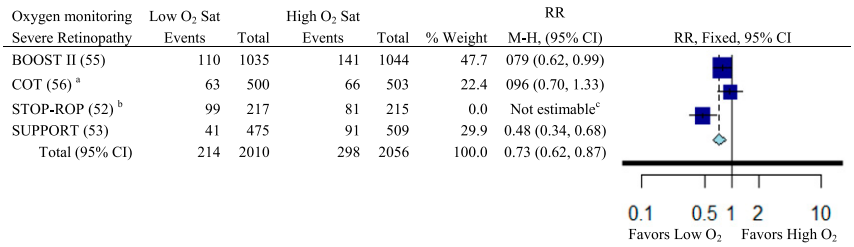

Figure 3. Meta-analysis of risk of severe ROP in infants exposed to high versus low oxygen saturations. Test for overall effect: Z = 3.66 (*P*<.01). Heterogeneity: χ^2=8.61, df=2 (*P*=.01); I^2=77%. Statistical method: Mantel-Haenszel, Fixed Effect model. Interpretation: Among the 5 trials, 4,066 infants were evaluated; results from the meta-analysis showed a significantly reduced risk of severe ROP in the lower oxygen saturation group compared with the higher oxygen saturation (RR=0.73, 95% CI=0.62–0.87, *P*<.001; RD=-0.04, 95% CI=-0.06 to -0.02). However, results for heterogeneity were significant (*P*=.01, I^2=77%), indicating considerable inconsistency in effect sizes among trials (note the nonoverlapping confidence intervals observed in the forest plot). Similar to the evaluation of mortality, the STOP-ROP trial was not included due to differences in oxygen saturation target goals for the interventions. CI=confidence interval; M-H=Mantel-Haenszel (fixed effect); ROP=retinopathy of prematurity; RR=risk ratio.
[a]Survived to postmenstrual age of 36 weeks with 1 retinal exam.
[b]Oxygen saturation 89-95% vs. 96-99%.
[c]Not estimable if interventions differed, populations differed, events were not directly reported in article, or if conflicting data reported in article.

type 1 ROP, and treated ROP after changing from a biphasic target (85%–92% until 34 weeks' PMA and >94% at >34 weeks' PMA) to a static 90% to 95% oxygen saturation target range (independent of gestation at birth and PMA). (60)

There is evidence (from single-center retrospective trials and the NeOProM trials) that targeting a constant oxygen saturation range of 90% to 95% increases the risk of ROP and severe ROP. Thus, the question remains: "Which oxygen saturation target ranges would decrease ROP AND not increase mortality in extremely premature infants?" The answer may be found in 2 recent retrospective cohort studies that showed a significant decrease in the incidence of severe ROP, without an increase in mortality. (61)(62) Both studies showed that *gradually* increasing oxygen saturation targets prevents early hyperoxia, and later retinal hypoxia, when compared with static oxygen saturation targets.

In the Cayabyab et al study (61), oxygen saturation targets were gradually increased to mimic the increasing oxygen delivery and oxygen consumption ratios similar to fetal life. The incidence of ROP/severe ROP in extremely premature infants (24–27 weeks' gestation) from 2 periods was compared. In the 1995–2001 infant group (group 1), the oxygen saturation target ranges were 90% to 94% from birth to 35 weeks' PMA and greater than 94% starting at 36 weeks' PMA. In the 2003–2010 infant group (group 2), the oxygen saturation target ranges were 83% to 89% from birth to 32 weeks' PMA, 90% to 94% from 33 weeks to 35 weeks' PMA, and greater than 94% at 36 weeks' PMA ("graded oxygen saturation targets"). There was no significant difference in mortality between the 2 groups. However, there was a significant decrease in the incidence of severe ROP (48.3% in group 1 vs 21.3% in group 2) and the need for laser treatment (34.9% in group 1 vs 19.7% in group 2). Thus, the targeting graded oxygen saturation was deemed superior in this study.

In the Colaizy et al study (62), oxygen saturation alarm limits were set at 80% to 93%, with an oxygen saturation target range of 84% to 93% for infants of less than or equal to 26 weeks' PMA; alarm limits were 80% to 95% with a target of 86% to 94% for infants of 27 to 31 weeks' PMA; and alarm limits were 85% to 98% with an oxygen saturation target range of 90% to 95% at greater than 32 weeks' PMA. In epoch 1 (2002–2007), the oxygen saturation targets were not changed if infants were diagnosed with prethreshold ROP. In epoch 2 (2008–2012), in those infants who developed stage 2 ROP and were receiving low-flow nasal cannula oxygen (<1 L/min), the oxygen saturation targets were increased to greater than 94% (with alarm limits of 90%–100%). For infants receiving high-flow nasal cannula, mechanical ventilation, or nasal continuous positive airway pressure, the oxygen saturation target was also greater than 94% (alarm limits of 90%–100%) as long as the FiO_2 did not exceed 0.5. In both situations, the supplemental oxygen was not weaned below an effective oxygen level of 35% to 40% (floor) until the ROP had improved. There was a significant decrease in the progression beyond stage 2 during epoch 2 (23%) compared with epoch 1 (44%). The incidence of plus disease also decreased in epoch 2 (12.6%) compared with epoch 1 (18.9%). The rationale for the oxygen saturation targets used in this study was to decrease retinal hyperoxia and allow the physiologic development of retinal vessels to occur (birth to 31 weeks' PMA). After 32 weeks' PMA, higher oxygen saturations were targeted to decrease the risk of hypoxia and prevent the surge of VEGF in phase 2 ROP. Using the oxygen saturation targets from epoch 2, the overall survival was 90% among premature infants born at 23 to 27 weeks' gestation in 2018, whereas the incidence of severe ROP, laser therapy, and necrotizing enterocolitis was 1.6%, 0.8%, and 1.4%, respectively. (J. Klein, MD, personal communication, 2019)

It is known that infants with fluctuating oxygen saturations have an increased risk of severe ROP. (63) Attempts have been made to decrease these fluctuations using an automated oxygen control system (closed loop system) compared with a manual control system. A recent study of the closed loop system showed that preterm infants spent more time in the target range (manual vs automated: 48.4% vs 61.9%) with a significant reduction in time spent greater than 95% (hyperoxia), (41.9% vs 19.3%) but the time spent less than 90% increased (8.6% vs 15.1%). (64) Cerebral near-infrared spectroscopy can be used to improve oxygen monitoring. (65) These new technologies need further study.

