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Short- and Long-Term Follow-Up of Ophthalmological Findings in Preterm Infants and Children

BY

EVA LARSSON



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Abstract

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In a prospective population-based study in Stockholm County, 1998-2000, the incidence of retinopathy of prematurity (ROP) was investigated and was found to be 36% in prematurely-born infants with a birth weight of ≤ 1500 grams. Compared to a study performed ten years ago, the overall incidence was unchanged, but was reduced in "mature" infants and increased in immature ones. The incidence of ROP was 25% in infants with a gestational age of ≤ 32 weeks at birth. The main risk factors for ROP were the gestational age at birth, followed by the birth weight. Current guidelines for ROP screening in Sweden were modified.

A 10-year follow-up study of the ophthalmological findings in prematurely-born children, previously included in a prospective population-based incidence study of ROP, was performed. The children were compared with full-term ones.

Prematurely-born children ran a four times higher risk of refractive errors than full-term ones. The cryotreated children had the highest risk, but those without ROP also had more refractive errors than the full-terms. Within the group of prematurely-born children, the cryotreated ones had the highest prevalence of myopia, astigmatism and anisometropia, but no difference was found regarding hypermetropia.

The visual acuity of prematurely-born children was poorer than that of the full-terms. The cryotreated children and those with neurological complications had the most marked reduction, but the children without ROP and neurological findings also had a poorer visual outcome than the full-terms. The prevalence of visual impairment was 1.8% among the prematurely-born children, and was due to ROP in half the cases and cerebral lesions in the others.

The cryotreated children had constricted peripheral visual fields compared to the untreated prematurely-born and full-term children. The central visual fields tended to be reduced in the prematurely-born children compared to the full-terms, but no difference was observed within the preterm group.

Keywords: prematurity, follow-up, retinopathy of prematurity, ROP, infants, children, incidence, screening, refraction, visual acuity, visual fields

Eva Larsson, Department of Neuroscience, Ophthalmology, Uppsala University Hospital, Uppsala University, SE-75185 Uppsala, Sweden

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“The essence of a child-
born to shimmer, born to shine, born to radiate”

Shawn Mullins

To my family

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Larsson E, Carle-Petrelus B, Cernerud G, Ots L, Wallin A, Holmström G. Incidence of ROP in two consecutive Swedish population based studies. *Br J Ophthalmol* 2002;86:1122-1126.
- II Larsson E, Holmström G. Screening for retinopathy of prematurity: evaluation and modification of guidelines. *Br J Ophthalmol* 2002;86:1399-1402.
- III Larsson E, Rydberg A, Holmström G. A population-based study of the refractive outcome in 10-year-old preterm and full-term children. *Arch Ophthalmol* 2003;121:1430-1436.
- IV Larsson E, Rydberg A, Holmström G. A population-based study of the visual outcome in 10-year-old preterm and full-term children (submitted).
- V Larsson E, Martin L, Holmström G. Peripheral and central visual fields in 11-year-old children who had been born prematurely and at term. *J Pediatr Ophthalmol Strabismus* 2004;41:39-45.

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Abbreviations

BW	Birth weight
CRYO-ROP	The Cryotherapy for Retinopathy of Prematurity Cooperative group
CVI	Cerebral visual impairment
DLS	Differential light sense
ETROP	Early Treatment for Retinopathy of Prematurity Cooperative Group
GA	Gestational age
HRP	High-pass resolution perimetry
IGF	Insulin-like growth factor
IVH	Intraventricular haemorrhage
LE	Left eye
MAR	Minimal angle of resolution
MRI	Magnetic resonance imaging
NC	Neural capacity
PMA	Post menstrual age
PVL	Periventricular leukomalacia
RE	Right eye
ROP	Retinopathy of prematurity
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VF	Visual field
WHO	World Health Organization

INTRODUCTION

Prematurely-born infants and children run a higher risk of ophthalmological problems than those born at term. For many decades, retinopathy of prematurity (ROP) has been a well-recognised cause of visual impairment in prematurely-born children (Terry 1942). In the 1980s an international classification of ROP was adopted and treatment was recommended at a defined threshold stage, which resulted in a better ophthalmological outcome. Since then, screening for ROP has been introduced in most developed countries. In Sweden the recommendation for screening is based on an epidemiological study by Holmström et al (1993), which was performed in 1988-1990. The advantages of screening for ROP are counterbalanced by the high costs for society and the stressful examinations of the infants. The risk of developing ROP has been related to the immaturity of the infant. In the last decade, neonatal care has improved and more immature infants are surviving. It is therefore important to investigate the consequences of this development on the incidence of ROP and to evaluate whether the screening criteria need to be revised. These two issues will be discussed in the first part of the thesis.

Apart from ROP, prematurely-born children run a risk of other ophthalmological problems, such as visual impairment, strabismus, amblyopia, visual field defects and refractive errors. Severe damage is usually diagnosed and taken care of early, whereas minor defects may be detected later in life. Identification of children who need extra help is therefore important and requires follow-up programmes. However, such programmes are expensive and must be based on an accurate knowledge of the prevalence of ophthalmological disorders in the population. The second part of this thesis deals with a 10-year follow-up of the population-based prematurely-born cohort born in 1988-1990.

Preterm birth

Prematurity is defined by the World Health Organization (WHO) as a gestational age (GA) less than 37 weeks at birth. However, most follow-up studies include more immature infants and children. In Sweden the incidence of preterm birth, defined as live-born infants with a GA of ≤ 33 weeks at birth, is 1.7% (2001). If birth weight (BW) < 1500 grams is used as the criterion of immaturity, the incidence of preterm birth in Sweden is 0.8% (2001) (The National Board of Health and Welfare, Centre for Epidemiology, 2003).

There is an inverse relation between GA at birth and mortality rate (Finnström et al 1997, McElrath et al 2001, Tommiska et al 2001), but with improvements in neonatal care, such as antenatal steroids given to the mothers, surfactant therapy and oscillatory ventilation, survival rates have continually improved over the years (Chow 2003, Darlow 2003, Hack et al 1996, Harper et al 2002, The Victorian Infant Collaborative Study Group 1997). Despite the improvements, the prematurely-born infant is still vulnerable. The neonatal period may be complicated by pulmonary, circulatory, cerebral and ophthalmological dysfunctions. During the first years of life severe damages may be detected, such as necrotising enterocolitis, bronchopulmonary dysplasia, intraventricular haemorrhage, cerebral palsy, periventricular leucomalacia and blindness (Cust et al 2003, Darlow et al 2003, Finnström et al 1997, Hack et al 1996, Jacobsson 2002, The Victorian Infant Collaborative Study Group 1997). However, later in life, at preschool and school age, behavioural problems and cognitive impairments may appear (Bhutta et al 2002, Darlow et al 1997a, Hack et al 2000, Stjernqvist et al 1999).

Retinopathy of prematurity

Retinopathy of prematurity (ROP) was first described by Terry (1942). At that time it was referred to as retrolental fibroplasia. After the introduction of intensive neonatal care in the 1940s and 1950s, the survival of prematurely-born infants increased and ROP became the most common cause of blindness in the industrialised world (Gilbert et al 1997). Improvements in neonatal care, screening and treatment of ROP have reduced the incidence of blindness in many countries (Blohmé and Tornqvist 1997a, Fledelius et al 2000, Termote et al 2003). However, when middle-income countries introduce neonatal intensive care, the infant mortality rate declines and ROP is becoming a major cause of blindness in these countries (Gilbert and Foster 2001, Kocur and Resnikoff 2002). WHO's global initiative to eliminate

avoidable blindness has therefore given priority to screening and treatment of ROP (Gilbert and Foster 2001, Thylefors 1998).

Pathogenesis

Vascularisation of the embryonic retina starts in the fourth month of gestation. Mesenchymal endothelial cells develop a network of capillaries that precedes the definitive vessels, growing from the optic nerve. An increase in the metabolic demand promotes the development of retinal vessels (Chan-Ling et al 1995). These vessels reach the ora serrata nasally at 35 weeks of GA and temporally at about 40 weeks of GA (Ben Sira et al 1988, Petersen et al 1994). In children born before term, the retina is therefore not fully vascularised. The retinal vasculature is vulnerable and the normal outgrowth of vessels towards the periphery may cease in prematurely-born infants.

The aetiology of ROP is not fully understood, but is considered to be multi-factorial. Normal vasculogenesis is disrupted by an initial relative hyperoxia and down-regulation of vascular endothelial growth factor (VEGF) (Pierce et al 1996). A sustained hyperoxia may lead to an obliteration of the retinal circulation and an increase in metabolic demands followed by hypoxia, which may induce an overproduction of VEGF (Laschkari et al 2000). This stimulates neovascularisation (Alon et al 1995, Wheatley et al 2002, Zhang et al 1999) in the retina with arteriovenous shunts and fibrovascular proliferations, which later leads to retinal traction with detachment.

The role of oxygen in the pathogenesis of ROP has been studied extensively, but it remains obscure. Half a century ago, oxygen was a suspected cause (Patz 1952) and the incidence of ROP fell when the oxygen level in the incubator was reduced. However, hyperoxia, hypoxia (Phelps 1988, Shohat et al 1983) as well as fluctuations in oxygen tension (Cunningham et al 1995, Penn et al 1994, Saito et al 1993) have been associated with ROP. Several other risk factors for ROP have been proposed and are listed in Table 1. Maternal risk factors, such as preeclampsia (Seiberth and Linderkamp 2000), essential hypertension (Holmström et al 1996) and beta-blocking agents (Gallo et al 1993) have also been considered. Among the risk factors discussed, the immaturity of the infant – i.e., the GA at birth and BW still seems to be the major risk factor for ROP (Holmström et al 1998a, Hussein et al 1999, Seiberth and Linderkamp 2000).

Table 1. *Risk factors for ROP in the literature*

Risk factor	References
Hyperoxia, hypoxia, fluctuation in oxygen	Cunningham et al 1995, Patz 1952, Shoat et al 1983
Vascular endothelial growth factor (VEGF)	Alon et al 1995, Laschcari et al 2000
Growth hormone (GH)	Smith 2002
Hepatocytic growth hormone (HGH)	Smith 2002
Insuline-like growth factor (IGF-1)	Hellström et al 2003
Genetic factors	Flynn 1992, Hiroaka et al 2001
Vitamin E	Brion et al 2003, McColm and Fleck 2001, Mintz-Hinter et al 1983
Inositol	Friedman et al 2000
Poor weight gain	Wallace et al 2000
Apnoea	Shoat et al 1983
Acidosis	Holmes et al 1999
Bronchopulmonary dysplasia	Falciglia et al 2003
Hypercarbia, hypocarbia	Shoat et al 1983
Blood tranfusion	Englert et al 2001
Free iron	Hirano et al 2001
Necrotising enterocolitis	Arroe and Peitersen 1994
Persistent ductus arteriosus	Arroe and Peitersen 1994
Candida sepsis	Noyola et al 2002
Intraventricular haemorrhage	O’Keefe et al 2001
Retinal light exposure	Glass et al 1985
In vitro fertilisation	Watts and Adams 2000
Surfactant	Seiberth and Linderkamp 2000
Dopamine	Mizoguchi et al 1999
Dexamethasone	Parupia and Dhanireddy 2001, Termote et al 2000a
Hyperglycemia	Garg et al 2003
Indomethacin	Darlow et al 1992

Classification

In 1984 and 1987, ROP was classified according to the stage, localisation and extension of the disease (The Committee for the Classification of Retinopathy of Prematurity 1984, The International Committee for the Classification of Retinopathy of Prematurity 1987). Five stages were described. A distinct border, a demarcation line, between the vascular and avascular retina, is observed in stage 1. Stage 2 is characterised by a ridge developing at the demarcation line and stage 3 by fibrovascular proliferations. In stage 4, partial retinal detachment is present (4A-macula not involved, 4B-macula detached) and in stage 5, the retina is entirely detached. The extent of the retinal involvement is recorded as clock hours.

Finally, “plus disease” indicates progressive disease, and is characterised by dilated and tortuous vessels in the posterior fundus.

Moreover, ROP may be localised in three zones, all having the centre in the optic disc. Zone I is the inner zone of the posterior pole, with a radius of twice the distance from the optic head to the fovea. Zone II extends from zone I to the nasal ora serrata and zone III is the residual crescent temporally, outside zone II (The Committee for the Classification of Retinopathy of Prematurity 1984).

