Review article

Retinopathy of prematurity: an epidemic in the making

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Objective To explore the etiology, incidence and methods to prevent and treat severe retinopathy of prematurity (ROP), which is rapidly becoming a threat to the vision of babies in areas of the world where increasing numbers of premature babies are surviving.

Data sources The data used in this review were mainly from Medline and PubMed published in English. The search term was "retinopathy of prematurity and premature birth".

Study selection We discuss the historical perspectives, prevalence and incidence, classification and treatment methods of ROP in premature babies.

Results Peripheral retinal ablation for eyes with severe ROP can help prevent progression to blindness and several large clinical trials have shown the effectiveness of this treatment in high risk eyes. As a greater proportion of VLBW and ELBW babies survive, the population of babies at risk increases. In various regions of the world, different identification criteria are used to determine which babies are at risk of blindness in order to provide timely diagnostic examinations and treatment as needed. Methods for preventiing ROP include better ante-natal and obstetric care leading to a reduction in the rate of prematurity, the use of ante-natal corticosteroids, and better neonatal care practices. Recent developments have indicated that management of oxygen supplementation is important for the prevention of severe ROP; however, there is not yet known what oxygen saturation target should be adopted. Sepsis increases severe ROP in very preterm infants. Genetic associations and a telemedicine approach may be explored to detect ROP. Treatment of anti-VEGF therapy are potentially useful in eyes with severe ROP, but long term effects are not yet known and such treatment should be used with great caution.

Conclusions ROP is a potentially binding disease for premature babies which is becoming more prevalent with the development improving neonatal services in many countries in recent years. High priority should be placed on developing approaches to prevent ROP blindness by reducing preterm birth, improving care of premature babies in neonatal care units, and providing adequate ophthalmological services in those regions.

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Retinopathy of prematurity (ROP) was first noted as a significant cause of blindness in the 1940s and 1950s in industrialized countries as the survival rate of premature babies increased, mainly as a consequence of the use of unmonitored supplemental oxygen.[1-4] The dominant risk factor for this "first epidemic" was hyperoxia or at least unrestricted oxygen supplementation,[5] a finding supported by both basic science and epidemiological trials.[6,7] With restriction of oxygen in the mid-1950s, blindness from ROP decreased, but there were also increased rates of mortality and cerebral palsy in premature babies.[8] As neonatal care improved over the next few decades with increasingly accurate methods of monitoring oxygen supplementation and improved management of neonatal and perinatal complications, smaller and less mature babies survived and ROP blindness began to re-emerge (the "second epidemic of ROP").[6] Surgical treatment of established disease and improved neonatal care are probably the major factors responsible for reduction of blinding ROP observed during the 1980s and 1990s.[9] In industrialized countries blindness from ROP is now largely restricted to infants in the ELBW group.[10-13]

In the last decade or so, an increasing frequency of ROP blindness has been documented in middle income countries and urban areas of low income countries where neonatal care is rapidly improving with survival of less mature and smaller babies.[14-17] Studies of children in schools for the blind suggest that ROP is becoming an important cause of blindness in China,[18] Southeast[19] and South Asia,[20,21] Latin America[16,22] and Eastern Europe — especially in urban centers in newly industrializing countries.[14-17]

This is referred to as a "third epidemic". The reasons for this epidemic are mixed, as shown in Table 1. For nurseries in which care is similar to that found in

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Table 1. Epidemics of ROP (adapted with permission from Gilbert et al)[23]

Items	Historical perspective of ROP		
	1940–1950s1st epidemic	1960–1970s 2nd epidemic	1980s–present
Risk factors for ROP			
Prematurity	+	++	++++
Low birth weight	+	++	++++
High oxygen	++++	+++	+
Illness factors	+	+	+/–
<1000 g	High mortality No ROP	Mod mortality ROP +	Low mortality ROP +++
1000–1500 g	Improved survival ROP +++	Low mortality ROP ++	Very low mortality No ROP
Level of neonatal care provided	Poor	Moderate	Excellent

3rd epidemic encompasses babies represented in all three columns.

developed countries, low birth weight and very premature birth are the dominant ROP risk factors, while in other nurseries with more limited human and equipment resources, the inadequacy of neonatal care is likely the major contributor to the development of ROP.[23]

CLASSIFICATION OF ROP

As shown in Table 2, the current classification of ROP[24-26] has four major components for acute phase retinopathy: severity (stage), anterior-posterior location of the retinopathy (zone), the extent of the disease along the circumference of the vascularized retina (expressed in terms of 30-degree sectors), and the presence or absence of "plus disease" (defined as engorged and tortuous vessels of the posterior pole and indicating a more advanced and serious form of retinopathy). The convention established for designating the overall ROP status of an eye is to indicate the highest stage of retinopathy, the lowest zone in which retinopathy is observed, and the presence or absence of plus disease.

