My name is Christin Sylvester and today I will be presenting a lecture on an update of retinopathy of prematurity. This is geared towards anyone interested in learning more about retinopathy of prematurity, medical students, residents, pediatricians, neonatologists and ophthalmologists.

In 1942 retinopathy of prematurity was originally termed retrolental fibroplasia by Terry. He was the first to connect this condition to premature birth. By 1950 retrolental fibroplasia had become the largest cause of irreversible childhood blindness in the U.S.

Retinal vascularization begins in the 16th week of gestation. The nasal retina is completed by 32 weeks and temporal retina by 40 to 42 weeks. Therefore the retinas of infants born prematurely are incompletely vascularized.

If we look at a picture of the eye you can see what a normal retina looks like, you can see the optic nerve with the blood vessels extending out into the periphery and that’s what normal blood vessel vascularization looks like. I’ll later show you what retinopathy prematurity looks like.

Retinopathy prematurity is a two-phase disease. Phase one begins with delayed retinal vascular growth after premature birth and phase two follows phase one with induced hypoxia releasing factors to stimulate new blood vessel growth.
So look at phase one in more detail. Developing retinal blood vessels undergo hyperoxic vaso-obliteration when exposed than higher than in utero oxygen concentration. The delicate capillary buds drop out and a hypoxic environment with an avascular retina.

Phase two, once that tissue hypoxia sets in that’s when the ischemic phase begins. The vascular endothelial growth factor also known as VEGF and other angiogenic factors are upregulated. Angiogenesis then resumes often with a hyperproliferative response and this is the abnormal blood vessel growth that we worry about with retinopathy of prematurity.

To look at VEGF in more detail, within the first few days or weeks of postnatal life, the VEGF levels decrease due to new hyperoxic conditions. High supplemental oxygen levels initially support the avascular retina. As oxygen is weaned the avascular retina becomes ischemic. The ischemic retina now stimulates VEGF transcription and the angiogenesis resumes. The angiogenesis can be uncontrolled and the retinal vessels may now leave the retinal plane and enter the vitreous gel which is Stage III retinopathy of prematurity.

Factors directly related to growth and development may be contributing to retinopathy of prematurity. Other factors like insulin growth factors directly mediate growth hormones. Insulin growth factor control VEGF activation and endothelial cell survival.
To look at IGF in more detail, after birth the levels decrease due to the loss of IGF provided by the placenta and amniotic fluid. The loss of IGF affects the activation of VEGF and the survival of vascular endothelial cells.

What about oxygen? Oxygen is a tricky balance. I just talked about both the hyperoxic stage followed by hypoxic stage so where does that leave us with oxygen? High inhaled concentrations of oxygen during early life is a risk factor for the development of retinopathy of prematurity. The target pulse oximetry levels should remain between 85 to 93 percent. Possibility that higher levels of oxygenation after ROP has developed might reverse ROP or prevent the progression. This led to the STOP-ROP trial which was supplemental therapeutic oxygen for threshold retinopathy prematurity in 2000.

Supplemental oxygen or that between 96 and 99 percent did not cause additional progression of threshold ROP but it also did not significantly reduce the number of infants requiring retinal surgery. A subgroup analysis suggested a benefit in infants which pre-threshold disease without plus disease and we’ll talk about these in more detail later.

This is a nice slide showing or detecting what happens to the retina. If you think of a baby in utero the partial pressure of oxygen is around 70 percent. As a baby is born prematurely it’s exposed to the hyperoxic environment where the partial pressure of oxygen is higher. So initially the IGF and VEGF level are normal in utero. Now with premature birth those levels suddenly fall because there’s a hyperoxic environment. As the maturing retina starts to develop, slowly those IGF levels
begin to rise and the VEGF levels begin to rise. Now a baby might be doing better, being weaned off a ventilator and those oxygen levels are returning to normal. The retina feels that its behind and the VEGF levels increase significantly leading to abnormal blood vessel growth and neovascularization. Two things can then happen, either the blood vessel regress and normal retinal vascularization ensues or you develop proliferative retinopathy of prematurity which could progress ultimately to a retinal detachment.