Regressed ROP is classified separately. It is divided into peripheral and posterior vascular changes such as retinal avascularity, abnormal branching of vessels and severe displacement of major retinal vessels, or into peripheral and posterior retinal changes, such as pigmentary changes, retinovitreal interface and distortion of the fovea (The International Committee for the Classification of Retinopathy of Prematurity 1987).

The stages of ROP are usually grouped into no, mild (stages 1 and 2), and severe ROP (stages 3-5) (Holmström et al 1993). In an American study on the potential benefit of cryotherapy, ROP was also divided into prethreshold ROP and threshold ROP. Prethreshold was defined as any stage of ROP in zone I, or stage 2 with “plus disease” or stage 3 in zone II. Threshold disease was defined as five contiguous or eight cumulative clock hours of ROP stage 3 in zone I or II, in the presence of “plus disease” (The Cryotherapy of Retinopathy of Prematurity Cooperative group (CRYO-ROP) 1988).

Onset and regression of ROP

The onset and involution of ROP are related to the child’s maturity – i.e., the postmenstrual age (PMA) (Brenner et al 2003, Fielder et al 1986, Holmström et al 1993, Repka et al 2000). This has implications for screening guidelines, especially for determining when to start the examinations. In the Swedish population-based study by Holmström et al (1993), the mean onset of ROP was at 31 weeks PMA and of severe ROP at 32 weeks PMA, in accordance with Reynolds et al (2002). However, Subhani et al (2001) described prethreshold ROP at 28 weeks PMA in prematurely-born infants of 23-25 weeks of GA at birth, which would suggest that the onset may occur earlier in the most immature children (Holmström 2002). Most ROP regresses spontaneously at a mean PMA of 39 weeks (Fielder et al 1992, Repka et al 2000). In the study by Holmström et al (1993) approximately 73% of all ROP regressed without any treatment.

Prevention of ROP

The aim of several studies has been to prevent ROP or progression of the disease. According to some authors the harmful effect of oxygen free radicals can be reduced by vitamin E. Plasma levels are low in preterm

infants and vitamin E supplements have therefore been given in clinical trials to reduce the incidence of ROP. The beneficial effect, however, is still disputed (Brion et al 2003, Phelps et al 1987, Raju et al 1997).

The effect of light reduction has been evaluated, but a prospective, randomised multi-centre study found no reduction in the incidence of ROP (Reynolds et al 1998).

Therapeutic administration of oxygen has been recommended to down-regulate retinal neovascularisation and reduce the progression from prethreshold to threshold ROP. An American multi-centre study (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) 2000) failed to confirm this, although no exacerbation of prethreshold ROP to threshold ROP was detected. Further, prevention of ROP has been studied by monitoring of the amount of oxygen given to the infant (Patz 1967), but the findings were inconclusive and more recently, the results have been contradictory (Askie et al 2003, Chow et al 2003, Tin and Wariyar 2002).

Lately, it has been reported that a low level of IGF-1 is associated with ROP (Hellström et al 2001, Hellström et al 2003). IGF-1 is related to nutrition and poor postnatal weight gain has previously been linked to the risk of developing severe ROP (Wallace et al 2000). It remains uncertain whether improvement in neonatal nutrition or intervention with growth factors can prevent or reduce ROP.

Treatment

Xenon arc photocoagulation and cryotherapy were introduced as a treatment for severe ROP in the 1970s (Ben-Sira et al 1980, Nagata et al 1977, Sasaki et al 1976). The initial aim was to close the proliferating vessels, but later, cryotherapy anterior to the fibrovascular ridge came to be regarded as more effective. As in other ischaemic retinopathies, the destruction of tissue was thought to reduce the release of vasoproliferative factors (Ben-Sira et al 1980, Nissenkorn et al 1984). In 1986, an American multi-centre trial was started to evaluate the efficiency and safety of cryotreatment. Prematurely-born infants with a birth weight of less than 1251 grams were screened for ROP. The criterion for treatment -i.e., “threshold disease” was defined as the level of severity when the risk of blindness was 50%. Approximately 300 eyes that fulfilled this criterion were randomised to treatment and an equal number that also fulfilled the criterion served as controls. The outcome was defined as unfavourable if posterior retinal detachment, a retinal fold in the macula or retrolental tissue were seen. The treated group had only half of the number of eyes with such an outcome as in the control group. On the basis of this multi-centre study, treatment was therefore recommended for eyes with “threshold” disease (CRYO-ROP 1988). The long-term results of the American CRYO-ROP study, at ten years of age, has revealed a more

favourable outcome in treated eyes than in control eyes, Table 2 (CRYO-ROP 2001a). The visual field was slightly more constricted in the cryotreated eyes (CRYO-ROP 2001b) and the prevalence of myopia was about the same in both groups, although cryotreated eyes had a higher frequency of myopia exceeding eight diopters (Quinn et al 2001).

Table 2. *Outcome of the American study of cryotherapy for retinopathy of prematurity*

	Control eyes	Cryotreated eyes
Distance visual acuity ≤ 0.1	62.1 %	44.4 %
Near visual acuity ≤ 0.1	61.6 %	42.5 %
Unfavourable outcome of fundus structure	47.9 %	27.2 %
Retinal detachment	41.4 %	22.0 %

However, cryotreatment has side effects. Systemic complications, such as bradycardia and cyanosis, may occur. Chemosis, oedema, haemorrhages in the retina and vitreous or retinal artery occlusion are rare ocular complications (Ben-Sira et al 1988, CRYO-ROP 1988).

Shortly after the recommendation for treatment was adopted (CRYO-ROP 1988), laser therapy was introduced as an alternative to cryotherapy. Clinical trials concluded that laser treatment is at least as good as cryotherapy (Hunter and Repka 1993, Iverson et al 1991, McNamara et al 1991, McNamara et al 1992). Cryotherapy causes retinal, choroidal and scleral damage with formation of scar tissue (Vrabec et al 1994), whereas laser photocoagulation tends to induce less scleral (Smiddy 1992) and chorioretinal damage (Park et al 2001). Follow-up at ten years shows a better structural and functional outcome as well as less myopia in laser-treated than cryotreated eyes (Connolly et al 2002, Ng et al 2002). The disadvantages include accidental treatment of the lens and macula, long duration of treatment and the need for a well-dilated pupil and clear media (McNamara et al 1992).

Laser treatment has gained widespread acceptance in the treatment of ROP and is now used frequently, but some authors have reported the advantage of a combination of cryo- and laser therapy (Eustis et al 2003, Laatikainen et al 1995). Cryotherapy is used in the anterior part of the retina and laser therapy in the posterior. This procedure increases the technical ease and therefore shortens the duration of treatment.

In most centres in Sweden treatment is performed at an earlier stage of ROP than in the American CRYO-ROP study –i.e., when ROP stage 3 is present in at least four contiguous clock hours, even in the absence of “plus disease” (The National Board of Health and Welfare 1997). The criteria for treatment have been a topic for discussion (CRYO-ROP 2002, Goble 1997, Holmström et al 1999). Early treatment may preserve the retinal function with less pronounced sequelae than if treatment is introduced at a later stage of ROP (Sternberg et al 1992, Tasman 1992) and there are reports showing better structural outcome when an earlier treatment than at threshold disease has been performed (Vander et al 2001, Vardhan Azad et al 2003, Recsan et al 2003). Recently, the American multi-centre study of earlier treatment for ROP (Early Treatment for Retinopathy of Prematurity Cooperative Group (ETROP) 2003) presented their results. At nine months of age they found reduced unfavourable outcome in treated eyes with high-risk prethreshold ROP than in eyes treated at threshold stage. Their recommendation is to consider retinal ablation for eyes with any stage of ROP with “plus disease” in zone I, ROP stage 3 with or without “plus disease” in zone I or ROP stage 2 or 3 with “plus disease” in zone II.

Vitreoretinal surgery –i.e., scleral buckling or vitrectomy is required if ROP progresses to stage 4 or 5. The aim of surgery is to reattach the retina and, in ROP stage 4, also to halt the progression to stage 5 (Trese et al 1994). It is important to recognise ROP stage 4 A, because at that stage, the macula is not yet detached and the surgical treatment may have a better functional outcome (Ben-Sira et al 1988). Scleral buckling in ROP stage 4 has been advocated in many studies (Beyrau and Danis 2003, Hinz et al 1998, Trese et al 1994) but in patients with tractional detachment of the retina in ROP stage 4 and stage 5, lens-sparing vitreous surgery is preferred (Kono et al 2000, Trese and Droste 1998, Zilis et al 1990). In most cases, the anatomic results are good, but the functional results are poor (Noorily et al 1992, Quinn et al 1996a, Terasaki and Hirose 2003). More recently, Capone and Trese (2001) reported that lens-sparing vitrectomy in ROP stage 4 A is better than scleral buckling. They found an improvement in anatomic success rate and hope for a better visual outcome, but their long-term results have not yet been published.

Incidence

The incidence of ROP has been investigated by many authors, but the results are difficult to compare because of different populations and methods, as illustrated in Table 3. The degree of immaturity varies, most studies of the incidence are hospital-based and only a few are population-based. In Stockholm County, Sweden, a population-based incidence study, including infants with a birth weight of 1500 grams or less, was performed by

Holmström et al (1993). The incidence of ROP was 40% (20% mild and 20% severe ROP).

Table 3. *The incidence of ROP in various population- and hospital-based studies.*

Incidence	Inclusion	Study design	Country	Reference
49%	≤ 1700 grams	Population-based	United Kindom	Ng et al 1988
21%	< 1500 grams	Population-based	New Zealand	Darlow et al 2003
10%	< 1750 grams or < 32 weeks	Population-based	Denmark	Fledelius and Dahl 2000
40%	≤ 1500 grams	Population-based	Sweden	Holmström et al 1993
10%	< 1500 grams	Population-based	Norway	Haugen and Markestad 1997
66%	≤ 1250 grams	Hospital-based	United States	CRYO-ROP 1994
37%	< 1500 grams or < 32 weeks	Hospital-based	The Netherlands	Termote et al 2000b
46%	≤ 1500 grams or ≤ 33 weeks	Hospital-based	Vietnam	Phan et al 2003

Continuous improvements in neonatal care and the survival rate of immature infants may change the incidence of ROP. Some consecutive hospital-based studies report a reduced incidence (Chow et al 2003, Bullard et al 1999, Rowlands et al 2001), whereas others have found an increased or unchanged incidence over time (Kennedy et al 1997, Termote et al 2000b). Only a few population-based consecutive studies have been performed. In a retrospective study from Switzerland, Bossi and Koerner (1995) compared two study periods (1983-85 and 1989-91) and found increase in the number of survivors and increase in the incidence of total ROP, as well as of severe ROP. Fledelius and Dahl (2000) prospectively followed a cohort in Denmark from 1982 to 1997, and in contrast reported a reduced incidence of ROP, even among the immature infants. Recently, Darlow et al (2003) reported on two consecutive population-based studies from New Zealand (1986 and 1998-99), demonstrating an increase in the survival rate and an unchanged overall incidence of ROP. However, infants with BW < 1000 grams had a reduced incidence of severe ROP.

Screening

Compared to many other medical conditions, ROP easily meets the requirements for screening (Fielder 2003, Werkö 2003, Wilson and Junger 1968). The natural history is known, severe ROP may cause blindness, which is a health problem, the examination is well-established and a relatively safe and effective treatment is available. In many countries, screening programmes are therefore mandatory, and they aim to find infants with severe ROP, and ensure that treatment is given at an appropriate time (Holmström 2002). All screening programmes, including that for ROP, are labour-intensive and expensive. A recent study from the United Kingdom estimated that it takes the ophthalmologist 19 hours to detect one single case of threshold disease (Brennan et al 2003). However, the authors calculated that the estimated cost of the ophthalmologist was justified by saving a person from a lifetime of blindness, which is in accordance with other studies (Javitt et al 1993).

Screening examinations can be stressful for the infant (Kumar et al 2002, Laws et al 1996, Shinomiya et al 2003). The number of infants screened must therefore be kept to a minimum. The various incidences of ROP underline the importance of adapting the screening programmes to the local communities (Fledelius and Dahl 2000). Some countries have developed national guidelines, which take into account their own epidemiology and neonatal care, see Table 4 (American Academy of Pediatrics, American Association for Pediatric Ophthalmology, American Academy of Ophthalmology 2001, Darlow and Clemett 1990, Fledelius and Dahl 2000, Lee et al 2001, The Report of a joint working party of the Royal Collage of Ophthalmologists and the British Association of Perinatal Medicine 1996).