Stage of retinopathy is indicated based on the appearance of the abnormality at the junction between the vascularized and avascular retina. Stages 1 and 2 usually indicate mild disease. Stage 3 is more serious disease as vessels extend into the vitreous. In stages 4 and 5, the retina has detached either partially (stage 4) or totally (stage 5). The 2005 ICROP-revisited included as category to indicate the most severe ROP, usually seen in the most immature babies. Aggressive Posterior ROP (AP-ROP) can be difficult to recognize since the posterior pole abnormalities of tortuosity and dilation dominate with a sometimes unremarkable peripheral retinopathy that is located in the posterior retina (Figure).[24]

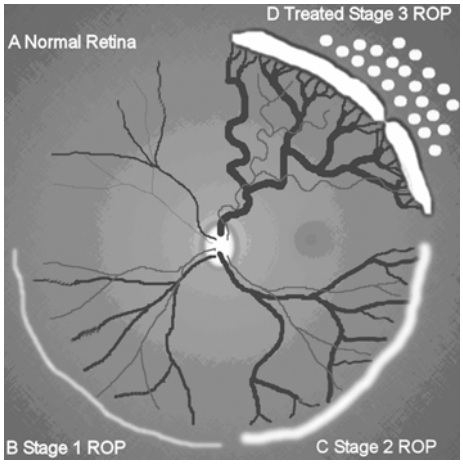

Figure. The picture shows a schematic view of posterior retina. Located in the center of the diagram is the optic disc where the nerves and blood vessels supplying the retina enter and leave the eye. The dark lines are arterioles and venules of the inner retina. The quadrant labelled "A" shows immature retinal vascular pattern with gentle feathering out of the tips of the vessels. In quadrant "B", stage 1 ROP is present showing a sharp line between the vascularized and avascular retina. Stage 2 ROP is shown in quandrant "C" and more serious ROP (Stage 3) is shown in quadrant "D." The white spots beyond the retinopathy indicate where laser treatment of the peripheral avascular retina was performed (Reprinted from "UK Retinopathy of Prematurity Guideline May 2008" with permission of the Copyright holder: The Royal College of Paediatrics and Child Health (RCPCH) *http://www.rcpch.ac.uk/ROP*).

The anterior or posterior location of the retinopathy is indicated by dividing the surface of the retina into three concentric zones centered on the optic disc. The most severe retinopathy tends to occur in zone I (the most posterior), most ROP occurs in zone II, and ROP that occurs in the most peripheral zone (zone III) tends to be mild.

Table 2. International classification of retinopathy of prematurity (revised)

Characteristics	Classification
Anterior-posterior location	Zone I: retinal area within a circle with the disc in the center and a radius of twice the distance from disc to foveal
	Zone II: retinal area from the edge of zone I to the edge of circle with a radius from the disc to the nasal ora serrata
	Zone III: a crescent-shaped retinal area from the edge of zone II to the ora serrata
Severity	
Stage of ROP	Stage 1: a sharp line of demarcation between vascularized retina and avascular retina
	Stage 2: ridge at the junction between vascularized and avascular retina
	Stage 3: ridge with extension of fibrovascular tissue into the vitreous
	Stage 4: partial retinal detachment 4A: extrafoveal 4B: involves the fovea
	Stage 5: complete retinal detachment
AP-ROP	Aggressive posterior ROP recognized by: marked tortuosity and dilation of posterior pole vessels difficulty to document ROP stage between vascularized and avascular retina may occur in zone I or zone II
Extent	Clock hours of ROP along the circumference of the vascularized retina
Posterior pole vascular abnormalities	Dilated and tortuous vessels of the posterior pole in the presence of ROP*
Plus disease	Abnormal vascular dilation and tortuosity insufficient for diagnosis of plus disease*
Preplus disease	

*Vascular abnormality required in two or more quadrants.