The supplemental oxygen group had an increased rate of exacerbation of chronic lung disease, pneumonia, the use of diuretics or steroids, prolonged oxygen requirement and prolonged hospitalization. So what we do do today to target those oxygen levels. We’ve now lowered the alarm limits on the pulse oximetry machine. They’re set between 85 to 83 percent, this study was done in 2006. And those levels are maintained until 32 weeks gestation or until oxygen saturation levels were about 93 percent on room air. There has been reduction in infants developing threshold retinopathy of prematurity.

Interestingly, are we accurate? This study was done to see how close the NIC-Us were following this protocol. Centers met their intended target anywhere from 16 to 64 percent of the time meaning 20 to 73 percent of the time they were above range. There’s also going to be a future study looking at pulse oximetry alarms at the prospective clinical trial that is underway to measure the time spent outside of the target oxygen saturation range. Perhaps the future practice will be to aim to avoid the human oxygen saturation monitoring by the nurses by an automated adjustment of the inspired oxygen by a device such as a ventilator. This may keep us within the target levels more accurately.
What are the most important risk factors for the development of retinopathy of prematurity? There was a study out of New Zealand and Australia that defined severe ROP at Stage III or higher and the most important risk factors were number one, prematurity, the risk of severe ROP increases with decreasing gestational age. Infants with a gestational age under 25 weeks have a 20 times greater odds of severe ROP than infants with gestational age over 28 weeks. Birth weight, the more growth restricted infants have a greater risk of more severe ROP and infants below the third percentile of weight for gestational age have a four times greater odds of severe ROP than those between 25 and 76 percentile. The average weight in this study was actually 930 grams ranging from 756 to 1100.

Also interestingly male gender was an important risk factor. Females had a survival advantage equivalent to 1 additional week of gestational age to male. It’s been suggested to result from a different hormonal makeup associated with increased organ maturation as compared to male infants of the same gestational age.

Other risk factors, independent and predictive factors include prolonged artificial ventilation, apnea, Caucasian race, and this is perhaps due to the protective of melatonin in African-American infants, sepsis in particular Candida has been studied, intraventricular hemorrhages. More recently published in 2011 is clinical chorioamnionitis and elevated maternal white count which may play a role in the fact that systemic maternal inflammation could be part of the pathogenesis of retinopathy of prematurity and further studies will be looking at this in the future. Broncho-pulmonary
dysplasia, blood transfusions, anemia, multiple gestations, dopamine and low platelets, again all independent but associated in predictive risk factors.

Do genetics play a role? The genes associated with the Wnt Receptor Signaling pathway have been found to be associated with the development of advanced retinopathy or prematurity. The three genes in this pathway are the F2D4 for fizzled 4, LPR 5 for low density lipoprotein receptor related protein 5 and ND for the Norrie Disease Protein.

The fizzled 4 gene and the LPR 5 gene are found on chromosome 11 and are associated with FVR. FVR is a familial exudative vitreoretinopathy. It is a vitreoretinal dystrophy, very closely resembles ROP clinically but this occurs in full term infants. This led to the investigation of these genes to see if they were also associated with the potential development of retinopathy of prematurity.

FEVR is inherited on an autosomal dominant or x-linked recessive fashion. The x-linked disease involves a mutation in the Norrie Disease gene. A small study in 1997 revealed missense mutations in this gene in 4 patients with severe ROP. And then a larger study in 2001 concluded that the Norrie Disease gene mutation can account for about 3 percent of cases of advanced ROP.

So now that we know all of the risk factors and some of the genetics, who do we screen. Babies born less than 30 weeks gestation, babies born under 1500 grams or those deemed high risk by the NIC-U staff. And the screening should begin usually 4 to 6 weeks after birth or by 31 to 33 weeks post conceptional age, whichever comes first.
In 2006 the guidelines were modified both by the American Academy of Pediatrics, the American Academy of Ophthalmology and the American Academy of Pediatric Ophthalmology and Strabismus. That’s the American Association of Pediatric Ophthalmology and Strabismus. The examination criteria as I mentioned both under 1500 grams or 30 weeks. Infants with a birth rate between 1500 or 2000 grams if unstable medical course by the NIC-U. Or only infants with bilaterally fully mature retinal vasculature on the first exam will require one exam. All others require at least two examinations.