Table 4. *National screening guidelines in various countries*

Country	Screening criteria
Sweden	≤ 32 weeks
Denmark	< 32 weeks and/or < 1750 grams
United Kingdom	≤ 31 weeks and/or ≤ 1500 grams
United States	≤ 28 weeks or < 1500 grams
Canada	≤ 1200 grams
New Zealand	< 31 weeks or < 1250 grams

Although screening is well-established, there is an on-going discussion about which infants should be screened and when (Andruscavage and Weissgold

2002, Brennan et al 2003, Fielder 2003, Hutchinson et al 2003, Lee et al 2001, Mathew et al 2002, Quinn 2002, Reynolds et al 2002, Wright et al 1998). The continuous improvements in neonatal care and the increasing survival rate of immature infants also require regular revision of screening guidelines (Holmström 2002).

In Sweden, the recommendation for screening, stated by The National Board of Health and Welfare (2000), is based on the study by Holmström et al (1993) in the late 1980s. It includes prematurely-born infants with a GA of ≤ 32 weeks at birth. Examinations start at five weeks of age and continue at intervals of 1-2 weeks until the retina is fully vascularised. If the criterion for treatment is met, it is given within 72 hours.

Visual acuity and visual fields – general aspects

Central vision, with optimal resolution, is expressed as visual acuity (VA) and peripheral vision as visual fields (VF). Visual information is first received by the retina and the photoreceptors –i.e., the cones and rods. In the fovea and foveola, the most central part of the fovea, the cones are densely packed, whereas the rods are more frequent in the periphery. The photoreceptors are connected with the bipolar cells, which further connect with the ganglion cells. The axons of the ganglion cells conduct the visual information into the optic nerve. In the chiasm, axons from the ganglion cells of the nasal side of one eye cross and join axons from the ganglion cells of the temporal side of the other eye, forming the optic tract. The ganglion cells synapse in the lateral geniculate nucleus and the signal is transferred into the optic radiation to reach the visual cortex in the occipital lobe (Figure 1) (Boyd et al 2003).

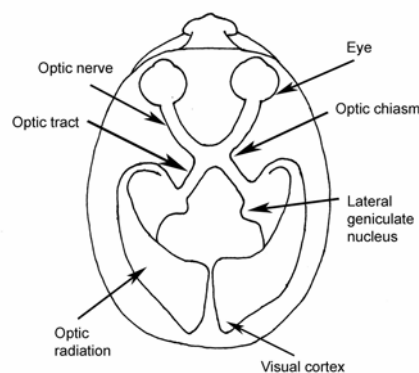


Figure 1. The visual pathway. Drawing by Eva Nuija.

A lesion in any of these structures may cause visual dysfunction, expressed as reduced VA and/or a VF defect. There are also associated pathways, connected with the visual cortex, which interpret orientation, motion, colour and recognition (Bruce and Green 1992).

The visual system undergoes marked development at the time of preterm birth. At 26 weeks of gestation the photoreceptors have only rudimentary inner segments and no outer segments. The central retina matures later than the peripheral, and the rods in the central retina develop before the cones in the fovea (Hendrickson and Drucker 1992). The latter contains immature cones and several layers of neural cells, which later become displaced laterally. A central depression gradually deepens and forms the foveal pit that is present at 36 weeks of gestation. However, the fovea is not fully matured at term and histological findings show that maturation occurs several months after birth (Hendrickson 1992) and cone density is at birth about 20% of that of an adult (Sharma and Ehringer 2003). Retinal ganglion cells and neurons in the lateral geniculate nucleus develop early. Approximately two-thirds of the axons, developed in the optic nerve, are eliminated by week 33 of gestation (Provis et al 1985). Myelination starts in mid-gestation and progresses from the geniculate bodies to the optic nerve at about 32 weeks of gestation (Takayama et al 1991a). In the retrogeniculate pathway, myelin has been observed at 29 weeks of gestation and myelination of the cerebral white matter increases from 35 weeks of gestation and onwards (Huppi et al 1998). Cortico-synaptogenesis is particularly intense after 25 weeks (Ajayi-Obi et al 2000). The volume of the grey matter increases four-fold during the last ten weeks of gestation (Huppi et al 1998). However, in the cortex, there is also an overproduction of neurons, and apoptosis has been reported during the last two months of gestation (Rabinowicz et al 1996). In an infant born three months before term, this process occurs after birth and is vulnerable because of the immaturity of the visual system.

With normal visual development, maturation is gradual throughout infancy and childhood. The visual system has plasticity and a clear retinal image is necessary for neuronal development (Wiesel and Hubel 1963, 1965). The greatest improvement in VA occurs during the first months of life (Atkinson 1984). There is a critical period, in which the development of VA can be modified, which lasts until 8-10 years of age (Daw 1998, von Noorden 1996).

Peripheral vision (the VF) also develops rapidly in early childhood (Heersema et al 1989, Mohn and van Hof-van Duin 1986). The temporal VF develops before the nasal (Lewis and Maurer 1992). After infancy, the VF slowly extends until 11-12 years of age, when the adult VF is reached (Wilson et al 1991).

Assessment of visual acuity and visual fields

Various psychophysical methods are used to measure VA and VFs. The ability to co-operate and the age of the child who is to be examined determine which technique should be used.

The optimal resolution in the fovea is measured as the VA. The resolution limit, the minimal angle of resolution (MAR), is the limit where two objects can be seen separately. The VA is expressed as $1/\text{MAR}$ on a linear scale, Snellen's visual acuity or Snellen's fraction, or as MAR, usually on a logarithmic scale, logMAR (Westheimer 2003). VA assessed by the identification of letters is affected by cognitive factors and sometimes called recognition acuity (McDonald 1986). Optotypes that are easier for a child to recognise can be used (Hyvärinen 1980). VA can also be assessed by pure resolution techniques, resolution acuity (McDonald 1986). The preferential looking technique or Teller acuity test (Teller et al 1986), frequently used in infants and children, is an example of this.

Although standard procedures for measuring VA have been recommended (Colenbrander 1988, Hofstetter 1981, International Standard Organization 1994, Ricci et al 1998), the testing procedures may vary both in clinical practice and in research (Dong et al 2003, Enoch 1998, Ricci et al 1998). This can make comparisons difficult.

There is also a variability in the test situation and the visual capacity is not always characterised by a single value (Frisén 1990). When reading a test chart with lines of letters of different sizes, there is a continuous decrease from 100% to 0% correct answers. If the criterion for VA is 100% correct answers, one misread letter will have a large impact. It can be misread because of inattention or true inability (Frisén 1990, Martin 2000). The frequency-of-seeing procedure reduces the effect of variability in the VA test. The percentage of correct answers ranging from 100% and 0% correct answers can be plotted on a graph with VA on the x-axis, Figure 2.

The frequency-of-seeing curve is theoretically sigmoid; however, such a curve is difficult to obtain with only a few observations. If logMAR is plotted on the x-axis, the frequency-of-seeing curve can be drawn as a straight line (Frisén 1990, Hedin and Olsson 1984, Ricci et al 1998). When using the frequency-of-seeing procedure to assess VA, the 50% value of correct answers is least affected by measurement errors and is therefore appropriate for comparing groups (Frisén 1990, Ricci et al 1998).

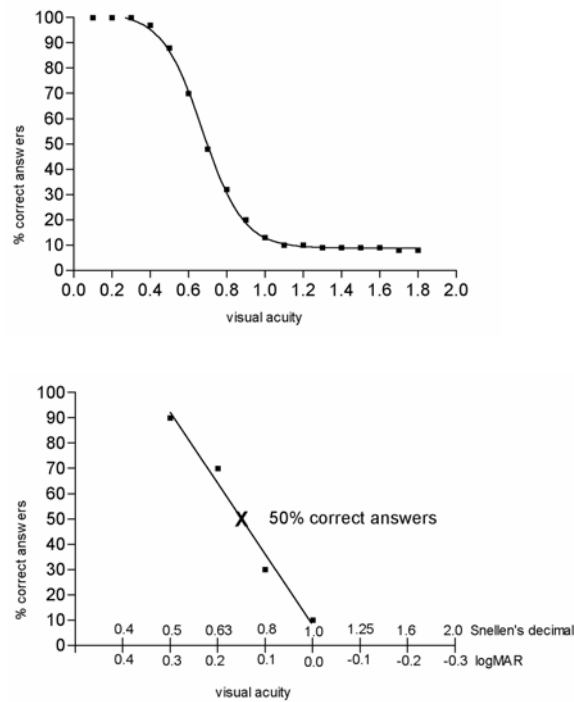


Figure 2. Percentage of correct answers (y-axis) and VA (x-axis), expressed as decimal Snellen's visual acuity on a linear (above) and in a logarithmic scale.

The measurement of the VF in children depends on the child's maturity and ability to concentrate, which are very important up to 7-8 years of age (Morales and Brown 2001, Tschopp et al 1999). VF testing comprises two techniques, the kinetic and the static. With kinetic methods, a stimulus of a given size and intensity is moved from a blind area into a seeing one, usually from the periphery into the centre. The points in the VF where the stimulus is detected are determined. Perimetry according to Goldmann, the most commonly used kinetic technique, has been used in many studies of children (de Souza et al 2000, Myers et al 1999, Quinn et al 1996b). In young children who cannot take part in this procedure, the VF is measured by a confrontation technique. The child fixates one object while a second object is moved from the periphery into the centre. Eye or head movement towards the second object indicates the size of the VF (Atkinson et al 2002, van Hof-van Duin and Mohn 1984). The double-arc perimetry method uses the same principle (Quinn et al 1996c, Wilson et al 1991).

With static methods, the threshold in a given location in the VF is measured by changing the intensity or the size of the stimulus.

Commercially available apparatuses, such as the Humphrey and Octopus perimeters as well as the high-pass resolution perimeter (HRP), are automatic and computerised and measure the VF to 30-60° peripherally.

The VF methods can also be classified according to the kind of stimulus that is used. In differential light sense (DLS) perimetry, the ability to detect an object of higher luminance than the background is measured. Kinetic Goldmann perimetry and most of the static techniques are examples of DLS methods. HRP differs from the DLS techniques because it measures resolution thresholds. The test targets are spatially, high-pass frequency-filtered ring-shaped targets, with the space average luminance equal to the background. The targets are of various sizes and are detected and resolved or invisible (Frisén 1993). This method measures spatial resolution and the threshold values correlate directly with the number of functional retino-cortical channels. The number, expressed as the percentage of age-corrected normal values, is called neural capacity (NC) (Frisén 1988). Static techniques have been used in children in several studies (Donahue and Porter 2001, Morales and Brown 2001, Safran et al 1996, Tschopp et al 1999), but the HRP method in only two studies (Maraffa et al 1995, Sampolesi et al (1995).

Refraction – general aspects

Before term, the refractive state is probably myopia, while at term it has changed into hypermetropia (Cook et al 2003, Fledelius 1992, Gordon and Donzis 1985). Refraction of the eye depends on the relationship between the ocular components, such as the corneal curvature, anterior chamber depth, the lens power and axial length. During growth refraction continually changes towards emmetropia. (Mayer et al 2001, Saunders et al 1995, Troilo 1992, Zadnik et al 1993). This process of emmetropisation is passive and controlled by genetic factors or active and dependent on visual regulation (Troilo 1992). In some individuals, however, the normal process of emmetropisation is arrested, which result in refractive errors. The degree and prevalence of refractive errors depend on the population examined and also on the definition of refractive error. At ten years of age, most children are still slightly hypermetropic (Fledelius 1976, Saunders 1995, Zadnik et al 1993). As regards astigmatism, both the degree and prevalence decline with age (Abrahamsson et al 1990a, Montes-Mico 2000, Saunders 1995). The prevalence of anisometropia, however, remains about the same, although there are individual variations (Abrahamsson et al 1990b, Abrahamsson and Sjöstrand 1996, Saunders 1995, deVries 1985).