Disease extent is indicated by the number of 30 degree sectors of retinopathy along the junction between the vascularized and avascular retina. By documenting the extent of disease in terms of sectors, the examiner can indicate stage of ROP in the various sectors.

Plus disease is diagnosed when tortuosity and/or dilation of the peripapillary arterioles and venules is judged by the clinician to be at least as severe as standard reference images that have been used in clinical trials in the US.[10,12] Diagnosis requires that the arterioles and venules must be sufficiently abnormal in at least two of the four quadrants. An intermediate category was included in the 2005 classification[24] in an effort to recognize that posterior pole vascular abnormalities in ROP represent a continuum from normal appearing vessels to plus disease. The use of the term "preplus disease" was suggested to indicate that the peripapillary vessels are not normal appearing, but not sufficiently abnormal to be designated as plus disease. Other signs of serious ROP activity include vitreous haze, iris vascular engorgement and pupils that do not dilate well with topical medication.

TREATMENT OF ESTABLISHED ROP

Two large randomized clinical trials have shown that peripheral retinal ablation for eyes with severe ROP can help prevent progression to blindness. The multicenter cryotherapy for ROP (CRYO-ROP), which enrolled babies between 1986 and 1987, randomly assigned babies with bilateral "threshold" disease (i.e. 5 or more clock hours of Stage 3 with "plus" disease) to cryotherapy in one eye and no cryotherapy for the fellow eye (control). During the study, approximately 15% of all babies born in the US with birth weights of less than 1251 g were enrolled in the 23 participating centers. Results showed a beneficial effect on visual function and structure in eyes assigned to receive cryotherapy,[10,25] a benefit that lasted through the last study examination at age 15 years.[26-31]

Since almost half of eyes treated in the CRYO-ROP trial had a visual acuity of worse than 20/200 at age 15 years,[31] the effect of an earlier intervention was investigated in the multicenter Early Treatment for ROP trial (ETROP). A risk model including not only the ROP status of the eye, but also demographic characteristics and pace of disease, based on the results of the CRYO-ROP study, was used to determine which eyes were "high risk" for developing a poor outcome.[32] The randomized, controlled clinical ETROP trial assigned eyes with high risk ROP to either undergo immediate retinal ablative therapy or to be followed up and treated if the classic "threshold" ROP developed. A beneficial effect was found in high risk eyes that underwent peripheral retinal ablation compared to the cohort of eyes that were treated at "threshold" ROP if it developed.[13] Results of the ophthalmologic follow-up of these children at age 6 years should be available soon.

In the ETROP study, laser photocoagulation was used more often than cryotherapy due to less discomfort intraoperatively and postoperatively when using laser photocoagulation. Further there is direct visualization of the area during treatment and less pigmentation appears to result from the therapy.[33-35]

Follow-up studies of vitreoretinal surgical treatment for Stages 4 and 5 have shown mixed results–very likely dependent on whether the detachment is total and/or longstanding.[36-39] For eyes with total detachment, functional vision is very unlikely.[38,40,41]

PREVALENCE AND INCIDENCE OF ROP

In most cases, ROP begins at 31–32 weeks postmenstrual age[12,42-44] with peak severity developing over the next 2–5 weeks. Regression of ROP usually occurs without serious residua in eyes with stages 1, 2 and early stage 3[42,45] while blindness or serious visual impairment results from progression to retinal detachment or severe distortion of the posterior retina.[46-50]

In the large clinical studies in countries with long established neonatal intensive care units, the majority of ROP occurs in babies with birth weights of <1500 g with an even greater proportion of babies developing ROP in <1000 g birth weight babies and an even greater proportion in babies with birth weights of <750 g.[11,12,44,51,52] ROP is also more likely to occur in males than females.[52] Serious retinopathy occurs in 10%–15% of babies less than 1250 g birth weight.[11,12] As a greater proportion of VLBW and ELBW babies survive, the population of babies at risk increases.[16]

