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The 'ideal' management of retinopathy of prematurity

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Abstract

Aim **Retinopathy of prematurity continues to be a serious, but largely preventable cause of blindness and its detection and treatment is of increasing importance as survival rates of premature babies increase. This is particularly important in Medium Human Development Countries where the guidelines for detection used in the US or UK may not be appropriate.**

Method **This report addresses identification of infants at risk for retinopathy of prematurity, detection, and treatment of serious disease, and what to do when treatment fails.**

Results and conclusions **Retinopathy of prematurity occurs almost exclusively in small premature babies, but the demographic characteristics of these babies vary depending on where they are born. Detection of serious retinopathy requires carefully timed examinations and the treatment criteria will continue to evolve as new therapies are developed. Timely detection and treatment of serious retinopathy of prematurity minimizes the likelihood of blindness, but it is not always successful.**

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When designing a programme for the detection and treatment of serious retinopathy of prematurity (ROP), a multifaceted plan must be developed which takes into account a series of complex logistical and medical questions. Since ROP is emerging as a significant cause of blindness and visual handicap in Medium Human Development Countries,[1,2] standard approaches used in the US, UK, Canada, and Australia may not apply.[3,4] The questions that need to be addressed are:

(1) How do you identify the population at risk for ROP?
(2) How do you detect retinopathy that needs treatment?
(3) What should the treatment consist of?
(4) What do you do when treatment fails, as it inevitably will do in some cases?

How do you identify the population at risk for ROP?

The development of ROP requires that the retinal vasculature is incomplete and, in general, the retinal vessels reach the nasal ora serrata at about 32 weeks postconception and the temporal ora serrata about term.[5] As the centripedal development of the retina proceeds, metabolic demand increases, leading to secretion of vascular growth factors (VEGF is best known and studied) that promote retinal vascular development. In a complex interplay between inhibition or promotion of retinal vascular development[6–8] and the medical status of the prematurely born baby, the advancing retinal vessels are stimulated to produce the exuberant vascular abnormality termed ROP.

Since ROP is seen exclusively in babies in whom retinal vasculature is incomplete, the babies are usually born sufficiently premature to require hospitalization for many weeks before they are mature and stable enough to be discharged to home. This ensures that the population at risk is a 'captive' one—well identified and in the hospital. In hospitals that have an already established mechanism to conduct the ophthalmic examinations that screen for ROP, almost all babies have at least started the examinations prior to discharge and the families are instructed to attend outpatient follow-up eye examinations as medically indicated.

There have been numerous risk factors found to be associated with the development of ROP, the strongest of which indicate the immaturity of the baby, that is, gestational age or birth

weight. Both of these factors are inversely related to the incidence and severity of the retinopathy.[9,10] In addition, the role of supplemental oxygen has been extensively studied in several controlled clinical trials that compared various levels of oxygen supplementation restriction.[11,12] Thus far, however, no 'safe' level of supplementation has been identified.[13] Recent studies, such as the BOOST (Benefits of oxygen saturation targeting) trial[14] and Chow *et al*,[15] have led to a renewed interest in the topic and there is the opportunity to undertake large, multicentered studies to define the safe upper and lower limits of oxygen supplementation. The BOOST trial prospectively targeted two oxygen-saturation ranges: 91–94% (termed standard) and 95–98% (termed high saturation).[14] Babies who were randomly assigned to the high saturation group did not appear to have better growth or development, but did have a higher likelihood of needing supplemental oxygen at 36 weeks and a higher frequency of home-based oxygen treatment than did those babies assigned to the standard group. There is a need for further study to define oxygen level targets for the preterm baby that balance the risk of ROP against systemic needs and complications.[16]

Other factors have been observed to affect either the incidence of ROP or its severity. Prenatal steroids appear to decrease the incidence of retinopathy,[17] while postnatal blood transfusion increases the likelihood that the baby will develop ROP.[18] The latter is probably a surrogate for the 'illness' of the baby, as are the occurrence of sepsis, necrotizing enterocolitis, and intraventricular haemorrhage—all of which have been associated with an increased incidence of ROP. Ethnic origin also plays a part in the likelihood of developing retinopathy with one study showing that south Asian infants were more likely to develop serious retinopathy than Caucasian babies[19] and another study showing that African-American babies were less likely to develop ROP than Caucasian babies.[20] Indeed, whether the baby was born in the hospital with a neonatal intensive care unit or the baby had to be transported to the nursery from an outside hospital has been identified as a factor in the risk for the development of ROP. Babies who are transported are more likely to develop retinopathy.[9]

Finally, where the baby is born has been identified as a significant risk factor for ROP. Gilbert *et al*[1] found that babies born in countries with a medium level of human development were more likely to develop serious ROP and also that a higher proportion of children in blind schools in such countries were blind from ROP.

