

Retinopathy of prematurity

S P Donahue

We should focus our screening efforts to target those most at risk

Despite major advances in the treatment of retinopathy of prematurity (ROP), this disease remains a significant cause of blindness in the developed world. ROP as we know it probably did not exist before the advance in prenatal care that occurred in the mid-1950s, with enhanced survival that allowed children to live at an age where retinal vascularisation was incomplete and ROP could develop.

Additional recent advances in neonatology have influenced the incidence and severity of ROP in a dichotomous fashion. While many children who would have fought for survival two decades ago now remain quite healthy throughout their neonatal stay, others for whom death was nearly certain now fight for survival with reasonable odds. Thus, older children are healthier and probably at a decreased risk of ROP, whereas smaller children who would have died now live and are at high risk. How the interplay of these changes has influenced the incidence and severity of ROP is controversial.

In this issue of the *BJO* (p 1122), Larsson *et al* examine this question. The previous studies they cite were generally small, retrospective, and poorly controlled. Larsson *et al*, however, were able to utilise the geography of Stockholm, Sweden, to perform a rigorous evaluation of the effects of advances in neonatal care on the incidence and severity of ROP.

In 1993, these investigators published results from 350 children born weighing 1500 g or less, in a well defined geographical area of Stockholm where it is highly likely that all such live births were identified (1990 cohort). Sixteen per cent of the children died before 7 weeks of age, and follow up data were available for 260 children. Overall, 40.4% developed some ROP, 20% developed stage III ROP, and 10.8% were treated (at a slightly earlier stage than utilised in the CRYO-ROP). The authors compared these data with those obtained in the same manner, from the same location, 10

years later (2000 cohort), virtually eliminating many of the biases found in other comparison studies. In that cohort, 88% of the 331 liveborn infants <1500 g during the study period survived, and they were able to follow 253. ROP developed in 36.4%, and progressed to stage III or greater in 18.2%. Thirty one (12.3%) of these children needed treatment. These percentages were statistically indistinct from those reported a decade earlier. However, the distribution of ROP had shifted so that younger and smaller children accounted for the majority of the cases of ROP.

I believe the important message of this paper is the major shift in the distribution of ROP; while 16% of children >30 weeks' gestational age had severe ROP in the 1990 cohort, and half were treated, only two children (1%) of the similar 2000 cohort developed severe ROP, and neither progressed sufficiently to require treatment. The results were similar, but slightly less striking for the 750–1000 g infants as well: 18.4% of the 1990 cohort had at least stage III ROP compared to fewer than 9% of the 2000 cohort. These results were statistically significant by a wide margin.

Most of the children who develop severe ROP now would have died had they been born a decade ago

How can one reconcile the virtual elimination of ROP in children over 1000 g with the similar overall incidence data between the cohorts? There are two possible explanations: either very small children are developing ROP at a higher rate now than they did 10 years ago, or some type of bias is involved in the sampling. I believe it to be the latter: most of the children who develop severe ROP now would have died had they been born a decade ago. Children born at 26 weeks or less of gestational age represented fewer than 10% of the 1990 cohort, but 23% of the 2000 group. The rate of severe

ROP for such young children in 2000 was 61%, and nearly all of those progressed to require treatment. Assuming similar rates of premature births in the two cohorts, one can calculate that the 2000 cohort includes approximately 23 children of 26 gestational weeks at birth who survived but would have died a decade earlier, and at least 20 of these 23 children developed ROP. If these 23 children are eliminated from the analysis of ROP incidence, the overall incidence of total ROP for the 2000 cohort drops to 72/230 (31%), severe ROP to 14% (32/230), and treatable ROP to 17/230 (7.4%). These numbers are consistent with the approximately 30% decrease in ROP incidence reported in other studies. Thus, the authors' observation that the overall incidence of ROP is unchanged is an epiphenomenon caused by the tremendous increase in survival rate of infants at 26 weeks of age, all of whom appear to be at high risk of severe disease. This then begs the question of whether Swedish intensive care units (ICUs) are now saving children that American ICUs did a decade ago, or if some other factor either decreases the survival rate, or the ROP rate, of similarly aged premature children in the United States.

A major result not pointed out by the authors concerns the effect of treatment: in 1990, seven children (2.7%) developed stage 4 or 5 disease. This decreased to only two children in 2000. It is unclear whether this improved result comes from an advantage of laser treatment over CRYO therapy for ROP, an inherent but unconscious bias to treat higher risk children earlier, or a statistical aberration, but it warrants further investigation.

ROP will continue to be a blinding disease despite further research investigating the pathophysiology of this disease, and new studies (such as ETROP) that help define which children will develop treatable disease. Therefore, it is imperative to determine with more accuracy which children are at highest risk and need to be screened. The authors are to be commended for a rigorous and valid report that helps to focus our screening efforts to target those most at risk.

Br J Ophthalmol 2002;86:1071

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What do you do about ROP screening in "big" babies?