When the criteria was modified in 2006 this is the first time we had a very definitive time table for screening and followup recommendations. There’s also a chart with the timing of the first exam and what it shows is that the lower the gestational age the longer you can wait until you first screen essentially because ROP develops typically between around 32-33 weeks of age. However, most infants are usually screened by 31, again as I mentioned whichever comes first.

How do we screen the babies? They’re dilated usually by the nurses in the NIC-U with Cyclomydril which is cyclopentolate .2 percent and phenylephrine 1 percent. One drop of each is given approximately 5 minutes apart and repeated for a total of 2 to 3 steps. We use a lid speculum and a scleral depressor with an indirect ophthalmoscope to perform an exam. This is typically the gold standard examination for screening retinopathy of prematurity.
The newer techniques involve telemedicine. There’s a study at Stanford University called the SUNDROP study, the PHOTO-ROP Multicenter study and Ells, Holmes and Astle Pilot Study for Telemedicine. All of these studies have proved successful sensitivity and specificity with a negative predictive value of 100 percent with the primary outcome of treatment warranting disease.

The way the Telemedicine is utilized is using typically a RETCAM type of machine and either a nurse or a practitioner, photographer will place the instrument on the infant’s eyes and capture images which will then be read by someone at another facility. Recently in 2011 the SUNDROP Study published their 36 month experience with Telemedicine Screening. They had a total of 230 infants or 460 eyes. They were imaged without any disease warranting treatment being missed, that’s 100% sensitive and 99.5% specific.

Some of the questions involved with Telemedicine are is this screening or is this examining for ROP? In rural areas this is going to become more of a problem, which I’ll touch on later. Even in our own State of Pennsylvania I’ve been confronted by some rural areas that have asked for us to utilize Telemedicine for ROP screening because they’ve recently lost their ROP screeners. A question becomes who should capture the images? Should it be an RN, a photographer, a technician, a physician or a PA? What clinical information is also necessary to make the diagnosis? Should they include the birth weight, the gestational age, any other of those independent or associated risk factors that I mentioned, and should Telemedicine be include in the guidelines that I’ve discussed? The AAO has convened a specific taskforce to determine certification standards for Telemedicine
evaluations and the Ophthalmic Mutual Insurance Company will soon be developing a protocol for Telemedicine screening but so far those guidelines have not been established.

The guidelines do recommend that the neonatologists and ophthalmologists must establish unit specific criteria with respect to gestational age and birth weight for ROP screening and that these policies should be in writing in the NICU. So if Telemedicine is part of the screening this should be in writing with the protocol who is performing it, who is capturing the images and it should all be documented.

Shifting gears to the classification of ROP, the international classification defines the disease stages by zones to indicate the location and clock hours to indicate the extend of disease. The zones include I, II and III, the higher the zone the better, that’s more peripheral retina, and the stages 1 through 5, the lower stage the better, 5 being a total retinal detachment, clock hours based on the clock and plus disease which I will define. This is a typical drawing that you might see for someone who is drawing retinopathy of prematurity. As you can see, the zones: Zone I is centered around the optic nerve, twice the diameter from nerve to macula; Zone II then extends out with a small temporal crescent remaining as Zone III.

We’ll go through the stages of ROP. Stage 1 is a demarcation line between vascularized and avascularized retina; Stage 2 that demarcation line develops a broad thick ridge and as you can see it’s thicker and more white in appearance; Stage 3 is the stage that we worry about, which is extraretinal fiber vascular proliferation, it’s usually on the ridge or the posterior surface or it can
extend into the vitreous jelly and be elevated; Stage 4 is a subtotal retinal detachment, the retina is then pulled anteriorly as you can see from this photo; 4A, the retina is not involving the fovea and 4B the retinal detachment involves the fovea and these are ultrasound photographs that can show this funnel looking image which is the actual retinal detachment; and Stage 5 is a total retinal detachment, it is in the shape of that funnel and that’s mainly because of the tractional forces on the blood vessels. If we look at this from the side again Stage 1 the demarcation line; Stage 2 the ridge; Stage 3 is the proliferative stage or that neovascular stage; Stage 4 subtotal retinal detachment and Stage 5 total retinal detachment.