Long-term follow-up of prematurely-born children

Long-term follow-up studies are important because prematurely-born children are at greater risk of ophthalmological and neuro-developmental dysfunctions than those born at term (Bhutta et al 2002, Cats and Tan 1989, Schaliij-Delfos et al 2000, Stjernqvist et al 1999). Many follow-up studies up to school-age (7-10 years) have been performed, but the ophthalmological findings are often difficult to compare because of differences in epidemiology and methodology. Some studies are hospital-based (Cats and Tan 1989, CRYO-ROP 2001a,b, McGinnety and Bryars 1992, Quinn et al 2001), whereas others are population-based (Darlow et al 1997b, Fledelius 1996a-d, Gallo and Lennerstrand 1991, Hård et al 2000, O'Connor et al 2002). There are only a few studies, performed on children of school age, that are strictly population-based and in which the children were screened prospectively for ROP in the neonatal period (Darlow et al 1997b, Fledelius 1996a-d, O'Connor et al 2002). The ophthalmological outcomes were reported in a cohort of 7-10-year-old children in Denmark by Fledelius (1996a-d), in 7-8-year-old children in New Zealand by Darlow et al (1997b) and in a cohort of prematurely-born children at 10-12 years of age in the United Kingdom by O'Connor et al (2002). All three studies found a higher prevalence of ophthalmological disorders in preterm children, such as reduced VA, strabismus, refractive errors, defects in colour vision and arrested ocular growth.

Children with severe dysfunctions have probably been taken care of at an early age, but those with minor ones may be detected later. Long-term studies may result in follow-up programmes that aim to identify children who need extra help. Ophthalmic deficits, cognitive problems (Bhutta et al 2002, Horwood et al 1998, Stjernqvist et al 1999) or both (Jacobson and Dutton 2000, Msall et al 2000) may influence the educational outcome (Miller and Levine 1997, O'Connor et al 2001). Learning difficulties have also been associated with preterm birth up to early adulthood (Hack et al 2002). Recommendations for ophthalmological follow-up vary. Some focus on ROP and neurological disorders whereas others suggest that all prematurely-born children should be followed. The length of follow-up also varies, from the first to second year in life, up to school-age or even throughout life (Darlow et al 1997b, Holmström et al 1999, Laws 1997, Page et al 1993, Robinson and O'Keefe 1993, Schaliij-Delfos et al 2000, Terasaki and Hirose 2003).

Visual acuity in prematurely-born children

Several authors have found a reduction in VA in prematurely-born children (Cats and Tan 1986, Darlow et al 1997b, Fledelius 1996a, Gallo and Lennerstrand 1991, Hård et al 2000, McGinnety and Bryers 1992, O'Connor

et al 2002). ROP and cerebral lesions are the main risk factors for subnormal vision. Apart from the obvious sequelae of regressed ROP, some data also show photoreceptor dysfunction in children with mild ROP (Fulton et al 2001, Reisner et al 1997). Moreover, preterm birth has been associated with other abnormalities of the fundus, such as optic nerve hypoplasia, optic nerve coloboma, optic atrophy and increased tortuosity of the retinal arteries (Asproudis et al 2002, Fledelius 1996a, Hellström et al 2000, Tornqvist et al 2002).

Cerebral lesions in prematurely-born infants may affect the visual system. In the neonatal period, autoregulation of blood flow in the brain is limited. A change in blood pressure may cause an intraventricular haemorrhage (IVH) and/or periventricular leukomalacia (PVL). IVH may lead to a dilated ventricular system and hydrocephalus, with associated optic atrophy (O'Keefe et al 2001) and also damage the posterior visual pathways (Moore 1997). PVL is an ischaemic lesion of the cerebral white matter around the ventricles (Volpe 1997, 2001). A lesion in this area may affect the corticospinal tract and the optic radiation, causing cerebral palsy or cerebral visual impairment (CVI) or both (Lanzi et al 1998, Uggetti et al 1996). Visual dysfunction due to PVL affects not only VA, but also the VFs and various cognitive functions (Jacobson and Dutton 2000, Pike et al 1994). In addition, strabismus and nystagmus is reported both in children with previous ROP and in children with PVL (Holmström et al 1999, Jacobson et al 1998a, Lanzi et al 1998).

In Sweden, the overall prevalence of visual impairment in children is 10.9/10 000 (Blohmé and Tornqvist 1997b), according to WHO's criterion (1997), but in preterm populations, it is higher. Gallo and Lennerstrand (1991) reported a prevalence of visual impairment of one per cent, whereas Holmström et al (1999) found a prevalence of 2.5 %, of which half were due to ROP and half to cerebral lesions. Hård et al (2000) found visual impairment in six per cent in another Swedish preterm population of whom one third of the children were visually impaired due to ROP and two thirds due to neurological complications. However, Jacobson et al (1998b) reported the findings in a Swedish population of 18 prematurely-born visually-impaired children of whom sixteen were visually impaired due to cerebral lesions and none due to ROP. These studies clearly show the importance of both ROP and damage to the posterior visual pathways as risk factors for subnormal vision or visual impairment in prematurely-born children.

Reductions in near VA (CRYO-ROP 2001a, Fledelius 1996a, O'Connor et al 2002) and in ability to separate symbols –i.e., crowding (Jacobson et al 1996, Pike et al 1994) have also been reported in prematurely-born children. These probably disturb the ability to read (Atkinson 1988, Jacobson et al 1996) and may cause educational problems (O'Connor et al 2001). Cognitive dysfunction in the children with cerebral lesions, as reflected by difficulties with visual perception such as recognition, orientation, perception of depth,

motion and simultaneous perception (Dutton et al 1996) may also increase such problems.

Visual fields in prematurely-born children

Reduced sensitivity of the entire VF has been found in prematurely-born children (Takayama et al 1991b). However, most studies report on constricted peripheral VFs attributed to severe ROP per se and cryotreatment (CRYO-ROP 2001b, Luna et al 1989, Quinn et al 1996b, Takayama et al 1991b). At ten years of age, the American CRYO-ROP study (2001b) found a 27% constriction of the visual field in eyes with threshold ROP and a 32% constriction in cryotreated eyes, as compared to those without ROP. This finding indicates that cryotreatment per se constricts the VFs, but only to a limited extent, as compared to severe ROP. Further, constriction of the inferior visual field has been observed in children with PVL (Jacobson et al 1996, Jacobson et al 1997); it is probably caused by interruption of the neurons in the optic radiation (Jacobson and Dutton 2000).

Refractive errors in prematurely-born children

The frequency of refractive errors is higher in prematurely-born children than those born at term (Cats and Tan 1989, Connolly et al 2002, Darlow et al 1997b, Fledelius 1996c, Gallo and Lennerstrand 1991, Holmström et al 1998b, McGinnety and Bryers 1992, O'Connor et al 2002, Quinn et al 2001, Robinson and O'Keefe 1993, Schailij-Delfos et al 2000, Tuppurainen et al 1993), possibly because of an inhibition of the normal process of emmetropisation (Cats and Tan 1989, Quinn et al 1998, Saunders et al 2002, Shapiro et al 1980). A disturbance in ocular growth and development, with changes in the anterior segment and axial length of the eye has been reported. An increase in the corneal curvature, shallower anterior chamber, thicker lens and a too short or too long axial length has been described (Choi et al 2000, Fledelius 1992, Fledelius 1996d, Gallo and Fagerholm 1993, Kent et al 2000, Laws et al 1994, O'Connor et al 2002). Various explanations for the arrested emmetropisation have been given, such as temperature, light, visual deprivation, retinal dysfunction and bone deficiency in the preterm child (Fielder and Quinn 1997).

A high prevalence of myopia has been noted in many studies (Choi et al 2000, Fledelius 1995, Nissenkorn et al 1983, Pennefather et al 1995, Quinn et al 1992, Quinn et al 1998, Robinson and O'Keefe 1993), of which three types are associated with preterm birth: transient myopia, myopia without ROP –i.e., “myopia of prematurity” (MOP) and myopia induced by severe ROP (Fielder and Quinn 1997). The first type of myopia is physiological and disappears in the first or second year of life (Fledelius 1995, Holmström et al 1998b). The other two types are sequelae of preterm birth or previous severe

ROP (Fledelius 1996c, Holmström et al 1998b, O'Connor et al 2002, Quinn et al 1998). Children treated for severe ROP also have a high prevalence of myopia (Connolly et al 2002, Kent et al 2000, Laws et al 1997, Quinn et al 2001, Seiberth et al 1990). Studies comparing cryo- and laser treatment have found that laser-treated eyes seem to be less myopic than cryotreated ones (Connolly et al 2002, Knight-Nanan and O'Keefe 1996, Laws et al 1997). However, the American CRYO-ROP study (Quinn et al 2001) reported that eyes with threshold disease had the same prevalence of myopia as those given cryotreatment, which would suggest that severe ROP per se, rather than the treatment, is the cause of myopia.

The prevalence of hypermetropia is rarely discussed in studies of prematurely-born children. However, a few studies report about the same prevalence of hypermetropia in prematurely-born and full-term children (Dowdeswell et al 1995, Fledelius 1976, Tuppurainen et al 1993), which suggests no association between hypermetropia and prematurity.

The prevalence of astigmatism is disputed. Some authors report an increase in the prevalence (Fledelius 1996c, Holmström et al 1998b), whereas others have found no difference between prematurely-born and full-term children (Dowdeswell et al 1995, Tuppurainen et al 1993). The degree of astigmatism has been associated with the stage of ROP, and cryotreatment (Holmström et al 1998b, Kent et al 2000, Laws et al 1992, Quinn et al 2001).

The prevalence of anisometropia is higher in prematurely-born children than in those born at term (Fledelius 1996c, Gallo and Lennerstrand 1991, Holmström et al 1998b), especially among those with severe ROP and those who have been cryotreated (Pennefather et al 1995, Seiberth et al 1990).

AIMS

- ∄ To perform a prospective population-based study on the incidence of ROP in preterm infants born in a defined area in Sweden.
- ∄ To compare the present incidence of ROP with that of a previous study performed a decade ago.
- ∄ To evaluate the risk factors for ROP and compare them with the previous study.
- ∄ To evaluate present screening guidelines for ROP and to determine whether they should be modified.

- ∄ To perform a population-based study on the ophthalmological findings in 10-year-old prematurely-born children and compare these with children born at term.
- ∄ To analyse refraction, visual acuity and visual fields in the prematurely-born children and compare the results with those born at term.
- ∄ To compare the ophthalmological findings within the group of prematurely-born children –i.e., children without ROP in the neonatal period, children with untreated ROP and children treated for ROP

MATERIAL AND METHODS

Incidence and screening of ROP (Papers I and II)

Prematurely-born infants with a BW of ≤ 1500 grams (Paper I) or a GA of ≤ 32 weeks at birth (Paper II), born between 1 August 1998 and 31 July 2000, were prospectively included in two separate studies. They were born in the Stockholm area, the same geographical area as a previous population-based study of the incidence of ROP (Holmström et al 1993). During the period of inclusion, 38 430 infants were born alive in Stockholm County. Fundus examinations were started at five weeks after birth and were repeated at intervals of 1-2 weeks until the retina had become entirely vascularised. If ROP was present, the frequency of examinations was increased. Infants were excluded if they had had their first examination too late -i.e., later than eight weeks after birth or after completed vascularisation. They were also excluded if the examinations were stopped too early -i.e., before the retina was completely vascularised. Indirect ophthalmoscopy was done after dilation of the pupil with a mixture of cyclopentolate 0.5% and phenylephrine 0.5%. Lid speculum and indentation were used if the border between the vascularised and unvascularised retina could not be seen. The international classification of ROP (Committee for the Classification of Retinopathy of Prematurity 1984, 1987) was used. ROP was subdivided into mild (stages 1-2) and severe ROP (stages 3-5). Laser treatment was given within 72 hours if ROP met our criterion for treatment -i.e., ROP stage 3 in at least four contiguous clock hours in zone II, even in the absence of "plus disease".

Paper I

Infants with a BW of ≤ 1500 grams were compared with the previous incidence study performed one decade ago (Holmström et al 1993). Of the live-born infants, 331 (0.86 %) had a BW of ≤ 1500 grams and the survival rate at eight weeks was 87.9%, giving a study population of 291 infants. The drop-out frequency was 13.1% (38/291). Twenty-four infants were never referred for examination, 11 were excluded because of the exclusion criteria and three died before their eyes had been adequately screened. The

remaining 253 infants formed the study group. There were 121 girls and 132 boys; 201 infants were the products of singleton and 52 of multiple deliveries.

