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Retinopathy of Prematurity in Infants Born Before 27 Weeks of Gestation

*A National Population-based Study in Sweden
During 2004-2007*

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Abstract

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Background: Improved neonatal care has resulted in an increasing population of surviving infants. Neonatal morbidity in preterm infants is, however, high, and retinopathy of prematurity (ROP) is one of the major neonatal morbidities. Observations have suggested that ROP might have a different course in extremely preterm compared to more mature infants.

Aims: To study the incidence, natural history and treatment of the disease, and the implications regarding screening recommendations for the population of extremely preterm infants.

Methods: A national, population-based study of neonatal morbidity in infants born before 27 gestational weeks was performed in Sweden during 2004 to 2007. ROP screening started in the 5th postnatal week and continued until the retina was completely vascularized.

Results: Of the 506 infants surviving until the first ROP examination, 73% developed ROP; 38% mild ROP and 35% severe ROP. Ninety-nine infants (20%) were treated. A log-linear relationship was found between severe ROP and gestational age (GA) at birth, and the risk of ROP was reduced by 50% for each week of increase in GA at birth (Paper I).

Postmenstrual age (PMA) at onset of ROP was significantly related to GA at birth, as was the site of onset of ROP. ROP had a predilection to start in the nasal retina in the most immature infants. There were significant relations between PMA at onset of ROP and severity of ROP as well as between the site of onset of ROP and severe ROP (Paper III).

The most immature infants had a higher risk of reaching treatment criteria for ROP, a higher risk of progression from ROP 3 to treatment criteria, and they reached these criteria at an earlier PMA than the less immature infants (Paper II).

According to our results, the first examination can be postponed until a PMA of 31 weeks in infants born before 27 weeks of gestation, since onset of ROP 3 did not occur before this age, and criteria for treatment were not reached before 32 weeks. The majority of infants (75%) were treated during a limited period, i.e. before a PMA of 39 weeks (Paper IV).

Keywords: Retinopathy of prematurity, extremely preterm, population-based, epidemiology, treatment, natural history, screening

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List of Papers

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

- I. Austeng D, Källén KBM, Ewald UW, Jakobsson PG, Holmström GE (2009). Incidence of Retinopathy of Prematurity in Infants Born before 27 Weeks' of Gestation in Sweden. *Archives of Ophthalmology*. 127:1315-1319.
- II. Austeng D, Källén KBM, Ewald UW, Wallin A, Holmström GE (2010). Treatment for retinopathy of prematurity in infants born before 27 weeks of gestation in Sweden. *British Journal of Ophthalmology*. Published online November 30, 2009. doi: 10.1136/bjo.2009.170704.
- III. Austeng D, Källén KBM, Hellström A, Tornqvist K, Holmström GE (2010). Natural history of retinopathy of prematurity in infants born before 27 weeks of gestation in Sweden. *Archives of Ophthalmology*. In Press.
- IV. Austeng D, Källén KBM, Hellström A, Jakobsson PG, Johansson K, Tornqvist K, Wallin A, Holmström GE (2010). Screening for retinopathy of prematurity in infants born before 27 weeks of gestation in Sweden. *Archives of Ophthalmology*. In Press.

Due to publishing rules of the Archives of Ophthalmology, we are unable to reprint Papers I, III and IV.

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Abbreviations

APROP	Aggressive Posterior Retinopathy Of Prematurity
BW	Birth Weight
CI	Confidence Interval
CRYO-ROP	CRYOtherapy for Retinopathy Of Prematurity
ETROP	Early Treatment for Retinopathy Of Prematurity
EXPRESS	EXtremely PREterm infants in Sweden Study
GA	Gestational Age
IGF-1	Insulin-like Growth Factor 1
OR	Odds Ratio
PMA	PostMenstrual Age
PNA	PostNatal Age
ROP	Retinopathy Of Prematurity
VEGF	Vascular Endothelium Growth Factor