Human Milk and ROP

Background. Human milk, especially preterm milk, is rich in a number of bioactive factors. The bioactive factors that are available in preterm human milk that may help to prevent ROP include exogenous (carotenoids, retinol, and α- and γ-tocopherol) and endogenous (superoxide dismutase, glutathione peroxidase, catalase, and glutathione) antioxidants and growth factors (VEGF and IGF-1). (66) A few observational/cohort studies have investigated whether feeding human milk can decrease the risk of ROP/severe ROP and results have been conflicting. (67)(68)(69)(70)(71)(72)(73)(74) In these trials, the percentage of human milk that infants received varied significantly. Three meta-analyses of these clinical studies have been published, (75)(76)(77) and the conclusions are conflicting: human milk feeding (5 studies) potentially decreased the risk for ROP/severe ROP (75); human milk significantly decreased the risk of ROP and severe ROP (76); and no reduction of ROP, but a significant decrease in severe ROP (2 studies) was found with increased human milk exposure. (77)

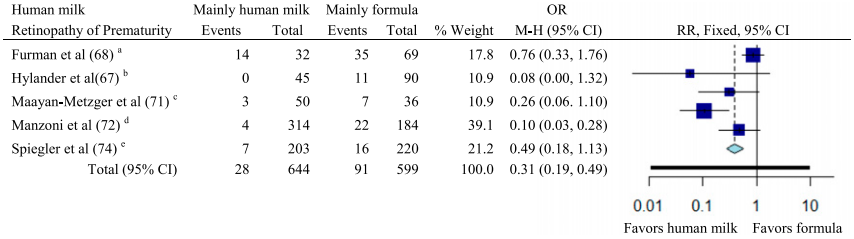

Figure 4. Meta-analysis of human milk and odds of any ROP. Heterogeneity: χ^2=10.60, df=4 (*P*=.03); I^2=62%. Test for overall effect: Z=4.95 (*P*<.001). Statistical method: Mantel-Haenszel, Fixed Effect model. Interpretation: A total of 1,243 infants, from 5 observational studies, were included in the meta-analysis to compare type of milk received. The odds of any ROP was significantly reduced when infants were fed human milk versus formula (OR=0.31, 95% CI=0.19–0.49, *P*<.001; RD=-0.011, 95% CI=-0.14 to -0.08); heterogeneity was significant (*P*=.03, I^2=62%), indicating substantial inconsistent effect sizes among these studies. Using risk ratios produced similar results. These inconsistencies may be accounted for by differences in milk feeding types, exclusive milk type vs not exclusive, enhanced human milk vs not enhanced; by differences in measures for retinopathy, any ROP vs severe ROP; and by bias associated with the study design. CI=confidence interval; M-H=Mantel-Haenszel (fixed effect); OR=odds ratio; ROP=retinopathy of prematurity.
[a]Any ROP; very low birthweight; daily volume of maternal milk ≥50mL/kg vs <25 mL/kg.
[b]Severe ROP, stage 3 and 4; very low birthweight; 80–100% human milk vs <20% human milk and formula.
[c]Severe ROP, stage 3; gestational age 24–28 weeks.
[d]Severe ROP, stage 3 (threshold ROP).
[e]Severe ROP, stage 3; exclusive breastmilk vs exclusive formula.

Meta-analysis of Human Milk and ROP Studies (Fig 4). Our meta-analysis (Fig 4, 5 studies) showed that the odds of any ROP was significantly reduced when extremely premature infants were fed human milk compared with formula (odds ratio [OR]=0.31, 95% CI=0.19–0.49, *P*<.001; RD=−0.011, 95% CI=−0.14 to −0.08). (67)(68)(71)(72)(74)

Discussion of Human Milk and ROP. A US study from 2017 showed that nearly 71% of extremely preterm infants received human milk from their mothers. (78) At many centers, donor human milk is used when the mother is not able to provide milk. Schanler et al found the incidence of severe ROP (stage 3) to be 5.6% in preterm infants of less than 30 weeks' gestation who were fed mother's milk compared with 19% who were fed donor human milk and 14% in those fed preterm formula. (79) In this study, the incidence of necrotizing enterocolitis was the primary outcome measure. A case control study of very low-birthweight infants found no difference in the incidence of ROP when infants were fed mother's milk compared with donor human milk. (80)

Omega-3 Fatty Acids and ROP

Background. Docosahexaenoic acid (DHA, omega-3 fatty acid) and arachidonic acid (omega-6 fatty acid) are essential fatty acids that are transferred to the fetus in the third trimester. Extremely preterm infants are DHA-deficient at birth, which worsens by 1 month of age; the most immature infants are at risk for the largest deficiency. (81) Omega-3