The Wilcoxon matched pair signed ranks test was used to compare both eyes for the stage of ROP, the unpaired t-test to evaluate differences between the study groups (1990 and 2000) when analysing continuous data, and the independence test of contingency tables to compare nominal or ordinal data. A two-way factorial ANOVA was used to evaluate the effect of “study period” (1990, 2000) and “ROP stage” on BW and GA. The interaction was significant and therefore the simple effects tests were performed concerning the factor “study period” for each level of the factor “ROP stage”. Stepwise logistic regression analyses were done to determine the most important risk factors for ROP in the two study groups. The predicted probability of ROP during both periods was calculated with the logistic regression model. When comparing the years 1990 and 2000, as regards various probabilities for ROP with an increase in GA, an interaction term between the factors “study period” and “gestational age” was included in this model. The severity of ROP was also graded – i.e., no, mild and severe. A logistic model was then used for the study groups (1990, 2000) and the predicted probability calculated for these stages of ROP in both study groups.

Paper II

Infants with a GA of ≤ 32 weeks at birth were evaluated. Of the live-born infants during the study, 533 (1.39%) had a GA of ≤ 32 weeks at birth. Forty-six of them died during the first seven weeks of life, leaving a total study population of 487 infants and a survival rate of 91.4 % at eight weeks. Sixty-two infants were never referred for examination, 30 were excluded in accordance with the exclusion criteria and three died before screening was completed. This gave a drop-out group of 19.5% (95/487) and a study group of 392 infants (181 girls) of whom 295 infants were products of singleton and 97 of multiple deliveries.

The Wilcoxon matched pair signed ranks test was used to compare the eyes for the stage of ROP and stepwise logistic regression analysis to determine the most important risk factor for ROP. The severity of ROP was also graded –i.e., no, mild and severe. The predicted probability was calculated from the logistic regression model.

10-year follow-up (Papers III, IV and V)

Material

In 1988-90, Holmström et al (1993) performed a prospective population-based study on the incidence of ROP in Stockholm County. This study included 260 prematurely-born children with a birth weight of ≤ 1500 grams and a survival of eight weeks or more. Forty per cent (105) of the children had ROP and 11% (28) had been cryotreated. The criterion for treatment was ROP stage 3 in at least four contiguous clock hours in zone II, even in the absence of plus disease. The children were followed for 3.5 years (Holmström et al 1998b, 1999). In the present study, at ten years of age, the prematurely-born children and their caregivers were asked by letter whether they wished to participate in an ophthalmological follow-up study. They had been located with the help of their ten-digit personal identification number, which is used in Sweden.

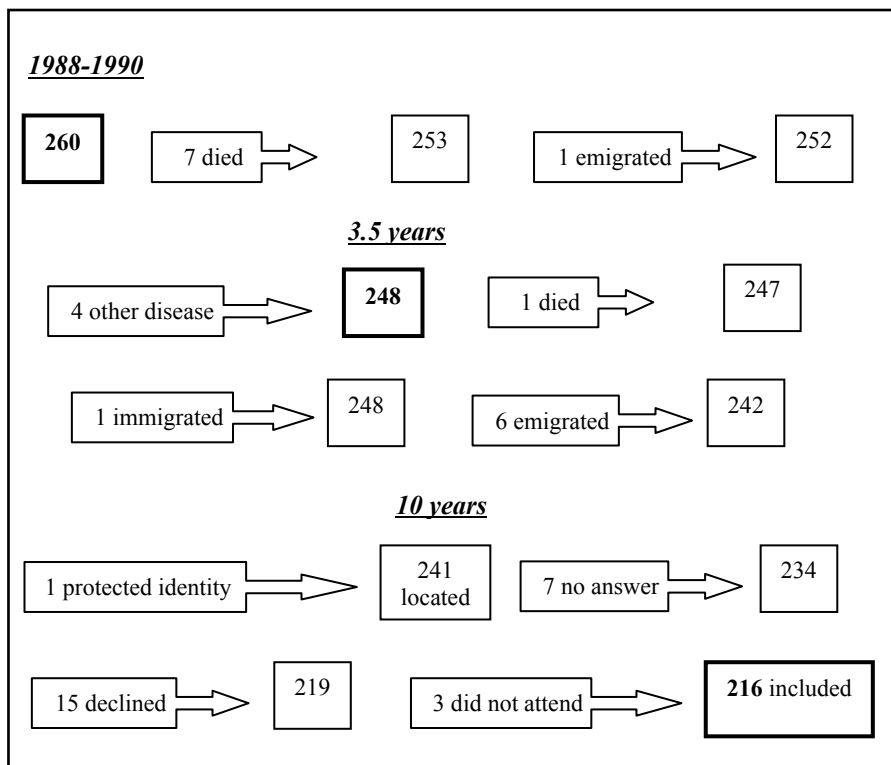


Figure 3. Prematurely-born children born in 1988-1990. Flow chart from birth to ten years of age.

Twelve of the 260 children were excluded during the 3.5-year follow-up (Holmström et al 1998b, 1999). Seven had died, one had emigrated, and four were excluded because of ophthalmological or other diseases unrelated to prematurity. Of the remaining 248 children one child had died and one child, who previously moved abroad, immigrated at ten years of age and could be relocated. Thirty-two children dropped out of the present study: six had emigrated, one had protected identity and 25 declined to participate. The remaining study-population in the 10-year follow-up therefore included 216 prematurely-born children (Figure 3), who were subdivided into the following groups: no ROP, mild ROP (stages 1 and 2) and severe ROP (stages 3-5). Infants with severe ROP were further divided into “severe untreated” and “cryotreated” ROP.

From the Swedish National Board of Health and Social Welfare a similar number of children, born at term (39-41 weeks) and having normal birth weights (3000-4000 grams), were obtained. The 217 full-term children had been randomly selected to provide a control group and were born in exactly the same period and in the same geographical area as the prematurely-born ones. These children and their families were contacted and asked to participate.

All children were examined at 10 years \pm 3 months except one prematurely born child, who was examined at 10.5 years of age. Data on demography and ROP stage are given in Table 5. The local Ethics Committee, Karolinska Institutet, approved the study.

Table 5. Demographic data of children born preterm and full-term

	No. RE/LE	Most severe ROP	Gender (M/F)	Gestational age at birth (weeks)	Birth weight (grams)
<i>Controls</i>	217/217		102/115	39-41	3000-4000
<i>Prematures</i>	216/216	216	105/111	29.1	1167
No ROP	134/137	131	65/66*	29.8*	1214*
Mild ROP	44/39	43	22/21*	28.4*	1141*
Severe ROP, untreated	14/15	17	9/8*	28.4*	1131*
Cryotreated	24/25	25	9/16*	27.5*	983*

Mean values for gestational age at birth and birth weight are given for preterm children. RE=right eye, LE=left eye, M=male, F=female

* according to the eye with severest ROP

Paper III

In the study of refraction, three prematurely-born children were excluded, two refused eye-drops and one had bilateral total retinal detachment. Therefore, 213 prematurely-born and 217 full-term children were included.

Paper IV

In the study of visual outcome, all 216 prematurely-born children were included. Medical records were obtained after permission from the caregivers in ten of the prematurely-born children who declined to participate, and their VAs at 8-11 years were included in some analyses. In three of the prematurely-born children, the VA could be assessed only binocularly and the results were recorded as the VA of the better eye. Finally, in the analysis of distribution of VA, nine children with exactly the same VA, but with different stages of ROP in their eyes were excluded, since the stage of ROP in the better or the worse eye could not be established. In the analysis of crowding, 212 prematurely-born children were included and in the analysis of near VA, 211 prematurely-born children participated. All 217 full-term children were included in all the analyses.

Paper V

In the study of VF, 62 prematurely-born and 24 full-term children (48 eyes) (Group 1) from the original study group were included at 11 years of age. The premature group was divided into 20 children (40 eyes) without ROP (Group 2), 22 (43 eyes) with untreated ROP, stages 2 and 3 (Group 3), and 21 (41 eyes) with cryotreated ROP (Group 4). Children in Groups 1-3 were selected to match the actual age of the cryotreated ones at the time of VF examination. All children were included in the analysis of the peripheral VF, but in the analysis of the central VF, seven right (RE) and eight left eyes (LE) were excluded by the perimetrist or the computer programme.

Methods

Paper III

Retinoscopy was performed in cycloplegia 45 minutes after instillation of a mixture of cyclopentolate 0.85% and phenylephrine 1.5%. Spherical equivalents were calculated. Myopia was defined as < 0 diopters (D), "moderate or high" myopia as < -3 D and "clinically significant" myopia as ≤ -1 D. Hypermetropia was defined as significant if $> +3$ D. Anisometropia

was defined as significant when the difference between the eyes was ≥ 1 D, and “high” if ≥ 2 D. Astigmatism was recorded as a negative cylinder and was defined as significant when ≥ 1 D and “high” when ≥ 2 D. The axes of astigmatism (≥ 1 D) were divided into “with the rule” ($0-15^\circ$, $165^\circ-180^\circ$), “against the rule” ($75^\circ-105^\circ$) and oblique ($16^\circ-74^\circ$, $106^\circ-164^\circ$). A significant refractive error of any kind was defined as hypermetropia of $> +3$ D, myopia ≤ -1 D, astigmatism of ≥ 1 D in one or both eyes and/or anisometropia ≥ 1 D. Right and left eyes were evaluated separately. When anisometropia and “significant” refractive outcome were analysed, the premature group was divided into no, mild, untreated severe and cryotreated ROP, according to the most severely affected eye. As regards the spherical equivalent and astigmatism, only RE are presented since there was no statistically significant difference between the eyes.

Wilcoxon matched pair signed ranks test was used to compare the RE and LE concerning the spherical equivalents and astigmatism, the independence test of contingency tables to compare nominal or ordinal data and the unpaired t-test for continuous data. Since the sample sizes were unbalanced and the variances not homogeneous, an ANOVA model with separate variance estimates was used (Proc Mixed in SAS®) to evaluate the spherical equivalents. Astigmatism and anisometropia were analysed, using the Kruskal Wallis ANOVA by ranks, followed by multiple comparisons. The p-values were corrected with the Bonferroni procedure. A stepwise logistic regression analysis was done to determine the effects of GA at birth, BW, stage of ROP and cryotreatment on the spherical equivalents and astigmatism ≥ 1 D.

Paper IV

Best-corrected distance and near VA were assessed with linear optotypes. A linear letter logMAR chart, designed for an observation distance of four meters was used (AH-chart) (Hedin and Olsson 1984). The frequency-of-seeing curves were constructed (Frisén 1990, Hedin and Olsson 1984). The percentage of correct answers (y-axis) was plotted on a diagram, with the minimum angle of resolution (MAR) on a logarithmic scale on the x-axis. The best-fitting straight line was drawn on the graph by the computer and the logMAR at 50% correct answers was found and converted into decimal Snellen acuity ($1/\text{MAR}$). The VA determined at 50% correct answers, “50%-VA”, was used to compare the groups as regards continuous data. To analyse the distribution of VA, an evaluation as in ordinary clinical practice was performed. Seven of the ten letters had to be identified correctly for approval of a line (Hedin and Olsson 1984). The preferential looking test with acuity cards was used if a child could not take part in tests with linear optotypes. The results were converted from grating acuity to linear acuity.

Crowding was determined by using a logMAR LH-chart with linear and single optotypes, at a distance of three meters (Hyvärinen 1980). The crowding ratio was calculated –i.e., the VA assessed with single symbols divided by the VA assessed with linear symbols. A crowding ratio of ≥ 1.5 was considered to be increased. Near VA was evaluated binocularly with a logMAR LH-chart at a distance of 0.4 meters. For approval of a line, the child had to identify four of five symbols on the line. RE, LE, better and worse eyes were analysed separately. When binocular VA was analysed, the premature group was divided into no, mild, severe untreated and cryotreated ROP, according to the most severely affected eye.

Neurological complication was defined as an IVH in the neonatal period and/or obvious neurological sequelae in the 3.5-year follow-up (Holmström et al 1999). With this definition, 34 (15.7%) of the 216 prematurely-born children had some kind of neurological complication. The fundus was evaluated after the pupil was dilated with a mixture of phenylephrine 1.5% and cyclopentholate 0.85%. Macular scoring was used (Holmström et al 1999): score 0 = clinically normal macula, score 1 = macular heterotopia, score 2 = macular pigment epithelial scarring, score 3 = posterior retinal folds, retinal detachment, retrolental mass.

To compare the nominal or ordinal data, an independence test of contingency tables was used and an unpaired t-test or one-way ANOVA to analyse continuous data. When variances were not homogeneous, the Mann-Whitney test or an ANOVA model with separate variance estimates (Proc Mixed in SAS®) was used. A stepwise regression analysis was used to evaluate the effects of GA at birth, BW, stage of ROP, cryotreatment, neurological complications and refraction on the “50% VA” in the better eye.