Introduction

During the past decade, neonatal care in the Western world has undergone several improvements. There has been increased centralization and implementation of new therapies including tocolytic treatment to stop uterine contractions, antenatal administration of corticosteroids to mothers in preterm deliveries, and surfactant treatment given to preterm infants to accelerate foetal lung maturation. These advances have contributed to an increasing population of survivors in neonatal intensive care units (Håkansson et al. 2004; Lemons et al. 2001; Serenius et al. 2004; Steinmacher et al. 2008). Recently, the Extremely Preterm Infants in Sweden Study (EXPRESS) Group reported an even higher survival than reported earlier among infants born before 27 weeks of gestation during the three-year period from 2004 until 2007 (The EXPRESS Group 2009). The one-year survival of infants born alive was found to be 70% and ranged from 9.8% at 22 weeks of gestation to 85% at 26 weeks of gestation. However, the neonatal period is complicated, with considerable morbidity in these infants due to their immaturity. In this population-based study, only 45% of the infants were discharged from the hospital without major neonatal morbidities, defined as intraventricular haemorrhage grade >2 , periventricular leukomalacia, necrotizing enterocolitis, severe bronchopulmonary dysplasia, and last but not least, severe retinopathy of prematurity, i.e. ROP (stage >2).

ROP was originally termed retrolental fibroplasia when first described (Terry 1942). The blinding disease was soon associated with excessive oxygen use (Campbell 1951; Crosse and Evans 1952; Jefferson 1952), which resulted in controlled studies (Kinsey et al. 1956; Lanman et al. 1954; Patz et al. 1952) and consequently restricted oxygen delivery in neonatal intensive

care units. Advances in neonatal care and increased awareness of the importance of monitoring blood gases resulted in a reduction in the incidence of ROP. However, the disease was not eradicated. In the 1970s there was a second epidemic in industrialized countries as a consequence of improvements in neonatal care resulting in an increased number of surviving premature infants. During recent years, blindness due to ROP has also been increasing in middle income countries, giving rise to a third epidemic with elements from both the first and the second epidemics (Gilbert et al. 1997). ROP is responsible for approximately 3-10% of all new cases of childhood blindness in high income countries, while in middle income countries ROP accounts for up to 60% of such cases (Gilbert et al. 2005). ROP is therefore now considered a major health problem and it has been included in the World Health Organisation program for prevention of childhood blindness.

The incidence of ROP and the population at risk of developing ROP are dependent on the availability, access to, and quality of neonatal care. Guidelines and screening programs that take into consideration the characteristics of local populations therefore have to be designed (Gilbert et al. 2005). The present ophthalmological study is part of the multidisciplinary EXPRESS study investigating mortality and morbidity and including both the short-term and long-term outcomes of infants born before 27 weeks of gestation. The project was initiated by the Swedish Association of Perinatology and the Swedish National Board of Health and Social Welfare and involves specialists in obstetrics, neonatology, neurology, psychology and ophthalmology. The ophthalmologic part of the study was organised separately.

In this thesis various aspects of ROP in a national population of infants born before 27 weeks of gestation are analysed and discussed. The main focus is on the incidence, natural history and treatment of the disease and the implications regarding new screening recommendations for the population of extremely preterm infants.

Background

Normal vascular development

The retinal vasculature is not fully developed before term. Early in foetal life the thin immature retina receives nutrients from the underlying choroidal vessels. From about 6 weeks of gestation the retina is supplied by passive diffusion of oxygen through the Bruch's membrane. When the retina develops and the neural density thickens, the choroidal vessels cannot provide the retina with sufficient nutrients, and at about 14-15 weeks of gestation development of the retinal circulation starts, driven by the metabolic demands of the retina (Provis et al. 1997). The retinal vessels migrate centrifugally from the optic disc and reach its anterior boundaries temporally at around term and nasally a few weeks earlier.