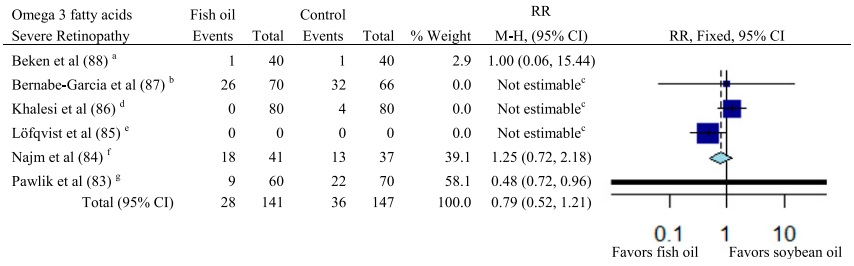

Figure 5. Meta-analysis of omega-3 fatty acids and risk of severe ROP. Heterogeneity: χ^2=4.63, df=2 (*P*=.10); I^2=56.77%. Test for overall effect: Z=1.06 (*P*=.29). Statistical method: Mantel-Haenszel, Fixed Effect model. Interpretation: Three studies, including 288 infants, were evaluated for the association between omega-3 fatty acid and severe ROP. Three studies were omitted in the final meta-analysis because either the number of events (ROP) was not reported or the interventions differed (see "Not estimable" in the table). Results showed a reduced risk of severe ROP in the fish oil group, although this was not significant (RR=0.79, 95% CI=0.52–1.21, *P*=.29). Although test results for heterogeneity were not significant (*P*=.10, I^2=57%), substantial inconsistency of effect sizes was found among studies. Note that data were sparse, especially for Beken et al. study (88), and most sample sizes were small. CI=confidence interval; M-H=Mantel-Haenszel (fixed effect); ROP=retinopathy of prematurity; RR=risk ratio.
[a]Severe ROP stage 3 plus; fish-oil vs soybean oil.
[b]Severe ROP stage 3; DHA vs sunflower oil; conflicting event counts.
[c]Not estimable if interventions differed, populations differed, events were not directly reported in article, or if conflicting data reported in article.
[d]Severe ROP grade III; Omega-3 fatty acids with breast milk vs sterile water.
[e]Severe ROP stage 3; 31 out of 90 infants; event counts per group not reported.
[f]Severe ROP stage 3 or treated for ROP; a 4-oil lipid emulsion vs refined olive + soybean oil.
[g]ROP requiring laser therapy; titrated dosage: an omega-3 fatty acid emulsion + olive/soybean oil vs olive/soybean oil alone.

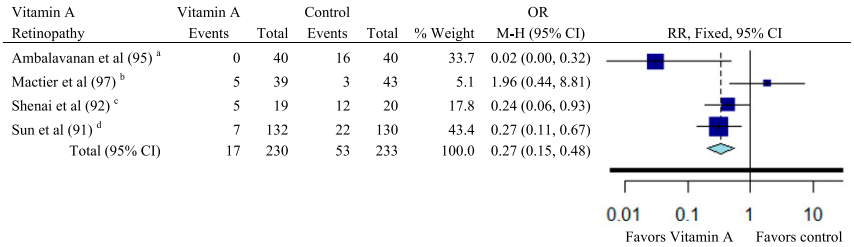

Figure 6. Meta-analysis of vitamin A and odds of any ROP. Heterogeneity: χ^2=10.15, df=3 (*P*=.02); I^2=70.43%. Test for overall effect: Z=4.41 (*P* <.01). Statistical method: Mantel-Haenszel, Fixed Effect model. Interpretation: A total of 463 infants, from 4 observational studies, were included in the meta-analysis to compare the association between vitamin A and any/severe ROP. The odds of any ROP was significantly reduced when infants received vitamin A supplementation (OR=0.27, 95% CI=0.15–0.48, *P*<.001; RD=-0.015, 95% CI=-0.22 to -0.09); heterogeneity was significant (*P*=.02, I^2=70%), indicating substantial inconsistent effect sizes among these studies. These inconsistencies may be accounted for by the differences in vitamin A dose or by differences in measures for retinopathy, any ROP vs severe ROP, or a result of bias inherit in the study design. CI=confidence interval; M-H=Mantel-Haenszel (fixed effect); OR=odds ratio; ROP=retinopathy of prematurity.
[a]Any retinopathy; 10,000 units vs standard 5,000 units.
[b]ROP requiring laser therapy; intramuscular injection.
[c]Any retinopathy.
[d]ROP includes both type 1 and 2.

fatty acids can be delivered to extremely premature infants via parenteral lipid emulsion or an enteral route.

Parenteral lipid emulsions have different polyunsaturated fatty acids; omega-6 fatty acids in soybean lipid emulsion and omega-3 and omega-6 fatty acids in fish oil lipid emulsion. Observational studies, RCTs, and meta-analyses are now available comparing the efficacy of fish-oil lipid emulsion with soybean lipid emulsion to decrease the incidence of severe ROP. (82)(83)(84)(85)(86)(87)(88)(89) The meta-analysis by Vayalthrikkovil et al (6 studies, 4 RCT, 1 prospective clinical trial, and 1 retrospective observational trial in premature infants <32 weeks' gestation/birthweight <1,500 g with ROP as the primary outcome) (89) concluded that use of fish-oil lipid emulsion was associated with a significant reduction in severe ROP/ROP needing treatment. However, the meta-analysis by Fang et al concluded that there was no impact on any stage ROP or severe ROP with the use of fish oil–based lipid emulsion. (77)

Meta-analysis of Omega-3 Fatty Acids Supplements and ROP (Fig 5). Our meta-analysis (Fig 5, 3 studies) showed a nonsignificant risk reduction of severe ROP in the fish-oil lipid emulsion group (RR=0.79, 95% CI=0.52–1.21, *P*=.29). (83)(84)(85)(86)(87)(88)

Discussion of Omega-3 Fatty Acids and ROP. Supplementation of lactating mothers with sufficient DHA (1,000 mg) led to an increased concentration of DHA in breast milk and consumption of this DHA-enriched breast milk decreased inflammation markers in extremely premature infants. (90) Whether supplementing lactating mothers with 1,000 mg of