Paper V

Peripheral VFs were measured with Goldmann perimetry. The VFs were measured monocularly along eight meridians (15°, 60°, 105°, 150°, 195°, 240°, 285°, 330°) with stimuli V4 and II4. Three trials were made in each meridian and the median values in each meridian were taken as the extent of the VF in that meridian. The sum of the median values in the eight meridians was taken as the total VF extent for that eye.

Central VF was assessed monocularly with HRP. The standard programme with 50 test locations in the central 5-30° field was used. Neural capacity was recorded and used for comparisons.

In the statistical analysis, Kruskal-Wallis ANOVA by ranks was used to compare the peripheral VFs and one-way ANOVA to analyse the central VFs. The RE and LE were analysed separately.

RESULTS AND DISCUSSION

Incidence and screening

Paper I

The incidence of ROP in the cohort of 253 infants with a BW of 1500 grams or less was 36.4% (92/253). Mild ROP (stages 1-2) was found in 18.2% (46/253) and severe ROP (stages 3-5) in 18.2% (46/253). Laser treatment was given to 31 (12.3%) infants, of whom two were operated on with a cerclage in one eye. The mean GA at birth of the study group was 28.5 (range 23-34) weeks and the mean BW was 1118 (range 462-1500) grams.

The results of the present study were compared to those of a study by Holmström et al (1993), performed a decade ago in the same geographical area and with the same inclusion criteria. The study design permitted exact comparisons of the incidence and severity of ROP in the population during the two periods.

In this study, there was an increase in the survival rate (87.9% versus 84%) of the prematurely-born population with a BW of ≤ 1500 grams and of infants with a BW of ≤ 1000 grams (76.5% versus 71%), as compared to the previous study. This was probably due to improved neonatal care during the past decade, including antenatal steroids, surfactant therapy and oscillatory ventilators. The number of infants, 253 (1998-2000) versus 260 (1988-1990), and the proportion of boys and girls, single and multiple births were similar. A slight difference was found in the mean GA at birth of the two groups, which reflected an increase in the number of surviving immature infants in the present study, but no difference was found as regards the BWs. The drop-out groups (13.1% versus 11.9%) were similar in both consecutive studies, but since screening for ROP has been well established during the last decade, a decrease in the drop-out frequency was expected in the present study.

The total (36.4% versus 40%), mild (18.2% versus 20%) and severe ROP (18.2% versus 20%) incidences were about the same in the two groups as a whole. However, when the infants were subdivided into groups, according to their GAs at birth or to their BWs, a significant increase in the total

incidence of ROP, particularly of severe ROP, was found in the most immature group and a reduction in the more “mature” group (Figure 4). Interaction analyses of infants with no, mild and severe ROP in the two study periods, showed significant reductions as regards GA at birth and BW in those with mild and severe ROP. In infants without ROP no difference was found.

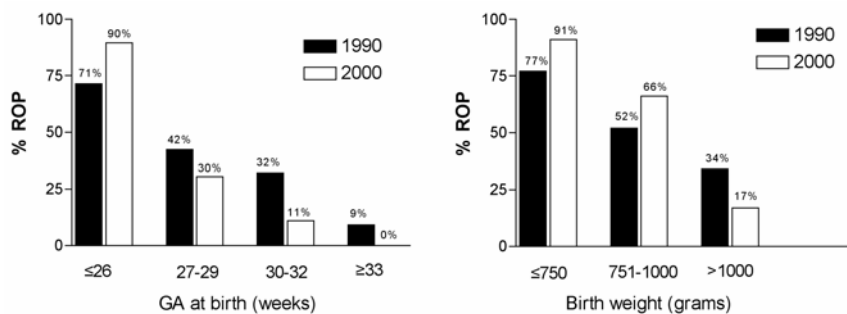


Figure 4. Relation of total ROP to gestational age at birth and birth weight in the two consecutive studies.

These findings accord with the predicted probability of ROP. In a multiple stepwise logistic regression analysis, GA at birth was found to be the most important risk factor for ROP, followed by BW, as in the previous study. Further interaction analysis revealed a significant difference between the two periods as regards the predicted probability of ROP in relation to GA at birth. In the latter study, the probability of ROP declined with higher GAs at birth and rose in lower GAs at birth.

Improvements in neonatal care probably explain the reduced risk of ROP in the “mature” infants. The increased risk of ROP in the most immature infants may reflect an increase in the number of surviving infants who are more vulnerable and prone to develop ROP (Repka 2002).

The number of infants treated for ROP was about the same (31 versus 28) in both periods. Although the same criterion for treatment was used, in the present study, the infants were given laser treatment instead of cryotreatment. Moreover, the treated infants had a mean GA at birth of 25.3 weeks versus 27.3 weeks ($p < 0.001$) and a mean BW of 781 grams versus 961 grams ($p < 0.001$) –i.e., similar to the findings in mature infants escaping ROP.

Comparisons of incidence studies are difficult because of differences in inclusion criteria and demography of the populations. Changes in the incidence with time can be evaluated only in population-based studies from the same geographical areas and with the same inclusion criteria. Only a few

such studies have been reported (Bossi and Koerner 1995, Fledelius and Dahl 2000, Darlow et al 2003). As in the present study, Bossi and Koerner (1995) reported on an increased incidence of total and severe ROP in infants < 1000 grams from 1983-85 to 1989-1991 in Switzerland. However, Fledelius and Dahl (2000) found a decline in the incidence of total ROP in infants \leq 1500 grams and in those < 1000 grams from 1988-1993 to 1994-1997 in a Danish county. Darlow et al (2003) found an unchanged overall incidence, like in the present study, but in contrast a reduced incidence among the most immature infants (BW < 1000 grams).

Several consecutive retrospective and prospective studies have been performed, but they have not been population-based. In accordance with the findings of the present study, Termote et al (2000b), Kennedy et al (1997) and Todd et al (1999) found no change in the incidence of ROP in the preterm population as a whole, whereas many others have noted a lower incidence with time (Blair et al 2001, Bullard et al 1999, Hussain et al 1999, Repka et al 1992, Rowlands et al 2001). However, to evaluate the effects of improved neonatal care on the incidence of ROP, it seems important to analyse the findings in mature and immature infants separately. Termote et al (2000b) and Kennedy et al (1997) reported an increase in ROP in the most immature infants, as in the present study. Todd et al (1999) compared two periods and also found an increase in the incidence of severe ROP in immature infants and Hussain et al (1999) found that threshold disease still was a risk in immature infants. Repka et al (1992) reported an unchanged incidence and Keith and Doyle (1995) a reduction of the incidence in immature infants. Finally, Chow et al (2003) recently noted that the incidence of severe ROP and the number of treated infants had decreased in a hospital-based study.

Despite differences in the findings of several consecutive studies, the increase in the incidence or higher risk of threshold disease in immature infants may be due to improvements in neonatal care with saving of infants who had not survived before.

Paper II

In the cohort of 392 prematurely-born infants with GA of \leq 32 weeks at birth, the mean GA at birth was 29.4 (range 23-32) weeks and the mean BW 1381 (range 462-2705) grams. The incidence of ROP was 25.5 % (100/392). The infants with ROP had a mean GA of 26.9 (23-32) weeks at birth and a mean BW of 987 (462-1885) grams. Mild ROP (stages 1-2) was found in 13.3 % (52/392) and severe ROP (stages 3-5) in 12.2 % (48/392).

The drop-out frequency of 19.5% was disappointing since screening has been well-established during the last decade. Most of the infants in the drop-out group had never been referred by the neonatologists and one-third of the drop-out group had been examined infrequently by the ophthalmologist. This

illustrates the need for continuous information to neonatologists and ophthalmologists about the criteria for screening. It also underlines the risk of losing infants, who are transferred to other wards or hospitals or discharged home (Demorest 1996, Haines et al 2002).

The aim of screening is to detect infants with severe ROP who need treatment (Good 2000, Guardian et al 2001). In the present study, severe ROP developed in 48 of the 100 (48%) infants who had developed ROP at a mean postmenstrual age (PMA) of 36.1 weeks; of these, 67% (32/48) progressed and met the criterion for treatment. Of the total cohort, 8.2% (32) underwent laser treatment at a mean PMA of 37 weeks. Two of the laser-treated infants were also operated on with cerclage in one eye. The treated infants had a mean GA of 25.4 (23-29) weeks at birth and a mean BW of 808 (462-1640) grams.

The timing of the first examination is important. The onset of ROP is closely related to the PMA (Fielder et al 1986, Palmer et al 1991, Repka et al 2000). Some authors claim that the first examination should be performed according to the PMA or chronological age, whichever comes first (Hutchinson et al 1998, Reynolds et al 2002). Others recommend the chronological age alone, as in the present study (The Royal Collage of Ophthalmologists and the British Association of Perinatal Medicine 1996, Subhani et al 2001), since the most immature infants may develop ROP earlier than expected (Coats et al 2000, Subhani et al 2001). Recently, Fielder (2003) emphasized this by stating "No ophthalmologist wants the fright of diagnosing ROP of such an advanced stage (threshold ROP) on the first examination". In the present study, the first examination was done at five to six weeks after birth in 96% of the infants and all treated infants had been examined at least once before they met the criterion for treatment.

In Sweden, screening for ROP is recommended for all prematurely-born infants with a GA of ≤ 32 weeks at birth (The National Board of Health and Welfare 2000). In a univariate logistic regression analysis, gender, single/multiple birth, GA at birth and BW were identified as independent risk factors for ROP, but in the multiple stepwise logistic regression analysis, GA at birth was the most important risk factor for ROP, followed by birth weight. Therefore, GA at birth was decided to remain the inclusion criterion for screening in our population.

In the present study, no infant with severe ROP – i.e., stage 3 or more had a GA at birth of > 31 weeks, and no infant treated for ROP had a GA at birth of > 29 weeks. This accords with the detailed analysis of the probability of ROP at various weeks of GA at birth, which showed a break-point between weeks 30 and 31 with no further reduction in the probability of ROP after the 31st week of gestation.

The effect of reducing the present screening criterion was analysed. If we had reduced the age of screening to ≤ 30 weeks, we would have missed one infant with severe ROP (stage 3), but no infant who met our criterion for

treatment. If we had reduced the age of screening to ≤ 31 weeks, five infants with mild ROP would have been missed, but no infant with severe ROP – i.e., is the goal of our screening.

Modifications of screening guidelines should be considered regularly, and the effectiveness of guidelines continuously discussed (Andruscavage and Weissgold 2002, Brenner et al 2003, Fielder et al 2002, Haines et al 2002, Hutchinson et al 2003, Lee et al 2001, Mathew et al 2002, Quinn 2002). National screening guidelines must take into account the local circumstances in the country, such as neonatal and maternal care and the national health care system (Fledelius and Dahl 2000, Todd et al 1999). The workload of screening for ROP should be minimised, but infants in need of treatment must not be missed (Andruscavage and Weissgold 2002, Hutchinson et al 2003, Lee et al 2001, Wright et al 1998). The conclusion of the present population-based evaluation of screening guidelines was that the screening criterion in our population could be reduced by one week to ≤ 31 weeks. This would reduce the workload by 24% (93/392), but would still enable us to detect ROP stage 3, the aim of our screening.

10-year follow-up

Paper III

Significant refractive errors were more common in prematurely-born children than in those born at term, Table 6 ($p < 0.001$). Cryotreated children ran the highest risk, but also those with untreated ROP or those without ROP were prone to develop significant refractive errors. The increased prevalence of refractive errors in prematurely-born children may be due to disturbed ocular growth and an arrested emmetropisation (Choi et al 2000, Fledelius 1996d, Gallo and Fagerholm 1993, Kent et al 2000, O'Connor et al 2002).

Table 6. *Significant refractive errors in prematurely-born and full term children. Significant refractive error defined as spherical equivalent $> +3D$ or spherical equivalent $\leq -1D$ or astigmatism $\geq 1D$ in one or both eyes and/or anisometropia $\geq 1D$.*

	Refractive errors No. (%)	Total
Control	17 (7.8%)	217
Premature	63 (29.6%)	213
No ROP	34 (26.2%)	130
Mild ROP	9 (20.9%)	43
Severe ROP, untreated	4 (26.7%)	15
Cryotreated	16 (64.0%)	25

In the present study, mean values of spherical equivalents in the control (0.64 D) and premature groups (0.52) were similar, but in the group of prematurely-born children, cryotreated eyes differed from the other subgroups and had a lower mean value (-1.27 D). A difference in the distribution of spherical equivalents was found between prematurely-born and full-term children ($p=0.008$), the former having a higher prevalence of hypermetropia (4.2% versus 0.9%) and clinically significant myopia (≤ -1) (7.8% versus 2.3%), and moderate or high myopia (< -3) was found only in the premature group (3.8%). There was also a significant difference when comparing the children without ROP – i.e., the “prematurity per se” group - with the controls ($p=0.02$), the former having a higher frequency of hypermetropia (4.5%) and moderate or high myopia (2.3%).