Vascularisation comprises two processes, i.e. vasculogenesis and angiogenesis. During vasculogenesis, primary vessels develop from vascular precursor cells on the retinal surface. The precursor cells proliferate and align into vascular cords, develop lumina, and further differentiate into primary vessels in the central retina (Ashton 1970). During angiogenesis, new vessels are budding from the primary cords, forming the remaining retinal vessels. Angiogenesis is responsible for increasing the vascular density in the central retina, vessel formation in the peripheral retina, and formation of a secondary vasculature in the depth of retina and the radial peripapillary capillaries (Chan-Ling et al. 1990; Hughes et al. 2000).

When the retinal thickness increases during normal maturation, local hypoxia develops in the tissue in front of the retinal vessels, described as a wave of physiological hypoxia preceding vessel growth (Chan-Ling et al.

1995). In the hypoxic region, astrocytes and Müller cells respond to the hypoxia by secreting vascular endothelium growth factor (VEGF), which stimulates growth, i.e. proliferation, differentiation and migration of the endothelium of the vessels (Stone et al. 1995). When the hypoxia is relieved by oxygen supplied by the new vessels, VEGF mRNA expression is suppressed and the VEGF is down regulated. VEGF is oxygen-dependent and plays a role in all phases of vascular development. Insulin-like growth factor (IGF-1) is also involved in the development of retinal vessels. IGF-1 is oxygen-independent and controls VEGF activation (Smith et al. 1999).

Pathophysiology of ROP

Retinopathy of prematurity is a disorder of the immature retinal vasculature in the preterm infant. The exact mechanism behind the disease is not fully known, but many interacting factors have been identified. It is evident that normal retinal vasculature is primarily inhibited and secondarily followed by an uncontrolled growth. Hence, the disease occurs in two phases.

The first phase, involving growth inhibition of both the neural retina and the retinal vasculature, is thought to be caused by low infant levels of IGF-1 after preterm birth. Foetal IGF-1 is provided mainly by the placenta, and the IGF-1 level normally rises in the third trimester. After preterm birth, the IGF-1 level falls, as preterm infants appear unable to produce adequate levels of IGF-1 compared to term infants (Giudice et al. 1995). IGF-1 is required for maximum VEGF activation of vascular endothelial cells and for retinal vessel survival (Hellström et al. 2001, 2002). A shortage of IGF-1 results in VEGF down regulation and subsequently capillary retraction.

When preterm infants are supplied with high levels of oxygen in the incubator, both the physiological hypoxia signals and VEGF synthesis are suppressed (Alon et al. 1995). Supplemental oxygen is found to suppress VEGF mRNA, and the lack of VEGF leads to regression of immature vessels. A VEGF Receptor 1 found on the endothelial cells is required for maintenance

of the immature retinal vasculature, and without stimulation of this receptor the vessels will be obliterated (Alon et al. 1995). Thus, both a low level of IGF-1 and supplemental oxygen suppress growth of the vessels in ROP phase 1.

In the hypoxia induced second phase of ROP, the retina develops anterior to the vasculature, resulting in localized hypoxia due to the increased demand for oxygen. Both animal studies and clinical observations have revealed a close relationship between VEGF and proliferative retinopathy, with an increase in VEGF before the development of neovascularisations (Provis 2001). A high level of VEGF has also been found in the vitreous of patients with neovascularisations with ischaemic retinal diseases (Aiello et al. 1994).

Further, when the preterm infant returns to room air and/or the IGF-1 level rises due to infant maturation, VEGF is up regulated on a large scale due to retinal hypoxia, leading to uncontrolled vessel growth or, in other words, ROP.

Risk factors for ROP

ROP is a multifactorial disease and many risk factors have been proposed since the disease was described by Terry in 1942. The most important will be mentioned below.