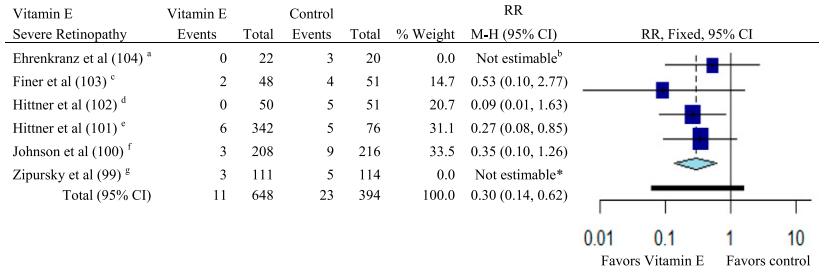

Figure 7. Meta-analysis of vitamin E and risk of any ROP. Heterogeneity: χ^2=1.20, df=3 (*P*=.59); I^2=0.00%. Test for overall effect: Z=3.21 (*P*<.01). Statistical method: Mantel-Haenszel, Fixed Effect model. Interpretation: The association of vitamin E and any/severe ROP was evaluated for 1,042 infants from 4 clinical trials. Previous systematic reviews included 2 other studies, shown as "Not estimable", because these articles did not report the number of events for ROP, or the outcome did include ROP. Results of the meta-analysis showed the risk of any/severe ROP was significantly reduced when infants received vitamin E (RR=0.30, 95% CI=0.14–0.62, *P*=.001; RD=-0.04, 95% CI=-0.07 to -0.02). An evaluation of heterogeneity was not significant (*P*=.75, I^2=0%), indicating findings from these studies are consistent with overlapping confidence intervals in the forest plot. CI=confidence interval; M-H=Mantel-Haenszel (fixed effect); ROP=retinopathy of prematurity; RR=risk ratio.
[a]Severe ROP stage III; no events reported.
[b]Not estimable if interventions differed, populations differed, events were not directly reported in article, or if conflicting data reported in article.
[c]Any retrolental fibroplasia; treatment titrated to 100 units.
[d]Retrolental fibroplasia grade III; treatment 100 mg/kg (not titrated).
[e]Severe ROP grade III; 1500 g birthweight or less.
[f]Severe ROP stage 3+; 8 of 9 in control group also received vitamin E in the late stage.
[g]Oral vitamin E for prevention of anemia; unreported events in article.

DHA can decrease the incidence of severe ROP needs further study.

Vitamin A Supplementation and ROP

Background. Vitamin A may have a role in the prevention of ROP. (91)(92)(93)(94)(95)(96) In a rat model of OIR, supplementation with retinoids inhibited VEGF expression and decreased neovascularization. (97) A meta-analysis of clinical trials of vitamin A supplementation showed a 33% decrease in any ROP with no effect on the incidence of severe ROP. (77)

Meta-analysis of Vitamin A and ROP (Fig 6). Our meta-analysis (Fig 6, 4 studies) showed that the odds of any ROP was significantly reduced when infants received vitamin A supplementation (OR=0.27, 95% CI=0.15–0.48, $P<.001$; RD=−0.015, 95% CI=−0.22 to −0.09). (91)(92)(95)(96)

Discussion of Vitamin A and ROP. Vitamin A supplementation, in addition to improving retinal function in premature infants (96), may decrease the incidence of ROP.

Vitamin E Supplementation and ROP

Background. Premature infants exposed to supplemental oxygen are at risk of abnormal retinal vessel development mediated by oxygen free radicals. Vitamin E, an essential fat-soluble vitamin obtained from the diet, is known to neutralize free radicals and reduce oxidative stress. A study in albino rats using the OIR model showed that vitamin E water-soluble analog, when compared to a vehicle, significantly decreased the area of avascular retina and increased capillary density. (98)

In the 1980s, clinical trials investigated the efficacy and safety of vitamin E as prophylaxis and treatment of ROP. (99)(100)(101)(102)(103)(104) Two meta-analyses found that the use of vitamin E did not reduce the incidence of ROP but significantly reduced the incidence of severe ROP (≥stage 3). (105)(106) In a third meta-analysis that only included the RCTs, vitamin E supplementation did not significantly reduce the risk of severe ROP. (77) One study found an increased risk of necrotizing enterocolitis and sepsis with vitamin E supplementation if the serum concentration of vitamin E exceeded the physiologic range. (100)

Meta-analysis of Vitamin E and ROP (Fig 7). Our meta-analysis (Fig 7, 4 studies) showed that the risk of any/severe ROP was significantly reduced with vitamin E (RR=0.30, 95% CI=0.14–0.62, $P=.001$; RD=−0.04, 95% CI=−0.07 to 0.02). (96)(97)(98)(99)(100)(101)

Discussion of Vitamin E and ROP. Vitamin E is low in the breast milk of mothers who smoke and in donor breast milk. (107)(108) In view of increased risk of necrotizing enterocolitis, selective vitamin E supplementation may be considered for infants of greater than 34 weeks' PMA with phase 2 ROP.

Strategies to Reduce ROP that DO NOT Work

IGF-1 and ROP. Animal and clinical studies have provided evidence that IGF-1 supplementation could reduce severe ROP. However, a phase 2 randomized study of recombinant human IGF-1 complexed with binding protein 3 did not show any significant decrease in severe ROP in extremely premature infants. (109)

Myo-inositol and ROP. A randomized clinical trial of myo-inositol did not show any reduction in severe ROP in extremely premature infants born at less than 28 weeks' gestation. (110)

Strategies to Reduce ROP with Some Evidence of Benefit

Light and ROP. In an OIR rat model, rearing in the dark prevented vaso-obliteration of retinal vessels from hyperoxia, thus preventing the development of phase 1 ROP. (111) In phase 2 ROP, light adaptation reduced rod photoreceptor oxygen consumption by 50% in the rat model and led to less retinal hypoxia and downregulation of retinal VEGF. (112) Gaynon et al routinely exposed the preterm infants at their center to ambient light to decrease retinal hypoxia in phase 2 ROP. (113) However, there are no clinical trials of this practice.

Other interventions that could increase, decrease, or have no effect on the risk of ROP include EPO supplementation (47), red blood cell transfusions (114), propranolol therapy (115) and hyperglycemia (47).