As in the present study, several authors have reported a high prevalence of myopia in prematurely-born children (Choi et al 2000, Nissenkorn et al 1983, Pennefather et al 1995, Quinn et al 1992). When comparing other population-based studies of children examined at ten years of age, the prevalence of myopia resembled that in a study by Fledelius (1996c). Darlow et al (1997b) and O'Connor et al (2002) both showed higher prevalences of myopia in their preterm populations. However, in the study by Darlow et al (1997b) the refraction was not measured in cycloplegia and O'Connor et al (2002) examined the children at an older age than we did, which could explain the differences.

The cryotreated children had the highest prevalence of myopia in the present study, which accords with the multiple regression analysis performed in the premature group. GA at birth, BW, stage of ROP, and cryotreatment were included as independent risk factors and only cryotreatment was significantly associated with a reduction in spherical equivalents ($p<0.001$). Although the prevalence was increased in cryotreated children, other studies have found severer myopia than in this study (Connolly et al 2002, Quinn et al 2001, Seiberth et al 1990). It is uncertain whether the high prevalence of myopia in the present population was due to the treatment or the severe ROP per se, because all eyes that met the criteria for treatment in the neonatal period were treated (Quinn et al 2001).

Hypermetropia ($> +3$ D) was more common in prematurely-born children than in full-term ones ($p=0.03$), unlike some other reports (Dowdeswell et al 1995, Tuppurainen et al 1993). However, like Darlow et al (1997b), we found no difference in the prevalence in the premature group and like Ricci (1999), cryotreated children had the same prevalence of hypermetropia as children without ROP. This may indicate that prematurity per se plays a role in significant hypermetropia.

The prevalence of astigmatism ≥ 1 D was significantly higher in the premature group (20.7%) than in the control group (4.1%) ($p<0.001$) also was the total degree of astigmatism (median value) ($p<0.001$). The finding of an increase in the prevalence of astigmatism accords with the study of

Fledelius (1996c), but not with that by Darlow et al (1997b) who found a lower prevalence than in the present study. In the premature group, the cryotreated eyes had the highest prevalence of astigmatism (58.3%) and also the severest astigmatism. In prematurely-born children, the degree of astigmatism has been found to increase with the severity of ROP (Laws et al 1992). In the present study, the stage of ROP and cryotreatment per se were shown to be risk factors for astigmatism ≥ 1 D in the univariate analyses. However, in the stepwise logistic regression analysis only cryotreatment ($p < 0.001$) remained an independent risk factor, which agreed with the findings of Kent et al (2000). Quinn et al (2001) compared cryotreated eyes, at ten years of age, with untreated eyes having “threshold” ROP, and found a tendency towards a higher frequency of astigmatism ≥ 1 D in treated than untreated eyes, indicating that the cryotreatment per se may induce astigmatism. This fact could not be evaluated in the present study, because all children who met our criterion for treatment had been cryotreated.

Anisometropia (median values) was significantly greater in the premature group than in the control group ($p < 0.001$). Moreover, the prevalence of anisometropia (≥ 1 D) was more common in prematurely-born children ($p < 0.001$), in accordance with the findings of Fledelius (1996c). In the premature group, the cryotreated children had the highest frequency of anisometropia (≥ 1 D), especially high anisometropia (≥ 2 D). However, as in the discussion of spherical equivalents and astigmatism, it remains uncertain whether the high prevalence of anisometropia in the cryotreated children was due to the treatment or the more severe ROP.

Paper IV

Prematurely-born children had poorer VA (50% correct answers) than those born at term, as regards RE, LE, better and worse eyes ($p < 0.001$). The distance VA has been evaluated in prematurely-born children of similar ages in several other studies (Cats and Tan 1989, Darlow et al 1997b, Fledelius 1996a, Gallo and Lennerstrand 1991, Hård et al 2000, McGinnety and Bryars 1992, Ng et al 2002, O’Connor et al 2002), but in only three population-based studies, apart from this one, had they also been screened prospectively for ROP in the neonatal period (Darlow et al 1997b, Fledelius 1996a, O’Connor et al 2002). Our findings accord with these three studies.

The distance VA was also better in the control group than in the group of prematurely-born children without ROP (RE, LE, better and worse eyes; $p < 0.001$), even when the children with neurological complications were excluded. This would suggest that prematurity per se affects the visual outcome. However, it remains unknown whether the cause is to be found in the retina or the posterior visual pathways. Olsén et al (1997) reported that 32% of prematurely-born children have MRI-verified PVL, which is a known risk factor for visual dysfunction (Jacobson and Dutton 2000,

Jacobson et al 1998, Pike et al 1994). Since MRI was not routinely performed in the present study, minor neurological lesions cannot be excluded. Moreover, at the time of premature birth, foveal development is not completed. A retinal lesion due to a disturbance in this development, by ROP or by the preterm birth per se may likewise have affected the visual outcome (Hansen and Fulton 2000, Hendrickson 1992, Isenberg 1986, Provis et al 2000, Reisner et al 1997).

In the cohort of prematurely-born children, VA was similar in those without ROP and those with untreated ROP. This does not accord with the studies by Fledelius (1996a) and Darlow et al (1997b), in which all children with ROP ran a higher risk of poorer VA than those without ROP. Cryotreated children, however, had poorer VA than the other subgroups of prematurely-born children ($p < 0.001$); this was also confirmed by multiple regression analysis. GA at birth, BW, stage of ROP (including cryotreatment), neurological complications, spherical equivalents and astigmatism were included as independent risk factors for poor VA in the better eye. Only cryotreatment, neurological complications and astigmatism ≥ 1 D proved to be significant risk factors in this analysis. It remains uncertain whether the poorer VA in cryotreated eyes was due to the treatment or the severe ROP per se. The American CRYO-ROP study (2001a) reported a more favourable visual outcome, defined as VA > 0.1 , in cryotreated eyes than in those with untreated threshold ROP. Such a comparison could not be done in this study, since all eyes that met the criterion for treatment had been treated (Holmström et al 1993).

The effect of neurological disorders or damage to the posterior visual pathways on VA was based on data from the 3.5-year follow-up of the same preterm cohort (see Methods). Like Fledelius (1996a), we found that children with neurological complications in the present study had poorer VA than those without. Although, Fledelius (1996a) also reported that children with myopia of prematurity had poorer VA, we could not confirm this, but in the multiple regression analysis, astigmatism seemed to affect the VA.

The distributions of VA were analysed. The prematurely-born children had an overall good VA, but the prevalence of good VA was lower and the prevalence of poor VA was higher than in the full-terms ($p < 0.001$). There were also differences between the prematurely-born children without ROP and the controls (better and worse eyes; $p < 0.001$), as well as in the premature group (better and worse eyes; $p < 0.001$).

Visual impairment by WHO's criterion (1997) – i.e., VA below 0.3 in the better eye- was found in four (1.8%) children. Two of these were visually impaired due to sequelae of ROP and two due to neurological complications, which demonstrates that although ROP causes less visual impairment in Sweden (Blohmé and Tornqvist 1997a), it remains a risk factor for visual handicap in our population. The prevalence of visual impairment was lower than in the other three population-based studies (Darlow 1997b, Fledelius

1996a, O'Connor 2002). However, in those studies no child was cryotreated, since they were born before the recommendation for treatment was introduced (CRYO-ROP 1988). Most of the blind children studied by Fledelius (1996a) and Darlow et al (1997b) were blind due to ROP. Since treatment of threshold ROP affects the long-term visual outcome (CRYO-ROP 2001a), the prevalence of blindness might have been lower in the other studies if they had been treated.

Macular changes were found in eight of the prematurely-born children, optic atrophy in two and in one optic hypoplasia. Thirteen of the prematurely-born children had nystagmus, all of whom had been cryotreated or had neurological complications. In the control group, one child had optic drusen and one slight optic hypoplasia, but none had macular changes or nystagmus.

Crowding, according to our definition (≥ 1.5), tended to be more frequent in the preterm (8.5%) than in the control (4.1%) group, but the difference was not statistically significant. Crowding is common in amblyopic eyes (Rydberg et al 1999), and it has also been found in prematurely-born children with brain lesions (Pike et al 1994, Jacobson et al 1996). Of those with crowding in the preterm group, three were classified as having neurological complications, seven had strabismus and one had both. Seven had neither neurological complications nor strabismus, but it is uncertain whether they had experienced minor cerebral lesions in the neonatal period. Of those with crowding in the full-term group, one had strabismus.

Near VA was significantly poorer in prematurely-born children than in those born at term ($p < 0.001$), in accordance with the findings of O'Connor et al (2002). The cryotreated children differed significantly from the other subgroups, except those with severe untreated ROP. It remains uncertain whether the poorer near VA in the former group was caused by the severe ROP per se or the cryotreatment (CRYO-ROP 2001a). Children with neurological disorders had poorer near VA than those without ($p = 0.001$). In the former, reduced accommodation may have contributed to the impairment in near VA.

The reduction in near VA and the tendency to an increase in crowding in prematurely-born children should be emphasized since these facts both may be important for reading (Atkinson 1988, Jacobson et al 1996).

Paper V

In the study of VFs, the children were examined at 11 years of age. At this age, visual field testing is regarded as reliable, the ability to concentrate may affect performance less (Tschopp et al 1999) and the peripheral VF is thought to be similar to that in adults (Wilson et al 1991).

The peripheral VFs were significantly constricted in the cryotreated children (Group 4) compared to the VFs in the full-terms (Group 1) and

prematurely-born children without ROP (Group 2) or untreated ROP (Group 3) ($p < 0.001$). This accords with the results of other studies (CRYO-ROP 2001b, Quinn et al 1996b, Takayama et al 1991b). The reduction in the VF extents in the cryotreated children was about 9% for stimulus V4e and about 13% for stimulus II4e, which was probably of no practical importance. Severe ROP per se has also been reported to constrict the peripheral VF (CRYO-ROP 2001b, Luna et al 1989). In the present study, it could not be determined whether the constricted VFs in cryotreated eyes were caused by the cryotreatment or by the severe ROP alone, since all eyes that met the criterion for treatment had been treated (Holmström et al 1993). Finally, neither the untreated children with ROP (Group 3) nor the prematurely-born ones without ROP (Group 2) – i.e., prematurity per se – had reduced peripheral VFs as compared to the full-term children.

The central VFs were examined with HRP, a method that has been reported to be reliable in children in a study by Maraffa et al (1995). Neural capacity – i.e., the number of functioning retino-cortical channels – was reduced in both eyes in the prematurely-born children (Groups 2-4) as compared to the control group (Group 1), but the difference was significant only in the left eyes ($p = 0.03$). No significant difference was found between the three groups of prematurely-born children (Groups 2-4).

The cause of the reduction in the number of functional retino-cortical channels may be found at any level between the retina and the cortex. Several authors believe that mild ROP may damage the photoreceptors (Fulton et al 2001, Hansen and Fulton 2000, Reisner et al 1997). Moreover, PVL, frequently found in prematurely-born children (Olsén et al 1997), often affects the posterior visual pathways. It remains uncertain whether the tendency to a reduced NC in the prematurely-born children was caused by damage at the level of photoreceptors or ganglion cells or along the posterior visual pathways. This reduction, however, did not seem to be associated with ROP or cryotreatment, but rather with the preterm birth per se.

The drop-out group (Papers III-V)

Theoretically, the drop-out group can be a source of bias (Fletcher et al 1996, Lagerberg 2001). In the 10-year follow-up study, 12.9% (32/248) were drop-outs, whereas Darlow et al (1997b) had an even smaller drop-out group of 9% of all survivors. On the other hand, Fledelius (1996a-d) reported the outcome on 48%, and O'Connor et al (2002) on 53% of their original populations. In the present study, the mean GA at birth of the drop-outs was lower than that of the preterm study group (28.3 weeks versus 29.1 weeks) ($p = 0.03$), but no difference was found concerning the BWs (1114 g versus 1166 g). The distribution of ROP in the eyes of the 32 children was: 20 right and 19 left eyes with no ROP, 5 right and left eyes with mild ROP, 5 right

and 6 left eyes with severe untreated ROP, and 2 right and left cryotreated eyes. Estimates of the visual and refractive outcomes of the drop-out group were done according to the stage of ROP (no, mild, severe untreated and cryotreated). When the findings of the drop-outs were included in the group of prematurely-born children, no change occurred in the significance of the results of the various analyses.