Plus Disease as I mentioned is defined as blood vessel dilation and tortuosity in at least two quadrants. So when we look at the optic nerve inside the eye the blood vessels look dilated and tortuous. This is the standard photograph that was used in the majority of the studies, the CRYO-ROP Study which I will talk about and the Early Treatment for Retinopathy of Prematurity Study.

The Cryotherapy for Retinopathy of Prematurity Study was in 1990, it defined threshold disease as 5 continuous clock hours of Stage 3 Zone II ROP with Plus Disease, or 8 noncontinuous clock hours of Stage 3 Zone II ROP with Plus Disease. Once you met this established criteria it was felt that treatment should be warranted. Eyes that developed threshold ROP had a 47% chance of progressing to a retinal detachment or a macular fold. This helped to define ROP disease severity with a prognostic significance of when to treat babies. Treatment was then utilized, originally cryosurgery and then later laser ablation to the peripheral avascular retina. This destroys the source of the neovascular growth factors and neovascularization regresses because the retina does not need
the new blood vessels anymore. If we look at a photograph here this is where the laser or cryotherapy was applied to the avascular retina sending the signals that the new blood vessel growth can cease and that retinopathy of prematurity can regress.

The 10 and 15 year outcomes from the CRYO-ROP Study Group were then established. There showed to be a continued reduction in unfavorable outcomes in the treated versus control eyes, however the Zone I eyes continued to demonstrate very poor outcomes even in the treated group, 94% for Zone I eyes and the Zone I is our most critical zone as I showed in the pictures.

This led to the Early Treatment for Retinopathy of Prematurity Study in 2003. This identified infants at high risk for an unfavorable outcome based on the natural history of the disease from the CRYO-ROP Study. We now have our new criteria or new classification, and the new treatment criteria. Type 1 Retinopathy of Prematurity is defined as Zone I Stage 1, 2 or 3 with Plus Disease, Zone I Stage 3 without Plus Disease, or Zone II Stage 2 or 3 with Plus Disease. With these new recommendations these are the babies that should be treated, and treatment should generally be accomplished when possible within 72 hours of determination of treatable disease to minimize the risk of retinal detachments. With this there was a reduction in unfavorable structural outcomes from 15.6% to 9.1%.

Next they defined low risk or Type 2 retinopathy of prematurity. Follow-up examinations should be in one week or less for Zone I, Stage 1 or 2, Zone II, Stage 3, one to two weeks for Zone I Immature Vascularization, which is also Stage 0 ROP, Zone I Regressing ROP or Zone II, Stage 2. They
further went on to define examination in two weeks for Zone II, Stage 1 ROP, Zone II Regressing ROP and follow-up and examination should be in two to three weeks for Zone III, Stage 1 or 2, Zone III Regressing or Immature Retinal Vascularization in Zone II. And examination should continue until there is full vascularization, Zone III vascularization without prior Zone I or Zone II ROP, post-menstrual age of 45 weeks and no Zone I or Stage 3, Zone II, or the regression of ROP. This helped to clearly define when physicians should be following ROP. 16% of the high risk eyes continue to progress to retinal detachments despite treatment, which is the devastating reality of this disease.

Plus Disease is our primary indication for the treatment of high risk Type 1 ROP. An assessment of Plus Disease can be highly subjective. In 2007 Chiang et al looked at the inter-expert agreement of Plus Disease diagnosis in ROP. They looked at 34 retinal photographs by 22 ROP experts. There was a 3 level categorization looking at Plus, pre-Plus or neither and they agreed on the same diagnosis in 4 of 34 or only 12% of images. There was also a 2-level categorization, Plus or no Plus, and they agreed in 7 of 34 images, or 21%. So Plus Disease, which is our main treatment criteria can be very subjective. This is the standard photograph as I mentioned, however some people argue that the standard photograph is, is highly magnified and perhaps an extreme example.

In 2005 the Revised International Classification then defined pre-Plus. It’s an intermediate level of vascular abnormalities that are insufficient for the diagnosis of Plus Disease but demonstrate more dilation and tortuosity than normal. This helped to clear up some of the ambiguous mild Plus. They also defined aggressive posterior ROP as a more virulent form of ROP observed in the very low birth
weight infants or those with Zone I disease. And as you can see, Zone I if severe there is not much retinal vascularization there and can be quite devastating.