How do you detect disease that needs treatment?

There have been dramatic changes over the last 20 years in the care of babies who develop ROP as clinical trials have demonstrated that retinal ablation of the avascular area is effective in decreasing the incidence of blinding disease. With the publication of the results of the large, multicentered Cryotherapy for ROP (CRYO-ROP) trial[21] that showed a benefit of treatment of serious disease, the role of screening in the nursery went from surveillance to detection and treatment of disease.

Large-scale studies were made possible by the widespread adoption of the International Classification of ROP (ICROP) in 1984[22] and 1987.[23] ICROP established a classification system that was based on the premise that 'the more posterior the disease and the greater the amount of involved retina, the more serious the disease.' The classification describes four parameters that must be taken into account when describing an eye with ROP. These include the antero-posterior location (zone), severity (stage), extent (circumferential involvement by clock hour of the retinopathy at the junction between the vascularized and avascular retina), and the presence or absence of posterior pole vessel dilation and tortuosity ('plus' disease).

Three zones are described in relation to the optic disc. Zone I is the area within a circle that has a radius of twice the centre of the disc to macula distance. Zone II is donut shaped, extends from the edge of zone I to the limit of a circle that has a radius of the distance from the centre of the disc to the nasal ora serrata, and zone III is the remaining area of the retina.

Five stages of retinopathy are described in ICROP:

(1) Stage 1—a demarcation line (a thin white line between the vascularized and avascular retina)
(2) Stage 2—a ridge arising in the region of the demarcation line with elevation above the retinal surface, but with an intact internal limiting membrane
(3) Stage 3—extraretinal new vessels arising from the ridge and extending into the vitreous through the internal limiting membrane
(4) Stage 4—partial retinal detachment
    (a) Stage 4A—peripheral
    (b) Stage 4B—macula involved
(5) Stage 5—total retinal detachment

The extent of ROP is described in terms of clock hours (30 degree sectors) of involvement along the junction of the vascularized and avascular retina.

A description of the pattern of vessels around the disc is also included in the classification. Marked venular dilation and arteriolar tortuosity of the posterior pole vessels is designated 'plus' disease and is an indication of more severe disease.

The largest data set currently available that describes the natural history of ROP is based on data from the CRYO-ROP study, conducted in a large number of

nurseries in the USA during 1986 and 1987.[9,21,24–29] ROP was observed in approximately two-thirds of all babies with birth weights of less than 1251 g.[9] The incidence of ROP clearly increased with decreasing birth weight with ROP found in 47% of babies with birth weights of 1001–1250 g, in 78% of babies with 751–1000 g, and in 90% of those with birth weights of less than 751 g. However, the incidence of disease should not be viewed as a static phenomenon. For example, recent reports have suggested that the incidence of disease may be decreasing[30] and increasing[31] in various regions of countries with high levels of human development.

The CRYO-ROP study established the efficacy of retinal ablation of the avascular retina when administered at a level of severity defined as 'threshold' ROP.[21] This was defined as: Stage 3 ROP in five continuous or eight cumulative sectors in zone I or zone II in the presence of plus disease. ROP of this severity was chosen as previous studies had shown such eyes had a 50% risk of developing serious retinal residua including detachment or a retinal fold involving the macula. The CRYO-ROP investigators found that approximately 6% of babies with birth weights of less than 1251 g develop ROP of this severity.

The results of the Early Treatment for ROP (ET-ROP) trial published in 2003[32] have added a layer of complexity to the decision about when to intervene. The study examined whether earlier treatment would benefit some eyes with near threshold (prethreshold) disease. Using a risk determination model derived from data obtained during the CRYO-ROP study,[33] eyes were selected based on the baby's demographic factors including birth weight and gestational age, the zone of vascularization, onset and pace of the development of ROP and the presence of plus disease. Based on the grating acuity results obtained at 9 months corrected age, there was a significant reduction ($\chi^2 = 6.60$, $P = 0.01$) in 'unfavourable' visual acuity with 14.5% of earlier treated eyes having poor vision outcomes, compared to 19.5% of those eyes that were conventionally managed (ie treated with retinal ablation if the eye developed 'threshhold' ROP and simply observed if the eye underwent regression of disease.). When retinal structure outcome at 6 months corrected age was considered, there was also a significant reduction in the rate of 'unfavourable' outcomes in the earlier treated eyes, compared to eyes that were conventionally managed, 4.9% compared to 10.0% (χ^2 9.2, $P = 0.02$).