SUMMARY

1. The incidence of ROP in the United States shows an increasing trend.
2. Severe ROP can increase the risk of visual and neurodevelopmental deficits in premature infants.
3. Laser therapy and intravitreal injection of VEGF inhibitors are effective in most infants with severe ROP. However, both laser surgery and VEGF inhibitors have many side effects.
4. In the NeoPrOM trials, mortality was increased in infants with a low oxygen saturation range (85%–89%) and the incidence of ROP was increased in infants with a high oxygen saturation range (91%–95%).
5. Recent studies have used increasing oxygen saturation targets, as premature infants mature, to mirror the pathogenesis of ROP and have not found an increase in mortality.
6. There is evidence that human milk, vitamin A, omega-3 fatty acids, and vitamin E can decrease the risk of ROP and are recommended in addition to adequate oxygen saturation monitoring.

ACKNOWLEDGMENTS

The authors wish to thank Ms Jane Tanner, Librarian, for her help with putting together the references and Mr Jared Shaw for his help with Figure 1.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the potential adverse effects of pharmacologic use of fat soluble vitamins.
- Know the differences between the composition of breast milk of the mother of a preterm infant and that of a term infant.
- Know the normal anatomy and ophthalmologic findings of the developing eye.

References

1. Dutta S, Raghuveer T, Vinekar A, Dogra MR. Can we stop the current epidemic of blindness from retinopathy of prematurity? *Indian Pediatr*. 2016;53(suppl 2):S80–S84
2. Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. *J AAPOS*. 2012;16(6):501–507
3. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039–1051
4. Ludwig CA, Chen TA, Hernandez-Boussard T, Moshfeghi AA, Moshfeghi DM. The epidemiology of retinopathy of prematurity in the United States. *Ophthalmic Surg Lasers Imaging Retina*. 2017;48(7):553–562
5. Isaza G, Donaldson L, Chaudhary V. Increased incidence of retinopathy of prematurity and evolving treatment modalities at a Canadian tertiary centre. *Can J Ophthalmol*. 2019;54(2):269–274
6. Venincasa VD, Bugg V, Dvorak J, Ding K, Bhatti F, Siatkowski RM. Temporal profile of retinopathy of prematurity in extremely premature compared to premature infants. *J Pediatr Ophthalmol Strabismus*. 2019;56(2):116–123
7. Msall ME, Phelps DL, DiGaudio KM, et al; Behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. *Pediatrics*. 2000;106(5):998–1005
8. Glass TJA, Chau V, Gardiner J, et al. Severe retinopathy of prematurity predicts delayed white matter maturation and poorer neurodevelopment. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(6):F532–F537
9. Molloy CS, Anderson PJ, Anderson VA, Doyle LW. The long-term outcome of extremely preterm (<28 weeks' gestational age) infants with and without severe retinopathy of prematurity. *J Neuropsychol*. 2016;10(2):276–294
10. Morin J, Luu TM, Superstein R, et al; Canadian Neonatal Network and the Canadian Neonatal Follow-Up Network Investigators. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. *Pediatrics*. 2016;137(4):e20153218. doi: 10.1542/peds.2015-3218
11. Natarajan G, Shankaran S, Nolen TL, et al. Neurodevelopmental outcomes of preterm infants with retinopathy of prematurity by treatment. *Pediatrics*. 2019;144(2):e20153218 10.1542/peds.2015-3218
12. Kennedy KA, Mintz-Hittner HA; BEAT-ROP Cooperative Group. Medical and developmental outcomes of bevacizumab versus laser for retinopathy of prematurity. *J AAPOS*. 2018;22(1):61–65.e1
13. Holmström G, Larsson E. Outcome of retinopathy of prematurity. *Clin Perinatol*. 2013;40(2):311–321
14. Quinn GE, Dobson V, Davitt BV, et al; Early Treatment for Retinopathy of Prematurity Cooperative Group. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity study: findings at 4 to 6 years of age. *J AAPOS*. 2013;17(2):124–128
15. Geloneck MM, Chuang AZ, Clark WL, et al; BEAT-ROP Cooperative Group. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: a randomized clinical trial. *JAMA Ophthalmol*. 2014;132(11):1327–1333
16. Mintz-Hittner HA, Geloneck MM. Review of effects of anti-VEGF treatment on refractive error. *Eye Brain*. 2016;8:135–140
17. Chen SN, Lian I, Hwang YC, et al. Intravitreal anti-vascular endothelial growth factor treatment for retinopathy of prematurity: comparison between ranibizumab and bevacizumab. *Retina*. 2015;35(4):667–674
18. VanderVeen DK, Bremer DL, Fellows RR, et al; Early Treatment for Retinopathy of Prematurity Cooperative Group. Prevalence and course of strabismus through age 6 years in participants of the Early Treatment for Retinopathy of Prematurity randomized trial. *J AAPOS*. 2011;15(6):536–540
19. Lambert SR, Capone A Jr, Cingle KA, Drack AV. Cataract and phthisis bulbi after laser photoablation for threshold retinopathy of prematurity. *Am J Ophthalmol*. 2000;129(5):585–591
20. Liang J. Systematic review and meta-analysis of the negative outcomes of retinopathy of prematurity treated with laser photocoagulation. *Eur J Ophthalmol*. 2019;29(2):223–228
21. Hartnett ME. Vascular endothelial growth factor antagonist therapy for retinopathy of prematurity. *Clin Perinatol*. 2014;41(4):925–943
22. Kong L, Bhatt AR, Demny AB, et al. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2015;56(2):956–961
23. Zhou Y, Jiang Y, Bai Y, Wen J, Chen L. Vascular endothelial growth factor plasma levels before and after treatment of retinopathy of prematurity with ranibizumab. *Graefes Arch Clin Exp Ophthalmol*. 2016;254(1):31–36
24. Wu WC, Lien R, Liao PJ, et al. Serum levels of vascular endothelial growth factor and related factors after intravitreous bevacizumab injection for retinopathy of prematurity. *JAMA Ophthalmol*. 2015;133(4):391–397
25. VanderVeen DK, Melia M, Yang MB, Hutchinson AK, Wilson LB, Lambert SR. Anti-Vascular endothelial growth factor therapy for primary treatment of type 1 retinopathy of prematurity: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2017;124(5):619–633