Since treatment of severe ROP is now available,[10,13] it is essential to identify babies at high risk of blindness so that timely diagnostic examinations can be undertaken. In the US, guidelines for detection of serious ROP indicate that diagnostic examinations should be undertaken for infants with birth weights of <1500 g or <30 weeks gestation, but also on high risk babies in the 1501 g–2000 g birth weight group.[53] In the UK, guidelines do not include babies over 1500 g birth weight and the PMA threshold for examination was raised to less than 32 weeks.[54] In Latin American countries, Eastern Europe, and in urban centers in newly industrializing countries in Asia, criteria for diagnostic examination should be determined by data obtained in the in-country (national or regional) nurseries, as evidence suggests that larger, more mature babies are at risk in these settings.[20,55-58] Although this raises concerns that policies which include larger more mature babies will dramatically increase the workload for examining ophthalmologists, recent evidence suggests that although the number of babies that need examination does increase the actual number of examinations needed to identify a baby needing treatment does not increase very much.[59]

PREVENTION OF ROP

Risk of ROP can be decreased by better ante-natal and obstetric care reducing the rate of prematurity, by the use of ante-natal corticosteroids when a preterm birth is inevitable, and by better neonatal care practices. The latter is simply demonstrated by the differences in the rates of severe ROP seen in developing countries compared with highly developed countries.[16] There are numerous threads of evidence supporting better neonatal care being associated with increased survival and decreased morbidity including ROP.[51] Some components of better neonatal care can be introduced even in resource-poor situations. These include good temperature control with avoidance of hypothermia; decreasing unpleasant or unneeded handling, and the use of analgesia for painful procedures. In addition, measures to decrease infection rates, improve growth and encourage breast feeding are components of good neonatal care. Most important of all is control of oxygen delivery and monitoring of oxygen saturations for babies receiving supplemental oxygen. There is still no clear answer to the longstanding question of what oxygen saturation target is optimal for preterm infants and several large studies around the world are attempting to answer this question.[60]

RECENT DEVELOPMENTS

Oxygen control and prevention of ROP

A number of recent studies have suggested that the standard oxygen saturation targets adopted for preterm infants might be too high. Two randomised controlled trials found that preterm infants randomized to a higher saturation target at several weeks of age had significantly more respiratory morbidity than similar infants randomized to lower saturation targets.[61,62] And two observational studies reported that preterm infants had higher rates of severe ROP when cared for in neonatal units adopting higher saturation targets.[63, 64] As a result of these studies many neonatologists have adopted lower saturation targets and further observational studies and small randomized controlled trials have been reported.[65-72] However the problem is that while hyperoxemia is likely to be associated with an increased risk of a range of morbidities, the same is true for hypoxemia, when increased mortality and adverse neurodevelopment are of particular concern.

To have sufficient power to address these competing outcomes large numbers of infants must be recruited and followed long-term to assess outcome. Five multicenter randomized controlled trials with a similar protocol are underway in the US, UK, Canada, Australia, and New Zealand (SUPPORT, BOOST II, BOOST-NZ, COT, BOOST UK) to compare oxygen saturation targets of 85%–89% and 91%–95% in infants of less than 28 weeks gestation. The investigators have agreed to pool the data in a prospective meta-analysis of all 5000+ infants, but the results will not be available for several years. The SUPPORT trial is the only one of these studies where the primary outcome is death or severe ROP (for the other studies the primary outcome is death or adverse neurodisablity at 2 years of age) and these early outcomes have recently been reported.[65] The SUPPORT trial randomized 1316 infants to the higher or lower oxygen saturation target and found no significant difference in the primary outcome. However, the high saturation target was associated with a significant reduction in severe ROP (P <0.001), and the low saturation target with a probable increase in mortality by hospital discharge (P <0.04). While important, these results do not answer the question as to what oxygen saturation target should be adopted for very preterm infants to minimize harm and we must await the long-term outcome from the current ongoing studies as well as SUPPORT to make that judgment. In the meantime it may be prudent to adopt the "middle" target range of 88%–92% for these extremely premature infants.

Sepsis and ROP

Recent data have again demonstrated that sepsis increases both mortality and serious morbidity, including severe ROP, in very preterm infants. In a study from the Israel Neonatal Network, early-onset sepsis in VLBW infants was shown to increase the risk of severe ROP two-fold (*OR*: 2.04 (95%*CI*: 1.32–3.16)).[73] While the key approach to preventing sepsis will continue to be prevention of cross infection through simple measures such as appropriate hand-washing, new prevention therapies are being investigated including probiotics and lactoferrin. In a randomized controlled trial, Manzoni and colleagues[74] recently showed that bovine lactoferrin, a natural glycoprotein with anti-infective and immunomodulatory properties, significantly decreased late-onset sepsis in VLBW infants and threshold ROP needing treatment from 11.3% in controls to 3.9% in lactoferrin treated infants (P=0.02).