What are the visual outcomes associated with retinopathy of prematurity? The CRYO-ROP Study published its 10 year visual and structural outcomes, 87% of children with ROP became myopic, 20% of those children are myopic by 1 year of age. Visual field loss occurs whether or not they undergo peripheral retinal ablation, the visual field can be reduced by 27 to 35% compared with premature infants without ROP, 5 to 7% additional loss in treated eyes. 14.7% incidence of strabismus in the first year of life, 20 to 25% by age 3, you can have anisometropia or structural retinal changes. Retinal detachments can occur, retinal dragging, glaucoma, cataracts, amblyopia even up to 26% of infants with severe ROP. The Early Treatment for Retinopathy of Prematurity Study further looked at myopia and strabismus. In those eyes that were high risk prethreshold and treated 65% developed myopia by 9 months of age, 26% with more than 5 diopters of myopia and 30% had strabismus at 9 months of age, these are large staggering numbers.

In 2006 a study looked at strabismus findings in the first year of life for those 730 infants with prethreshold ROP and birth weights less than 1251. At 6 months strabismus was higher for infants with high risk prethreshold ROP than the lower risk group. So it looked more closely at the high risk group, and they found interesting results. They compared them at 6 months and 9 months. 263 infants had normal alignment at 6 months, 45 of those that had normal alignment at 6 months now had strabismus at 9 months, 66 infants had strabismus at 6 months and 20 of those had normal alignment at 9 months, so that means that the stability of ocular alignment is delayed in infants in
particular with the high risk prethreshold ROP and conservative management is recommended through the first year of life, in particular with strabismus surgery.

As I mentioned Zone I ROP has a worse prognosis despite laser treatment those eyes still have done very poorly. In 2006 57 eyes with Zone I disease were looked at, 64% of patients with anterior Zone I disease required retinal detachment surgery following laser, and 100% of posterior Zone I eyes required surgical repair. So why are those eyes responding so differently? Flynn and Chan-Ling looked in 2006 at a retrospective analysis of the outcome differences between Zone I and Zone II ROP after cryo and laser. They combined the results of the CRYO-ROP, the STOP ROP and the ET-ROP which produced an unfavorable outcome of 42.1% in Zone I eyes versus 27.5% for Zone II eyes.

Zone I disease is correlated with aberrant vasculogenesis. Vasculogenesis is responsible for the major vascular arcades. Posterior ROP displays extreme disorganization and tangles of smaller vessels. These vessels are relatively insensitive to VEGF and to the effect of cryo or laser so there are poor anatomic and visual outcomes. Zone II disease, on the other hand, is angiogenesis dependent. Angiogenesis is driven by the hypoxia induced VEGF and ablative therapy is effective in the treatment of Zone II by destruction of the neurons and VEGF sources in the avascular retina, thus removing the hypoxia induced stimulus to produce VEGF. This led to some conclusions that therapy for Zone I disease should be directed at the inhibition of the pathologic vasculogenesis and potential therapies like VEGF inhibitors that attack the process of that abnormal vasculogenesis upstream from VEGF may be useful. It was at this time that people started to try Avastin for the
salvage treatment in threshold retinopathy of prematurity. I will go through some of the early single interventional cases that led to a larger study.

This was in 2007, an ex 23-week preemie with aborted laser for threshold ROP due to vitreous and anterior hemorrhage, Avastin was injected, the hemorrhages cleared and retinal elevation decreased. Eight weeks later laser was completed for disease recurrence. Also in 2007, another single interventional case, an ex 25-week preemie with aggressive Stage 3, Zone I disease, severe Plus and extensive epiretinal macular vascular proliferation, this was a combination of laser and Avastin. The Plus Disease decreased post-op day 1 and neovascular proliferation regressed by 1 week, very quickly.

At the Angiogenesis Conference in 2007 at Bascom Palmer Eye Institute some information was also presented. In Mexico City they were doing a non-comparative, prospective interventional case series of 18 eyes of 13 patients, Avastin was injected first line at the onset of threshold ROP in Zone I and II, and also after conventional failed laser. Neovascular regression occurred in 17 of those eyes and one patient required a vitrectomy.