26. Heidary G, Vanderveen D, Smith LE. Retinopathy of prematurity: current concepts in molecular pathogenesis. *Semin Ophthalmol*. 2009;24(2):77–81
27. Chan-Ling T, Gock B, Stone J. The effect of oxygen on vasoformative cell division. Evidence that 'physiological hypoxia' is the stimulus for normal retinal vasculogenesis. *Invest Ophthalmol Vis Sci*. 1995;36(7):1201–1214
28. Stone J, Itin A, Alon T, et al. Development of retinal vasculature is mediated by hypoxia-induced vascular endothelial growth factor (VEGF) expression by neuroglia. *J Neurosci*. 1995;15(7 pt 1):4738–4747
29. Ashton N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *Br J Ophthalmol*. 1954;38(7):397–432
30. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. *N Engl J Med*. 2012;367(26):2515–2526
31. Gammons MV, Bates DO. Models of oxygen induced retinopathy in rodents. *Methods Mol Biol*. 2016;1430:317–332
32. Pierce EA, Foley ED, Smith LE. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. *Arch Ophthalmol*. 1996;114(10):1219–1228
33. Jaquet K, Krause K, Tawakol-Khodai M, Geidel S, Kuck KH. Erythropoietin and VEGF exhibit equal angiogenic potential. *Microvasc Res*. 2002;64(2):326–333
34. Chen J, Connor KM, Aderman CM, Smith LE. Erythropoietin deficiency decreases vascular stability in mice. *J Clin Invest*. 2008;118(2):526–533
35. Hellstrom A, Perruzzi C, Ju M, et al. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: direct correlation with clinical retinopathy of prematurity. *Proc Natl Acad Sci USA*. 2001;98(10):5804–5808
36. Lineham JD, Smith RM, Dahlenburg GW, et al. Circulating insulin-like growth factor I levels in newborn premature and full-term infants followed longitudinally. *Early Hum Dev*. 1986;13(1):37–46
37. Connor KM, SanGiovanni JP, Lofqvist C, et al. Increased dietary intake of omega-3-polyunsaturated fatty acids reduces pathological retinal angiogenesis. *Nat Med*. 2007;13(7):868–873
38. Martin CR, Dasilva DA, Cluette-Brown JE, et al. Decreased postnatal docosahexaenoic and arachidonic acid blood levels in premature infants are associated with neonatal morbidities. *J Pediatr*. 2011;159(5):743–749.e1-2
39. Palmer EA, Flynn JT, Hardy RJ, et al; The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. *Ophthalmology*. 1991;98(11):1628–1640
40. Austeng D, Källen KB, Hellström A, et al. Screening for retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Arch Ophthalmol*. 2011;129(2):167–172
41. Penn JS, Tolman BL, Lowery LA. Variable oxygen exposure causes preretinal neovascularization in the newborn rat. *Invest Ophthalmol Vis Sci*. 1993;34(3):576–585
42. Pierce EA, Avery RL, Foley ED, Aiello LP, Smith LE. Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal neovascularization. *Proc Natl Acad Sci USA*. 1995;92(3):905–909
43. Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. *Proc Natl Acad Sci USA*. 1995;92(23):10457–10461
44. Simmons AB, Bretz CA, Wang H, et al. Gene therapy knockdown of VEGFR2 in retinal endothelial cells to treat retinopathy. *Angiogenesis*. 2018;21(4):751–764
45. Sato T, Kusaka S, Shimojo H, Fujikado T. Vitreous levels of erythropoietin and vascular endothelial growth factor in eyes with retinopathy of prematurity. *Ophthalmology*. 2009;116(9):1599–1603
46. Stahl A, Sapieha P, Connor KM, et al. Short communication: PPAR gamma mediates a direct antiangiogenic effect of omega 3-PUFAs in proliferative retinopathy. *Circ Res*. 2010;107(4):495–500
47. Raghuveer TS, Bloom BT. A paradigm shift in the prevention of retinopathy of prematurity. *Neonatology*. 2011;100(2):116–129
48. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach. *Med J Aust*. 1951;2(2):48–50
49. Kinsey VE. Retrolental fibroplasia; cooperative study of retrolental fibroplasia and the use of oxygen. *AMA Arch Opthalmol*. 1956;56(4):481–543
50. Avery ME. Recent increase in mortality from hyaline membrane disease. *J Pediatr*. 1960;57:553–559
51. Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med*. 1992;326(16):1050–1054
52. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics*. 2000;105(2):295–310PubMed
53. Carlo WA, Finer NN, Walsh MC, et al; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959–1969
54. Quine D, Stenson BJ. Arterial oxygen tension (Pa02) values in infants <29 weeks of gestation at currently targeted saturations. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(1):F51–F53
55. The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups.Oxygen saturation and outcomes in preterm infants. *N Engl J Med*. 2013;368:2094–2104
56. Schmidt B, Whyte RK, Asztalos EV, et al; Canadian Oxygen Trial (COT) Group. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA*. 2013;309(20):2111–2120
57. Askie LM, Darlow BA, Davis PG, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev*. 2017;4(4):CD011190
58. Cummings JJ, Polin RA, Committee on Fetus and Newborn. Oxygen targeting in extremely low birth weight infants. *Pediatrics*. 2016;138(2):e20161576
59. Manley BJ, Kuschel CA, Elder JE, Doyle LW, Davis PG. Higher rates of retinopathy of prematurity after increasing oxygen saturation targets for very preterm infants: experience in a single center. *J Pediatr*. 2016;168:242–244
60. Shukla A, Sonnie C, Worley S, et al. Comparison of biphasic vs static oxygen saturation targets among infants with retinopathy of prematurity. *JAMA Ophthalmol*. 2019;137(4):417–423
61. Cayabyab R, Arora V, Wertheimer F, Durand M, Ramanathan R. Graded oxygen saturation targets and retinopathy of prematurity in extremely preterm infants. *Pediatr Res*. 2016;80(3):401–406
62. Colaizy TT, Longmuir S, Gertsch K, Abràmoff MD, Klein JM. Use of a supplemental oxygen protocol to suppress progression of retinopathy of prematurity. *Invest Ophthalmol Vis Sci*. 2017;58(2):887–891