Pulmonary insufficiency requiring assisted ventilation as well as oxygen therapy has been a known risk factor since the 1950s (Kinsey et al. 1956; Lanman et al. 1954; Patz et al. 1952). Fluctuating arterial oxygen tension as well as hypoxia and hyperoxia can have serious consequences, as the relative hyperoxia may lead to retinal capillary damage, and subsequent ischaemia stimulates vasoproliferation. In the past 50 years it has not been possible to define safe levels of oxygen usage for these infants, but studies are currently being performed concerning optimal levels of oxygen supplementation (Sears et al. 2009).

Today, the major risk factor for ROP is the degree of immaturity of the infant. Both the incidence and severity of ROP are inversely related to GA and BW (Ng et al. 1988; Palmer et al. 1991), with GA most strongly associated with ROP (Darlow et al. 1992; Holmström et al. 1993). During the past decade, poor postnatal weight gain and low serum IGF-I levels during the first weeks of life have been shown to be significant predictors of ROP (Hellström et al. 2003; Löfqvist et al. 2006; Wallace et al. 2000).

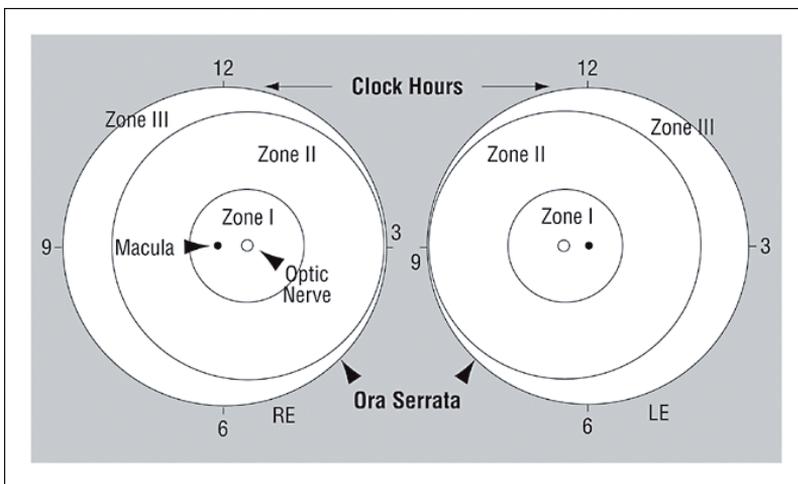
The quality of care that is provided is important regarding ROP development, infants born in large tertiary referral neonatal units have a lower incidence and severity of ROP, even though infants referred to tertiary units often are the most ill and also the most immature (Darlow et al. 1992; Schaffer et al. 1993). Ethnicity has also been associated with a risk of developing ROP. Both Asians and Alaskan natives have been found to be more likely to develop severe ROP compared to Caucasians (Lang et al. 2005; Ng et al. 1988), while black infants are less likely to develop ROP compared to white infants (Schaffer et al. 1993; Zacharias 1952). Finally, light has been proposed to cause retinal damage, to generate free radicals and thereby to cause ROP. A prospective randomised clinical trial found no significant association between light protection early in life and ROP development (Reynolds et al. 1998). Experiments have also been performed to test if vitamin E has a protective effect on ROP by suppressing free radical damage in the retina. A reduction in severity of ROP was shown, but because of serious side effects, vitamin E as a prophylactic agent is not recommended (Muller 1992).

Classification

Four decades after the first description of retrolental fibroplasias (Terry 1942), the name of the disease was changed to retinopathy of prematurity. The Committee for Classification of ROP published the first international classification of the disease in 1984 (Committee for the Classification of

Retinopathy of Prematurity 1984), and three years later the classification was expanded to include retinal detachment and ROP sequelae (ICROP Committee for Classification of Late Stages ROP 1987). In 2005 the classification was revised (International Committee for the Classification of Retinopathy of Prematurity 2005).