In Portugal 6 of 5 infants injected with Avastin as salvage therapy either monotherapy or in addition to laser, all injected eyes improved with regression of the retinal proliferation within 24 hours, very quickly. No additional treatment required and no local or systemic complications were noted.
Helen Mintz-Hittner in Texas then did a comparative retrospective interventional consecutive case series, 22 eyes of 11 infants, Avastin was used as first line therapy when Stage 3 occurred in both Zone I and posterior Zone II, all eyes were treated successfully. There was limited follow-up, but this led to her larger study, the BEAT-ROP Study which is that Bevacizumab eliminates the angiogenic threat of retinopathy of prematurity. It was a randomized multicenter interventional clinical trial investigating interventional Avastin versus conventional laser therapy for Zone I or Zone II posterior Stage 3 disease with Plus. Avastin was used at a dose of .625 mg. Outcome was recurrence of ROP in 1 or both eyes requiring retreatment before 45 weeks. Avastin was used due to its complete blockage of VEGF A, there is less retinal penetration and is more likely to restore VEGF homeostasis within the developing retina. It’s a full antibody which limits its ability to penetrate tissue.

150 infants were enrolled, 143 survived to 54 weeks, 67 had Zone I disease and 83 had Zone II posterior disease. 75 were randomized to each group, Avastin or conventional laser. The rate of recurrence with Zone I disease was significantly higher with conventional laser than with Avastin, 42% versus 6%. There were no retinal detachments in the Avastin group and 2 in the laser group. Now again this was for Zone I disease. The rate of recurrence with Zone II posterior disease did not differ significantly between laser and Avastin, 12% versus 5%. No RDs occurred in the laser group and 2 occurred in the Avastin group. This is for Zone II disease.

The Block-ROP Study is the Pan-VEGF blockade for the treatment of retinopathy of prematurity. This was a multicenter perspective longitudinal cohort study. Phase I completed enrollment to
evaluate the safety of intravitreal Avastin administered in a single dose as rescue therapy in one eye of infants who have not responded to standard of care laser in both eyes. Unfortunately it was terminated due to low enrollment. Phase II of the study will be a perspective multicenter head to head comparison of intravitreal Avastin to standard of care peripheral retinal ablation, so hopefully we will have more literature on Avastin in the future.

What are the potential side effects of VEGF therapy? The local complications can include endophthalmitis, retinal detachments, traumatic cataract, uveitis. Results during the first year of the VISION Trial is what showed us those local complications, the VISION Trial was for macular degeneration. Systemic complications include hypertension, increased rate of thromboembolic events, gastrointestinal perforations, myocardial infarctions and death. These are mainly seen in the intervenous injections for cancer patients; however it’s unknown what could happen in premature babies.

In the VISION Trial no serious adverse events in the 2 year safety data, the ANCHOR and MARINA Trials showed slightly higher risk of myocardial infarction and stroke in the .5 mg Lucentis dose compared to a control group and the SAILOR Study a slightly higher rate of stroke in the .5 mg than in the .3 mg dose of Lucentis.

A new study, the CATT Study is the comparison of age-related macular degeneration treatment trials. It’s a multicenter randomized clinical trial to assess the safety and efficacy of Lucentis versus Avastin, also looked at the complications of treatment as I mentioned, the dosing schedule and the
cost of treatment. This was published in the New England Journal of Medicine in April. Lucentis showed serious systemic adverse events in about 53 of 255 patients in the monthly treatment group and 61 in the as needed treated group. And endophthalmitis developed in 2 of 5,449 injections in 599 patients. Avastin had serious systemic adverse events in 64 of 255 patients in the monthly treated group and 77 in the as needed group. Endophthalmitis occurred in 4 of 5,508 injections in 586 patients. These of course are complications in adults and we do not know what the complications are in preemies.

Avastin is inexpensive, it’s administered at bedside, a single injection is often adequate and it decreases the high levels of VEGF in the vitreous gel. Comparing that to conventional laser it’s time consuming, it may require intubation, a laser room with standard precautions and may require further laser for inadvertent skip areas. There is clinically significant visual field loss and there is a high incidence of myopia and strabismus.