63. York JR, Landers S, Kirby RS, Arbogast PG, Penn JS. Arterial oxygen fluctuation and retinopathy of prematurity in very-low-birth-weight infants. *J Perinatol*. 2004;24(2):82–87
64. Van Zanten HA, Kuypers KLAM, Stenson BJ, Bachman TE, Pauws SC, Te Pas AB. The effect of implementing an automated oxygen control on oxygen saturation in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(5):F395–F399
65. Vesoulis ZA, Lust CE, Liao SM, Trivedi SB, Mathur AM. Early hyperoxia burden detected by cerebral near-infrared spectroscopy is superior to pulse oximetry for prediction of severe retinopathy of prematurity. *J Perinatol*. 2016;36(11):966–971
66. Gila-Diaz A, Arribas SM, Algara A, et al. A review of bioactive factors in human breastmilk: a focus on prematurity. *Nutrients*. 2019;11(6):E1307 10.3390/nu11061307
67. Hylander MA, Strobino DM, Pezzullo JC, Dhanireddy R. Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants. *J Perinatol*. 2001;21(6):356–362
68. Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. *Arch Pediatr Adolesc Med*. 2003;157(1):66–71
69. Heller CD, O'Shea M, Yao Q, et al; NICHD Neonatal Research Network. Human milk intake and retinopathy of prematurity in extremely low birth weight infants. *Pediatrics*. 2007;120(1):1–9
70. Porcelli PJ, Weaver RG Jr. The influence of early postnatal nutrition on retinopathy of prematurity in extremely low birth weight infants. *Early Hum Dev*. 2010;86(6):391–396PubMed
71. Maayan-Metzger A, Avivi S, Schushan-Eisen I, Kuint J. Human milk versus formula feeding among preterm infants: short-term outcomes. *Am J Perinatol*. 2012;29(2):121–126
72. Manzoni P, Stolfi I, Pedicino R, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections, Italian Society of Neonatology. Human milk feeding prevents retinopathy of prematurity (ROP) in preterm VLBW neonates. *Early Hum Dev*. 2013;89(Suppl 1):S64–S68
73. Patel AL, Johnson TJ, Engstrom JL, et al. Impact of early human milk on sepsis and health-care costs in very low birth weight infants. *J Perinatol*. 2013;33(7):514–519
74. Spiegler J, Preuß M, Gebauer C, Bendiks M, Herting E, Göpel W; German Neonatal Network (GNN); German Neonatal Network GNN. Does breastmilk influence the development of bronchopulmonary dysplasia? *J Pediatr*. 2016;169:76–80.e4
75. Zhou J, Shukla VV, John D, Chen C. Human milk feeding as a protective factor for retinopathy of prematurity: a meta-analysis. *Pediatrics*. 2015;136(6):e1576–e1586
76. Bharwani SK, Green BF, Pezzullo JC, Bharwani SS, Bharwani SS, Dhanireddy R. Systematic review and meta-analysis of human milk intake and retinopathy of prematurity: a significant update. *J Perinatol*. 2016;36(11):913–920
77. Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions to prevent retinopathy of prematurity: a meta-analysis. *Pediatrics*. 2016;137(4):e20153387 10.1542/peds.2015-3387
78. Chiang KV, Sharma AJ, Nelson JM, Olson CK, Perrine CG. Receipt of breast milk by gestational age - United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(22):489–493
79. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics*. 2005;116(2):400–406
80. Giuliani F, Prandi G, Coscia A, et al. Donor human milk versus mother's own milk in preterm VLBWIs: a case control study. *J Biol Regul Homeost Agents*. 2012;26(3 suppl):19–24
81. Lapillonne A, Eleni dit Trolli S, Kermorvant-Duchemin E. Postnatal docosahexaenoic acid deficiency is an inevitable consequence of current recommendations and practice in preterm infants. *Neonatology*. 2010;98(4):397–403
82. Pawlik D, Lauterbach R, Turyk E. Fish-oil fat emulsion supplementation may reduce the risk of severe retinopathy in VLBW infants. *Pediatrics*. 2011;127(2):223–228
83. Pawlik D, Lauterbach R, Walczak M, Hurkała J, Sherman MP. Fish-oil fat emulsion supplementation reduces the risk of retinopathy in very low birth weight infants: a prospective, randomized study. *JPEN J Parenter Enteral Nutr*. 2014;38(6):711–716
84. Najm S, Löfqvist C, Hellgren G, et al. Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial. *Clin Nutr ESPEN*. 2017;20:17–23
85. Löfqvist CA, Najm S, Hellgren G, et al. Association of retinopathy of prematurity with low levels of arachidonic acid: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(3):271–277
86. Khalesi N, Bordbar A, Khosravi N, Kabirian M, Karimi A. The efficacy of omega-3 supplement on prevention of retinopathy of prematurity in premature infants: a randomized double-blinded controlled trial. *Curr Pharm Des*. 2018;24(17):1845–1848
87. Bernabe-García M, Villegas-Silva R, Villavicencio-Torres A, et al. Enteral docosahexaenoic acid and retinopathy of prematurity: a randomized clinical trial. *JPEN J Parenter Enteral Nutr*. 2019;43(7):874–882. doi: 10.1002/jpen.1497
88. Beken S, Dilli D, Fettah ND, Kabataş EU, Zenciroğlu A, Okumuş N. The influence of fish-oil lipid emulsions on retinopathy of prematurity in very low birth weight infants: a randomized controlled trial. *Early Hum Dev*. 2014;90(1):27–31
89. Vayalthrikkovil S, Bashir RA, Rabi Y, et al. Parenteral fish-oil lipid emulsions in the prevention of severe retinopathy of prematurity: a systematic review and meta-analysis. *Am J Perinatol*. 2017;34(7):705–715
90. Valentine CJ, Dingess KA, Kleiman J, Morrow AL, Rogers LK. A randomized trial of maternal docahexaenoic acid supplementation to reduce inflammation in extremely preterm infants. *J Pediatr Gastroenterol Nutr*. 2019;69(3):388–392; 10.1097/MPG.0000000000002375
91. Sun H, Cheng R, Wang Z. Early vitamin a supplementation improves the outcome of retinopathy of prematurity in extremely preterm infants [published online ahead of print April 5]. *Retina*. 2019. doi: 10.1097/IAE.0000000000002543
92. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr*. 1987;111(2):269–277
93. Mactier H, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(2):F103–F108
94. Darlow BA, Graham PJ, Rojas-Reyes MX. Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants. *Cochrane Database Syst Rev*. 2016;8(8):CD000501