Since the computerized algorithm employed in the ET-ROP study might not be readily available to clinicians who need to make treatment decisions at the bedside, the investigators developed an algorithm based on the stage and zone of retinopathy. They suggested that retinal ablation should be considered in eyes with Type 1 ROP, consisting of

1. zone I, any stage of ROP with plus disease,
2. zone I, stage 3 with or without plus disease,
3. zone II, stage 2 or 3 ROP with plus disease.

In the ET-ROP study,[33] plus disease 'requires at least two quadrants (usually 6 or more clock hours) of dilation and tortuosity of the posterior retina vessels…' They also suggested more frequent than usual examinations, but not surgical intervention unless progression to Type 1 is documented, for eyes with Type 2 ROP described as

1. zone I, stage 1 or 2 ROP without plus disease,
2. zone II, stage 3 ROP without plus disease.

Thus, 'threshold' level of retinopathy that indicates the need for peripheral retinal ablation has been changed from that defined in the CRYO-ROP study to a somewhat lower severity of retinopathy.

One of the major questions in application of the ET-ROP recommendation is how many more eyes would be treated that would have regressed without intervention. Based on the results of eyes that were in the 'conventionally managed' arm of the trial, the investigators found that about one in three eyes in Type 1 ROP never developed conventional 'threshold' disease and therefore, would not have received retinal ablation using the CRYO-ROP protocol.[33]

Serious ROP develops in the eyes of most low birth weight babies over a relatively discreet time period, with most Type 1 or Type 2 level of severity developing between 33 and 39 weeks postconceptional age.[9] Therefore, programmes designed to detect serious ROP should have examinations during this time period, while realizing that there is a degree of individual variability in the development of retinal vasculature.

There are several approaches that might be used to detect eyes with serious ROP. The most commonly used approach is not actually a screening examination, but rather most babies undergo a diagnostic examination performed by ophthalmologists experienced in ROP. The ophthalmologist examines the eyes, determines the presence or absence of retinopathy, decides whether treatment is warranted, and determines the appropriate follow-up for the baby. Thus, a high degree of clinical expertise and familiarity with ROP is required for most current programmes.

Another approach that might be feasible in regions which do not have high levels of ophthalmic expertise available is to use other modalities that allow detection of eyes that need an expert opinion. There have been several recent studies that addressed this concept and used either remote reading by expert readers of digital images obtained during an ROP screening examinations or direct ophthalmoscopic observations by nonophthalmic personnel.

Although digital imaging was first reported with images recorded by physicians in 1998,[34] the RetCam,

which uses a lens allowing a 120 degree retinal field, has also been used by nurses in a larger scale screening study by Yen *et al*.[35] This study was designed to obtain digital images at just two time points when serious ROP is most likely to be detected (at 32–34 weeks and 38–40 weeks postmenstrual age) and concluded that nurses could be trained to obtain useful images. These investigators also noted that sensitivity and specificity of such remote readings were not sufficient to warrant replacing a diagnostic examination when such an exam is available. They also concluded that the 120 degree camera lens that comes in contact with the baby's eye is not ideally suited for the lid fissures of the smallest babies.

A further step toward using digital imaging for ROP screening was introduced by Ells *et al*.[36] She and her co-workers developed the concept of 'referral-warranted ROP' to identify eyes that needed an evaluation by an ophthalmologist experienced in ROP. Referral warranted ROP was defined as any of the following: '(a) any ROP in zone I; (b) the presence of plus disease; or (c) the presence of any stage 3 ROP.' Using a smaller tipped lens specifically designed for use in premature infants, Ells *et al* found that images could be obtained in the vast majority of babies (96%), and that 'referral-warranted ROP' could be detected with high sensitivity and specificity.

Saunders *et al*[37–39] have suggested that the appearance of posterior pole vessels alone can be used by non-ophthalmologists using a direct ophthalmoscope to screen for ROP. Although the fundus could not be examined in about 10% of the babies, detection of 'plus disease' had high sensitivity (90%), but low specificity (48%). The authors contend that, in the absence of personnel to perform expert diagnostic examinations, direct opthalmoscopy may have a role in screening.

In summary, in order to detect worrisome disease, familiarity with the classification and natural history of the retinopathy are essential. Further, a clear definition of the characteristics of eyes that are likely to develop sight-threatening disease must be developed and the most appropriate method for detection of that disease must be determined, whether using a diagnostic examination or a screening procedure to identify eyes that must be examined by an ophthalmologist experienced in treatment of ROP. If one determines that the optimal method to detect serious disease in a population is to develop a screening programme, then careful consideration must be given to the false negative rate, that is, those eyes that are not detected on screening, but have severe enough ROP to develop a visual handicap or blindness.