The control group (Papers III-V)

The control group may also be a source of bias, which however, can be reduced by selecting both the cases and the controls from the same population (Fletcher et al 1996). In this study, the two groups (preterms and full-terms) were born during the same period, in the same geographical area and the control group was randomly selected from the records obtained from the Swedish National Board of Health and Welfare. These studies aimed to compare preterm children with full-term ones and we therefore selected children with normal GA at birth and normal BW. Studies of full-term children have the same problems as those of prematurely-born ones, -i.e., methodology and epidemiology may vary and comparison of the studies may be difficult. When comparing the findings concerning VA and refraction (Paper III and IV) in the control group with those of approximately 10-year old normal children, they resembled those of other Scandinavian studies (Fledelius 1976, Jensen 1991, Jensen and Goldschmidt 1986, Laatikainen and Erkkilä 1980, Ohlsson et al 2001). The controls in the present study therefore seem to be representative of 10-year-old children in our population, as regards VA and refractive errors. The results of the peripheral VF (Paper V) also resemble those in other studies of healthy children (Myers et al 1999), but no studies are available on ophthalmologically healthy children regarding HRP.

The control group enabled us to detect minor changes in the premature group. The two groups were examined in exactly the same way, which ensured an accurate comparison and minimised measurement bias (Fletcher et al 1996). Such a comparison was more difficult to make in the other long-term population-based studies. Fledelius (1996a-d) compared the data with a control group, whom he had examined more than one decade before (Fledelius 1976). Darlow et al (1997b) compared their findings with a control group in New Zealand studied by others (Simpson et al 1984). Finally, O'Connor et al (2002) had a control group, whom they had examined in exactly the same way as regards VA, but not refraction.

GENERAL CONCLUSIONS

- ∄ The incidence of retinopathy of prematurity remained the same in two consecutive population-based studies, performed in the same geographical area in 1988-1990 and 1998-2000.
- ∄ The distribution of ROP has changed during the past decade - the “mature” infants were at a lower risk and the immature ones were at higher risk of developing ROP.
- ∄ Current Swedish screening guidelines for ROP could be modified by reducing the criterion for inclusion by one gestational week –i.e., from ≤ 32 weeks to ≤ 31 weeks.
- ∄ Prematurely-born children had a greater risk of refractive errors at ten years of age than those born at term. Cryotreated children had the highest risk, but also children without ROP had a higher risk.
- ∄ Although prematurely-born children had an overall good visual outcome, their visual acuity was poorer and the prevalence of subnormal vision was higher than in those born at term. The cryotreated children and those with neurological complications had the highest risk of poor visual acuity.
- ∄ The prevalence of visual impairment was 1.8%, of which half was due to the sequelae of ROP and half to neurological complications.
- ∄ Peripheral visual fields were constricted in cryotreated prematurely-born children, but not in those without ROP or with untreated ROP. The central visual fields, expressed as neural capacity, tended to be reduced in prematurely-born children.

SVENSK SAMMANFATTNING

Bakgrund

Med förbättrad neonatalvård överlever idag allt fler omogna prematurfödda barn. Dessa kan drabbas av många komplikationer på grund av den tidiga födseln. Beträffande ögonen och synen kan olika former av störningar uppstå. I nyföddhetsperioden kan näthinneförändringar, så kallad prematuritetsretinopati (ROP) förekomma. Synnedsättning, skelning, refraktionsfel och perceptionsstörningar upptäcks senare.

ROP har varit känt sedan 1940-talet. Sjukdomen drabbar de omogna kärlen i näthinnan. Den normala kärlutvecklingen avbryts och sjukliga förändringar uppstår. ROP klassificeras i 5 stadier där de lättare formerna (mild ROP) ofta går i spontan regress medan de mer allvarliga formerna (svår ROP) kan komma att kräva behandling. Ögonläkarens uppgift under barnets första levnadsmånader är att följa näthinnans utveckling genom regelbundna ögonbottenkontroller och i adekvat tid initiera behandling (frys- eller laserbehandling alternativt kirurgi) om avancerad ROP tillstöter. För 10 år sedan utfördes en populationsbaserad studie angående incidensen av ROP hos prematurfödda barn i Stockholmsområdet (Holmström et al 1993). Incidensen av ROP var 40% och behandlingskrävande ROP 11%. Studien låg till grund för den rekommendation för screening av ROP som finns idag i Sverige.

Många uppföljningsstudier av prematurfödda barn har utförts för att kartlägga syn och ögonmorbiditet. Svåra komplikationer upptäcks ofta i tidiga år medan mer subtila förändringar visar sig först i skolåldern när kraven på synfunktionen har ökat. Endast ett litet antal av de utförda uppföljningsstudierna är populationsbaserade och har genomförts efter att ROP-klassifikationen introducerades och efter att screening för ROP samt frys/laserbehandling blev allmänt accepterade. Dessa studier visar på en ökad förekomst av synnedsättning, skelning, glasögonbehov samt en rubbning av ögats tillväxt hos de prematurfödda barnen.

Syfte med studierna

Att utföra en prospektiv populationsbaserad incidensstudie av ROP i ett tidigare (1988-90) definierat område.

- ∅ Att jämföra incidensen av ROP i två konsekutiva populationsbaserade studier.
- ∅ Att utvärdera riskfaktorerna gestationsvecka vid födelsen och födelsevikt för ROP och jämföra resultaten med den tidigare studien.
- ∅ Att utvärdera nuvarande screeningkriterier för ROP och undersöka huruvida dessa kan modifieras.

Att utföra en populationsbaserad 10 årsuppföljning av syn- och ögonfunktion hos prematurfödda barn och jämföra med fullgångna barn.

- ∅ Att undersöka synskärpa, refraktion och synfält hos prematurfödda barn och jämföra med fullgångna barn.
- ∅ Att jämföra resultaten inom den prematurfödda gruppen och på så sätt utvärdera om ROP, behandling av ROP eller prematuriteten i sig påverkar syn, refraktion och synfält.

Arbete 1

Prematurfödda barn med födelsevikt ≤ 1500 gram, födda 1998-2000, i Stockholmsområdet inkluderades i studien. Inklusionskriteriet var det samma som användes för 10 år sedan (1988-1990). Incidensen av ROP undersöktes och jämfördes med incidensen i den föregående studien. Överlevnaden av prematurfödda barn hade ökat de senaste 10 åren. Samma antal barn ingick i de två studierna, men i den aktuella studien fanns fler omogna barn än i studien för 10 år sedan. Den ökade överlevnaden och den ökande andelen omogna barn i den senare studien berodde sannolikt på en förbättrad neonatalvård. Incidensen av ROP i hela gruppen var oförändrad (36% versus 40%). De barn som fick ROP hade emellertid lägre gestationsvecka vid födelsen och lägre födelsevikt, dvs de var mer omogna, än de barn som fick ROP för 10 år sedan. Detta gällde såväl mild ROP, men framför allt svår ROP och även de barn som hade behandlingskrävande ROP. Multipel logistisk regressionsanalys utfördes och från denna beräknades risken att få ROP vid varje gestationsvecka vid födelsen. Den visade att de mer ”mogna” barnen hade en minskad risk för ROP idag och att de mer omogna barnen hade en ökad risk för ROP än för 10 år sedan. Troligen beror detta på att fler omogna barn överlever och att dessa barn är känsliga och förmodligen mer benägna att utveckla ROP.

Arbete 2

Prematurfödda barn med gestationsvecka vid födelsen ≤ 32 veckor, födda 1998-2000, i Stockholmsområdet inkluderades i studien. Inklusionskriteriet var det samma som används för idag gällande screening av ROP i Sverige. Av dessa barn hade 25% ROP. Multipel logistisk regressionsanalys utfördes och gestationsvecka vid födelsen följt av födelsevikt befanns vara de största riskfaktorerna. Därför antogs det att gestationsvecka vid födelsen fortfarande är ett adekvat inklusionskriterium för screening. Analys av incidensen av total, mild, svår och behandlingskrävande ROP utfördes för varje gestationsvecka vid födelsen samt i relation till födelsevikten. Därefter analyserades screeningverksamheten och på vilket sätt denna skulle påverkas av en reduktion av inklusionsvecka. Screening är kostsam och ibland även krävande för barnet, varför antalet barn som utses för screening bör minimeras. Det är dock viktigt att inte missa något barn med behandlingskrävande ROP, eftersom detta i slutstadiet kan innebära blindhet. I studien fann vi att man kan reducera inklusionskriteriet för screening till gestationsvecka vid födelsen ≤ 31 veckor utan att riskera att inte upptäcka behandlingskrävande ROP i tid.

Arbete 3

Av 260 för tidigt födda barn, födda 1988-90, följdes 248 i 3,5 år. Vid 10 år kontaktades familjerna igen och 216 barn kom till ögonundersökning. Barnen undersöktes tillsammans med 217 barn födda i normal tid, med normal födelsevikt, födda i samma område och under samma tidsperiod som de prematurfödda barnen. Kontrollbarnen valdes slumpmässigt via medicinska födelseregistret. I delarbete 3 analyserades refraktionen hos barnen. Av de 216 prematurfödda barnen inkluderades 213 stycken och samtliga 217 kontrollbarn. De prematurfödda barnen hade 4 gånger så stor risk att ha någon form av refraktionsfel vid 10 år än barnen födda i normal tid. Framför allt hade de barn som genomgått s.k frysbehandling störst risk för refraktionsfel, men även barn utan ROP i neonatalförloppet hade ökad risk jämfört med kontrollbarnen.

Arbete 4

Hos de 216 prematurfödda barnen och 217 kontrollbarnen (se arbete 3) analyserades synskärpan på långt och nära håll. Journalhandlingar kunde beställas på ytterligare 10 prematurfödda barn och även dessa kunde inkluderas i vissa analyser. De för tidigt födda barnen hade sämre synskärpa än barnen födda i normal tid. Sämst synskärpa hade barnen som genomgått frysbehandling och de som hade neurologiska komplikationer. Detta konfirmerades av en multipel regressionsanalys där frysbehandling,

neurologisk komplikation och astigmatism visade sig vara oberoende riskfaktorer för dålig synskärpa. Det framkom dock att även prematurfödda barn utan ROP eller neurologiska komplikationer också hade sämre synskärpa än de barn som var födda i normal tid. Detta indikerar att den för tidiga födseln i sig påverkar den centrala synskärpan. Av de prematurfödda barnen var 1,8 % synskadade enligt WHO's definition. Synskadan var hos hälften av dessa barn orsakad av ROP och hos hälften av neurologiska komplikationer/hjärnskada. Crowding, dvs oförmågan att separera symboler såsom bokstäver presenterade på rad, analyserades. De för tidigt födda barnen hade ökad crowding, men ingen signifikant skillnad mot kontrollbarnen påvisades. En ökad crowding och nedsatt närsynskärpa skulle kunna bidra till svårigheter med läsning för barnet.

Arbete 5

Av de tidigare 216 prematurfödda barnen och 217 kontrollbarnen (se arbete 3) inkluderades 86 barn i en synfältsundersökning vid cirka 11 års ålder. Barnen indelades i 4 grupper. En kontrollgrupp, en grupp av barn utan ROP, en grupp av barn med obehandlad ROP och slutligen en grupp av barn med frysbehandlad ROP. Två typer av synfältsundersökningar utfördes, en av det perifera synfältet och en av det centrala.

Det perifera synfältet undersöktes med s.k. Goldmannperimetri. Denna visade en koncentrisk inskränkning av det perifera synfältet hos de frysbehandlade prematurfödda barnen. Barnen med obehandlad ROP och de utan ROP hade emellertid ingen påverkan av det perifera synfältet jämfört med barnen födda i normal tid.

Det centrala synfältet undersöktes med en datoriserad metod, kallad "High-pass resolution" perimetri. Metoden ger ett mått på antalet fungerande retinokortikala kanaler och har tidigare inte använts på för tidigt födda barn. Resultaten visade en reduktion av antalet fungerande retinokortikala kanaler hos de prematurfödda barnen jämfört med kontrollbarnen. Däremot förelåg inga skillnader inom prematurgruppen.

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