95. Ambalavanan N, Wu TJ, Tyson JE, Kennedy KA, Roane C, Carlo WA. A comparison of three vitamin A dosing regimens in extremely-low-birth-weight infants. *J Pediatr*. 2003;142(6):656–661

96. Mactier H, McCulloch DL, Hamilton R, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. *J Pediatr*. 2012;160(6):954–959.e1

97. Ozkan H, Duman N, Kumral A, et al. Inhibition of vascular endothelial growth factor-induced retinal neovascularization by retinoic acid in experimental retinopathy of prematurity. *Physiol Res*. 2006;55(3):267–275

98. Penn JS, Tolman BL, Bullard LE. Effect of a water-soluble vitamin E analog, trolox C, on retinal vascular development in an animal model of retinopathy of prematurity. *Free Radic Biol Med*. 1997;22(6):977–984

99. Zipursky A, Brown EJ, Watts J, et al. Oral vitamin E supplementation for the prevention of anemia in premature infants: a controlled trial. *Pediatrics*. 1987;79(1):61–68

100. Johnson L, Quinn GE, Abbasi S, et al. Effect of sustained pharmacologic vitamin E levels on incidence and severity of retinopathy of prematurity: a controlled clinical trial. *J Pediatr*. 1989;114(5):827–838

101. Hittner HM, Rudolph AJ, Kretzer FL. Suppression of severe retinopathy of prematurity with vitamin E supplementation: ultrastructural mechanism of clinical efficacy. *Ophthalmology*. 1984;91(12):1512–1523

102. Hittner HM, Godio LB, Rudolph AJ, et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. *N Engl J Med*. 1981;305(23):1365–1371

103. Finer NN, Schindler RF, Grant G, Hill GB, Peters K. Effect of intramuscular vitamin E on frequency and severity of retrolental fibroplasia: a controlled trial. *Lancet*. 1982;1(8281):1087–1091

104. Ehrenkranz RA, Ablow RC, Warshaw JB. Effect of vitamin E on the development of oxygen-induced lung injury in neonates. *Ann N Y Acad Sci*. 1982;393:452–466

105. Brion LP, Bell EF, Raghuveer TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. *Cochrane Database Syst Rev*. 2003; (4):CD003665

106. Raju TN, Langenberg P, Bhutani V, Quinn GE. Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. *J Pediatr*. 1997;131(6):844–850

107. Stone C Jr, Qiu Y, Kurland IJ, et al. Effect of maternal smoking on plasma and urinary measures of vitamin E isoforms in the first month of after extreme preterm birth. *J Pediatr*. 2018;197:280–285.e3

108. Hanson C, Lyden E, Furtado J, Van Ormer M, Anderson-Berry A. A comparison of nutritional antioxidant content in breast milk, donor milk and infant formulas. *Nutrients*. 2016;8(11):681. doi: 10.33901/nu8110681

109. Ley D, Hallberg B, Hansen-Pupp I, et al; study team. rhIGF-1/rhIGFBP-3 in preterm infants: a phase 2 randomized controlled trial. *J Pediatr*. 2019;206:56–65.e8

110. Phelps DL, Watterberg KL, Nolen TL, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Effects of myo-inositol on type 1 retinopathy of prematurity among preterm infants <28 weeks' gestational age: a randomized clinical trial. *JAMA*. 2018;320(16):1649–1658

111. Chan-Ling T, Barnett NL, Maccarone R, et al. Dark-Rearing (DR) precludes the initiating event in OIR and eliminates the pathology seen in the second phase of disease: rationale for novel non-invasive treatment for ROP. *Invest Ophthalmol Vis Sci*. 2016;157(12). Available at: https://iovs.arvojournals.org/article.aspx?articleid=2562899. Accessed January 8, 2020

112. Cringle SJ, Yu D-Y, Yu PK, Su E-N. Intraretinal oxygen consumption in the rat in vivo. *Invest Ophthalmol Vis Sci*. 2002;43(6):1922–1927

113. Gaynon MW, Wong RJ, Stevenson DK, Sunshine P. Prethreshold retinopathy of prematurity: VEGF inhibition without VEGF inhibitors. *J Perinatol*. 2018;38(10):1295–1300

114. Keir A, Pal S, Trivella M, et al. Adverse effects of red blood cell transfusions in neonates: a systematic review and meta-analysis. *Transfusion*. 2016;56(11):2773–2780

115. Kaempfen S, Neumann RP, Jost K, Schulzke SM. Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants. *Cochrane Database Syst Rev*. 2018;3:CD011893

Strategies to Prevent Severe Retinopathy of Prematurity: A 2020 Update and Meta-analysis

Talkad S. Raghuveer and R. Zackula

NeoReviews 2020;21;e249
DOI: 10.1542/neo.21-4-e249

Strategies to Prevent Severe Retinopathy of Prematurity: A 2020 Update and Meta-analysis

Talkad S. Raghuveer and R. Zackula

NeoReviews 2020;21;e249
DOI: 10.1542/neo.21-4-e249