What should treatment consist of?

In the ideal world, ROP would be prevented by prevention of premature birth, but that is not currently achievable. Therefore, prevention and treatment of ROP must take place on many levels. Prophylaxis includes such measures as good prenatal nutrition and care, maintenance of optimum nutrition (including antioxidant levels) for the baby after birth, prevention and/or aggressive treatment of necrotizing enterocolitis, sepsis, and intraventricular haemorrhage, and maintenance of as stable an extrauterine environment as possible in the fragile preterm neonate. Optimum levels of oxygenation have yet to be determined.[13,14,16,40]

Once serious ROP is established and detected, then consideration for peripheral retinal ablation must be given. At present, eyes with Type 1 ROP should be treated within a day or two, and eyes with Type 2 ROP should be more carefully observed than the routine weekly or every other week schedule.[32] These indications may change in future as our understanding improves.

The choice of method for retinal ablation obviously depends on the modalities available and the experience of the treating physician. At present, laser photocoagulation using a portable laser indirect ophthalmoscope is most commonly used, but transcleral cryotherapy is also employed. Both can be administered under sedation or general anesthesia, but advice and attendance should be sought from the baby's neonatologist. In both methods, the avascular region anterior to the active retinopathy is treated with confluent treatment as the goal. Both treatment modalities have acute and long-term complications including cataract formation for the laser[41] and more postoperative discomfort and swelling with cryotherapy.[42] Nonetheless, cryotherapy is extremely useful in eyes with extensive vitreous haze or a compromised view of the peripheral retina.

After treatment, topical steroid and antibiotics are often instilled for a few days. The eyes should also be carefully observed within a week or so for regression of the retinopathy, especially diminution of dilation and tortuosity of the posterior pole vessels. If there are extensive skip areas identified on follow-up and regression is not underway, retreatment should be considered.

The management of retinal detachment in eyes with ROP is not as straightforward as the management of eyes with Type 1 or Type 2 ROP. When the retina is totally detached, the outlook for visual function is dismal. In the largest study reported to date that used masked assessment of visual function, the CRYO-ROP study[43,43] found that, among 128 eyes that had developed stage 5 ROP, only one eye had vision better than light perception at age 5 years, regardless of whether the eyes had undergone vitrectomy or been observed. This eye had evidence of very low pattern vision and had not

undergone a vitrectomy procedure. However, Katsumi *et al*[45] reviewed a series of eyes and concluded 'there is some evidence that vitrectomized eyes function better than nonvitrectomized eyes.'

When only partial detachment is present, there is reason to be somewhat more optimistic about visual function. Capone *et al*[46] used a lens-sparing vitrectomy technique in eyes with only partial detachment, thus allowing optimal refractive correction and potential visual development for the baby.

What do you do when treatment fails, as it inevitably will do in some cases?

As noted above in the ET-ROP study, a small proportion of eyes that undergo evaluation at ideal intervals, that develop serious retinopathy, and that receive appropriate treatment in a timely manner may go on to develop blindness and serious retinal problems. In the ET-ROP study, about 15% of eyes, despite the best treatment available, had visual acuity, measured using a grating method, in the 'unfavourable' category, and about 5% of the earlier treated ET-ROP eyes developed 'unfavourable' structural outcomes. Thus, with our current treatment options and not even taking into account those babies in nurseries with inadequate or nonexistent diagnostic or screening procedures, we must be prepared to deal with inevitable treatment failures. The physicians responsible for the care, especially the eye care, of the child need to maintain contact with the family. The child's family must be informed of services for the visually impaired, including government agencies, educational programmes, mobility and orientation services, and other support.

Even children born prematurely who do not develop a visual handicap due to ROP should be evaluated for other vision problems. Strabismus is more common in prematurely born children than in children born at term, and its prevalence is more common in children who develop ROP.[47,48] Refractive error, in particular myopia, is more common in preterm children than in children born at term and again, the prevalence and severity of myopia increase with the presence and severity of ROP. Results from the CRYO-ROP study confirm that the myopia is not a result of surgical intervention, but rather the result of premature birth itself.[49–51]

Finally, it is clear that children who develop ROP should be followed and counseled throughout life as they are at higher risk for developing retinal tears and retinal detachments much later in life, regardless of whether they developed disease serious enough to require treatment in the first few weeks after birth.[52,53]

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