Insulin-like growth factor (IGF-1)

Recent work by Hellstrom and colleagues[75-78] on the role of insulin-like growth factor (IGF-1) has shed light on the pathogenesis of ROP and may point the way to therapeutic options for the future. They have documented that a slower than usual rise in serum IGF-1 levels in the 4 weeks after birth among premature babies was associated with an increased risk of "proliferative" ROP.[77] The authors are also exploring whether weight gain alone can be used to indicate preterm babies at risk of ROP. They have demonstrated that poor postnatal weight gain has been suggested as a risk factor for the development of severe ROP, but further work in different settings is required.[76,78,79] Such observations may eventually allow medical therapies to be offered to high at-risk babies for prevention of retinopathy.[80-83]

Role of genetics

A series of small studies have investigated the association of gene and severe ROP or failure of treatment.[84] They have implicated mutations and polymorphisms in the

Norrie disease pseudoglioma (NDP) gene, endothelial nitric oxide synthetase (eNOS) gene and vascular endothelial growth factor (VEGF) gene. Unfortunately, most studies do not show a significant association of genetic abnormalities and ROP. The influence of genes on the occurrence, progression and severity of ROP warrants further investigation in various populations and in larger cohorts.[85]

A telemedicine approach to detection of serious ROP

Digital images of the retina provide clinicians and researchers with new opportunities to document the findings in ROP within small at risk babies.[86] Such images are becoming an important tool ROP programs for the education of ophthalmologists and for raising awareness and knowledge for neonatologists, pediatricians, nurses, parents, and administrators about the disease that was not easily observed before imaging became relatively easy for both the baby and the imager. In addition, computer assisted digital analysis of vascular abnormalities will likely enable the development of quantitative scores that stratify the risk of eyes for the development of severe ROP, perhaps even before the severe disease is manifested.[87-93]

At present, several-small studies have been undertaken with different entry criteria and examining different components of a system for telemedicine in ROP.[93-96] These reports give different, sometimes contradictory results, but have a common goal of developing and validating an effective system of telemedicine for ROP.[97-100] There is a need for further work in this area before wide implementation of such programs.[102,103]

Anti-VEGF therapy

Vascular endothelial growth factor (VEGF) regulates angiogenesis in the retina and in other organs and also promotes the normal development of other tissues during fetal development such as the lung and kidney.[104] In the nervous system VEGF neurotropic and neuroprotective and maintains the blood-brain barrier.[105] Anti-VEGF treatment has been used with good result in babies with ROP, usually only once laser treatment has failed.[106-108] However, a critically important factor that has to be borne in mind is that VEGF is active in developing tissues throughout the body at the same time as anti-VEGF agents would be needed to treat ROP. We would advocate caution, however, before introducing this new, potentially exciting therapy, especially since large randomized clinical trials have shown the safety and effectiveness of peripheral retinal photocoagulation.[109,110] Since there is good evidence of increased vascular permeability in eyes with serious ROP, use of anti-VEGF drugs may result in greater systemic absorption of anti-VEGF preparations than has been observed in either adults or experimental animal models. Though the preliminary results of case studies have shown good effects on the ocular outcomes, there is an urgent need for well designed, adequately powered randomized clinical trials in which ocular, neurological and pulmonary long term outcomes are carefully documented.

CONCLUSIONS

ROP is rapidly becoming a threat to the vision of babies in areas of the world where increasing numbers of premature babies are surviving. There is also a rapidly developing understanding of ways to prevent or at least decrease the overall morbidity from the disease. There is a need to develop diverse approaches which prevent ROP blindness extending from policies and practices which reduce preterm birth, which lead to improved care of premature babies in neonatal care units, and which lead to the development of adequate ophthalmological services in those regions in which the current epidemic of blinding disease is occurring. Awareness of the possibility of blinding disease needs to be increased among neonatologists, ophthalmologists and neonatal nursing staff, as countries introduce increasingly sophisticated neonatal intensive care services.

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