The precautions with Avastin, as I mentioned, unknown systemic or local side effects. The retinal vessels will continue to advance to the point at which the vascular precursors have ceased migration, thus the far peripheral retina may never fully vascularize and does not differentiate. The recurrence of disease occurs much later than with conventional laser, 16 weeks for Avastin versus 6.2 weeks for conventional laser; therefore infants must be followed much longer with Avastin and late retinal detachments even up to 1 year have been seen.
At the more recent Angiogenesis Conference at Bascom Palmer Eye Institute there seemed to be a split between the retinal specialists, some were using Avastin as first line treatment and some were only using it if conventional laser therapy fails. It will depend on the retinal specialist or the pediatric ophthalmologist at your institution to determine what they want to use.

Another therapy that you will be hearing more about is Propranolol. It’s used to treat infant hemangioma so could it help with ROP? In a mouse model of ROP Propranolol was protective against retinal angiogenesis. Hypothesized that VEGF overexpression could be induced by Beta 2 adrenoreceptor stimulation and that Propranolol administered with Stage 2 ROP is detected could reduce the progression of disease; therefore the PROP-ROP Study is underway. This is the safety and efficacy of Propranolol in newborns with retinopathy of prematurity study. Preterm infants with Stage 2 ROP in Zone II or II without Plus Disease will receive Propranolol up to 90 days in addition to standard care and compare that with just standard treatment only. It’s important to remember that most Stage 2 ROP spontaneously regresses so could this disease have regressed on its own without the addition of Propranolol?

No studies of yet assessed the safety and efficacy of Propranolol in infants, the side effects do include bradycardia, hypotension, hypoglycemia and an unknown effect on neurogenesis and the central nervous system; therefore for Anti-VEGF and Propranolol treatment for ROP future studies will be necessary to determine the safety and long term efficacy of these treatments in premature babies.
I’d like to now go through some of the headlines in ROP prevention and prophylaxis. Some of the things that have been talked about or studied in the past include Vitamin E. This was actually one of the original first interventions used to prevent ROP in the 1940s. Vitamin E is an antioxidant that inhibits peroxidation of membrane lipids by free radicals. Vitamin E prophylaxis to reduce ROP demonstrated a 52% decrease in the incidence for Stage 3 with Plus Disease; however excess Vitamin E is associated with sepsis and necrotizing enterocolitis and Vitamin E deficiency is associated with anemia. This was a metaanalysis not a multicenter trial, there have been conflicting reports but further studies are certainly necessary.

There have also been studies on light, there was the LIGHT-ROP Study, or the Light Reduction in Retinopathy of Prematurity Study because premature babies shouldn’t have been exposed to light at such an early age. But it was found that light reduction does not play a role in reducing the progression of ROP.

Newer evidence now exists that dark adaptation increases the outer retinal oxygen consumption and thus increases retinal hypoxia. So therefore exposing an infant to light and photopic adaptation may decrease the retinal oxygen consumption and down regulate the hypoxic stimulus for VEGF. Again further research is necessary, but an interesting hypothesis of light adaptation in the future.

Erythropoietin, these studies are conflicting. It is a glycoprotein that regulates erythropoiesis and retinal vessel development. Retinal EPO decreases after birth along with the serum EPO levels. Animal models have shown a suppression of retinal EPO leading to a loss of retinal vessels in Phase
I ROP. Early administration of EPO prevents that retinal vessel loss, early EPO may help Phase I but it could accelerate Phase II ROP. Phase II may be lessened by correcting the anemia with red cell transfusions. Again the studies have been conflicting, but similar to oxygen the perfect balance must be sought and further research is necessary.

IGF-1, as I talked about earlier, retinal vessel development is dependent on IGF-1. Preliminary studies have shown exogenous IGF-1 infusion by either fresh frozen plasma with increased serum levels of VEGF-1 usually falling after preterm birth. There is a randomized multicenter Phase II and III trial of continuous infusion of IGF-1 from birth to 31 weeks underway to assess ROP prevention. VEGF-1 can be found either in breast milk or as an exogenous source as fresh frozen plasma as I mentioned.

Hyperglycemia, plasma glucose over 150 occurs in about 45% of infants less than 1000 grams and 80% of infants less than 750 grams. Retrospective studies have raised an association between hyperglycemia and ROP, the true causal relationship is unknown and further research is necessary but NIC-UUs are now keeping the glucose at a steady normal stage or below 120.