G E Quinn

Screening guidelines should not be considered generalisable to all nursery populations . . . regional differences must be taken into account

World Health Organization guidelines for effective screening programmes¹ demand several conditions be met, but these conditions are still being understood for retinopathy of prematurity (ROP) screening. There is little doubt that ROP is an important health problem in the premature infant population and that peripheral retinal ablation is an accepted treatment for patients with recognised disease. In addition, much is known about the natural history of the condition and the disorder can readily be detected by indirect ophthalmoscopy. However, as Andruscavage and Weissgold point out in their article in this issue of the *BJO* (p 1127), there is not yet an agreed policy on whom to treat as patients, in particular what should the criteria be for ROP screening in children with birth weights larger than 1250 g? Society must also address the cost of finding cases that only rarely occur in higher birthweight, but still preterm, babies.

Results of the randomised Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP)² have shown that, for 10 year old children with birth weights of <1251 g born in the United States in 1986 and 1987, treatment within 72 hours of the diagnosis of threshold disease resulted in a 28.5% reduction in the number of treated eyes with visual acuity of 20/200 or worse ($p < 0.001$) compared to control eyes. There was also a 43.2% reduction of treated eyes with retinal folds involving the fovea or total retinal detachment, compared to eyes in the control group ($p < 0.001$). The cohort of children that constitutes the CRYO-ROP study population accounted for approximately 15% of the <1251 g birthweight children born in the United States during the enrolment period,³ and 291 children were enrolled in the treatment arm of the study, representing 6% of the study population.

We do not know the prevalence of severe ROP in the larger birthweight preterm infants, though retinopathy of this severity does occur in children with

birth weights of greater than 1250 g.⁴ The two cases reported by Andruscavage and Weissgold represent 1.2% of the 162 children screened and only 0.65% of the survivors with birth weights greater than 1500 g eligible for ROP screening according to their nursery criteria. There are two interesting aspects to the ocular findings in these children: (1) the four eyes that required treatment reached threshold severity nearly at term, somewhat later than most threshold disease in <1251 g birthweight children,⁵ and (2) all four eyes had good structural and functional outcomes with no significant refractive error. Though little can be made of the findings in such a small sample, it is in agreement with my clinical impression that threshold ROP is less virulent in larger birthweight babies.

The recent screening guidelines for ROP from the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association of Pediatric Ophthalmology and Strabismus⁶ provide little guidance in determining which preterm infants with higher birth weights should be examined. The statement recommends that ROP screening should be performed at least twice in "selected infants between 1500 g and 2000 g with an unstable clinical course who are believed to be at high risk by their attending pediatrician or neonatologist." The risk factors that identify "unstable clinical course" are left to the individual clinician to define.

The cost effectiveness of treatment for threshold ROP for infants <1251 g has been demonstrated in two studies. Javitt *et al.*,⁷ using data from the CRYO-ROP study, predicted a cost per quality adjusted life year gained was from \$2488 to \$6045 (£1583–£3845), depending on how frequently the eyes were examined. The overall cost savings in the cohort of infants born annually in the United States ranged up to \$64.9 million (£41.3 million). In addition, they suggested that blindness could be avoided in 320 children per year if a timely intervention strategy for severe ROP were used. More recently, Brown *et al.*⁸ calculated cost

effectiveness of laser therapy or cryotherapy for threshold ROP and suggested that the cost effectiveness is somewhat higher for laser treatment, but that both were "excellent values" since they had long term benefit for those children who were prevented from going blind by the treatment. At our present level of understanding, the cost effectiveness of screening for higher birthweight infants cannot be calculated for a number of reasons: (1) we have not defined the population at risk; (2) we have not described the natural history of severe ROP in infants with birth weights of >1251 g; and (3) we have not developed an effective strategy for examining these children who are most likely to be discharged from the hospital before development of threshold disease.

The current database that has provided much of our knowledge of the natural history of ROP has been collected in tertiary care nurseries in the industrialised world. The prevalence of blinding disease in the newly industrialising countries is largely unknown and older, larger babies may be at risk in these areas.⁹ Therefore, screening guidelines for ROP should not be considered generalisable to all nursery populations, but regional differences must be taken into account.

In summary, Andruscavage and Weissgold have begun to help us unravel the complex question of what to do about detecting and treating blinding disease in higher birthweight preterm infants, but much remains to be done. Certainly missing the opportunity to treat threshold ROP and to prevent blindness in an infant is recognised by all as tragic, but we have yet to grapple with issue of staff levels to accomplish the necessary screening examinations and we are still trying to identify those children at risk. Perhaps, when there is an adequate understanding of the ROP in these children we will be able to develop an algorithm similar to that being used in the Early Treatment for ROP (ET-ROP) study¹⁰ currently under way in the United States to determine which infants to examine and when to treat their retinopathy.

Br J Ophthalmol 2002;86:1072–1073

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