In 2011 in February the Fish Oil Fat Emulsion Supplementation may Reduce the Risk of Severe Retinopathy of Prematurity in Very Low Birth Weight Infants was published. The rods and cones in the retina are highly enriched with DHA. Infants born prematurely are at increased risk of DHA deficiency due to the lack of the mother’s third trimester lipid stores. An observational study comparing fish oil supplementation in infants less than 1250 grams to placebo was performed. The
primary study outcomes were the occurrence of ROP and the need for laser therapy and cholestasis. There was a significantly lower risk of laser therapy for infants who received an emulsion of soybean, olive oil and fish oil. The fish oil based fat emulsion administered from the first day of life may be effective in the prophylaxis of severe ROP.

Another study, this was in 2009, looked at lutein and zeaxanthin supplementation in preterm infants. Preterm infants are at high risk of oxidative stress induced damage and disease including severe multifactorial outcomes of prematurity such as ROP, necrotizing enterocolitis and bronchopulmonary dysplasia. This was a randomized control trial comparing lutein and zeaxanthin in formula of very low birth weight infants less than 33 weeks versus placebo. The incidence of ROP requiring laser was lower in the treated group versus the placebo group, 54 treated versus 53 placebo. This was preliminary data but it did show a trend toward a lower incidence of ROP.

The WINROP algorithm is something that you may also hear about. This was a study in Sweden and Boston aimed at identifying infants at risk for developed proliferative ROP. It detects the slowing of weight gain or slowing in the rise of IGF-1 compared to a reference curve. Infants were identified 9 to 10 weeks prior to needing laser treatment. Using weight alone that had a sensitivity of 100%, it was broken down into no alarm, alarm at low risk or alarm at high risk.

So what do all of these preventions in this WINROP algorithm mean? In Neonatology in 2011 an interesting article was published, a paradigm shift in the prevention of ROP. This did summarize some of those major things that I just discussed, and it also talked about the future of ROP
prevention and the prophylaxis to combine some of the aforementioned interventions during a critical time window to affect Phase I or Phase II ROP process. So perhaps in the future combining all of these interventions may allow prophylaxis or prevention of ROP requiring laser surgery. The future of ROP, this is an exciting time for research in ROP and an exciting time for research with the modulation of angiogenesis during a critical time window. It’s also an exciting time for the prevention and prophylaxis to decrease the disease severity.

I can’t talk about ROP without also mentioning that a crisis is on the horizon for screening and treatment. Everyone has probably heard of some of the staggering awards scaring doctors away from screening or treating ROP. OMEC even issued a statement saying it’s distressing to hear more and more ophthalmologists say they are unwilling to become involved in the ROP screening because of the risk of potentially staggering malpractice awards. Some of those staggering awards have included those up to $20 million where the hospital is responsible for 60%, the neonatologist for 35%, the pediatric ophthalmologist for 4 and the pediatrician for 1.

The updated recommendations that I discussed have significantly increased the number of babies who should be screening for ROP. Based on the estimates of premature births from the March of Dimes and other organizations, the new guidelines will require screening more than 50,000 babies annually. The expanding screening criteria comes at a time when the number of ophthalmologists who specialize in ROP has been steadily declining. More importantly parents must be kept informed of the nature and possible consequences of ROP and this should be documented in the chart. If hospital discharge or transfer is contemplated before retinal maturization into Zone III or an infant
that is treated is not fully regressed appropriate ophthalmologic examination must be assured and specific arrangements for that examination must be made before discharge or transfer occurs. Most of the malpractice cases have been due to loss of follow-up, so the parents must understand the importance of examination and timely examination. So it must be understood and documented in the chart that severe visual loss including blindness as an outcome, there’s a critical time window to be met if treatment is to be successful and a timely follow-up is essential. This information should be transmitted to the parents both orally and in writing, and if arrangements after transfer or hospital discharge cannot be made then the infant should not be transferred or discharged from the hospital.

Retinopathy of prematurity is a lifelong disease, therefore the entire healthcare system must work together to screen and treat our youngest and tiniest patients. Thank you very much.