The localization of the retinopathy is described by zones centred at the optic disc. Zone I is a circle with a radius twice the disc-fovea distance. Zone II extends from the edge of zone I to the nasal ora serrata. Zone III encompasses a crescent temporally. The scheme below of the retinas of the right eye (RE) and the left eye (LE) shows zone borders and clock hours used to describe the location and extent of ROP (Committee for the Classification of Retinopathy of Prematurity 1984):



The severity of the abnormal vascular response is divided into 5 stages. In stage 1, a grey demarcation line separates the vascularised from the nonvascularised retina. In stage 2, the line has extended in volume and rises from the retinal plane as a ridge. In stage 3, in addition to the ridge there are fibrovascular proliferations. Stage 4 is characterised by partial retinal detachment, not involving (4A) or involving (4B) the macula, while stage 5 is the end-stage and encompasses total retinal detachment.

Additional signs indicating the severity of active ROP are increased venous dilatation and arterial tortuosity of the posterior retinal vessels, i.e. plus disease. A diagnosis of plus disease is defined by standard photography (Committee for the Classification of Retinopathy of Prematurity 1984) and at least two quadrants of the fundus must be involved for the diagnosis (The STOP-ROP Multicenter Study Group 2000). Recently, the revised classification defined pre-plus disease, classified as more vascular abnormalities of the posterior pole than normal, but not enough for the diagnosis of plus disease. The new classification also includes Aggressive Posterior ROP (APROP) (International Committee for the Classification of Retinopathy of Prematurity 2005), an uncommon rapidly progressing severe form of ROP which, if untreated, usually progresses to stage 5 ROP. APROP is located in the posterior pole and is characterised by plus disease and by usually not progressing through the classic stages 1-3. The retinopathy may appear as only a flat network of neovascularisations in the posterior pole of the fundus.

Natural history

When designing screening guidelines, different aspects concerning the natural history of ROP are of managerial importance, including symmetry of the disease, age at onset, site of onset, rate of progression and the resolution of the disease. Knowledge about the natural history of ROP is based to a large extent on studies of 1980-cohorts (Fielder et al. 1986, 1992a; Holmström et al. 1993; Palmer et al. 1991; Quinn et al. 1992, 1995; Repka et al. 2000; Schaffer et al. 1993; Schulenburg et al. 1987). Although more recent studies have yielded additional knowledge regarding the natural history of the disease (Carden et al. 2008; Eliason et al. 2007; Good et al. 2005; Larsson et al. 2002; Reynolds et al. 2002), the data from the CRYO-ROP study in the 1980s still form the basis for the treatment recommendations used today (Early Treatment For Retinopathy Of Prematurity Cooperative 2003). The studies performed before the first treatment recommendations were pub-

lished have provided knowledge about the course of ROP in nontreated eyes and are the references used when performing natural history studies and when comparing new treatment modalities today.

Treatment

A major aim of treatment for ROP has so far been to remove the stimulus for vessel growth by ablating the peripheral avascular retina. Cryotherapy and xenon arch photocoagulation have been used since 1967 (Nagata 1968), but it was not until 1988 that retinal ablative therapy was confirmed as effective (Cryotherapy for Retinopathy of Prematurity Cooperative 1988). The threshold for treatment was reached when ocular findings indicated a 50% risk for retinal detachment and blindness, i.e. 5 continuous or 8 cumulative clock hours of stage 3 ROP in zone 1 or 2 with plus disease. In infants who reached threshold disease at the same time in both eyes, the eyes were randomised either to cryotherapy or to the control group. A significant reduction in unfavourable structural and functional outcome was seen at follow-up at ages 1, 3.5, 5.5, and 10 years and at the final control at 15 years (Cryotherapy for Retinopathy of Prematurity Cooperative 1990a, 1993, 1996, 2001; Palmer et al. 2005). However, 10 years after treatment, 45% of treated eyes had a visual acuity of 0.1 or worse, and the percentage of eyes with visual acuity of 20/40 or better was similar to that of control eyes, 25%. This raised the question as to whether the threshold for treatment was set too high, and also if more effective approaches to treatment would be helpful.

In the prolongation of the CRYO-ROP study, with the aim of examining whether or not some eyes with ROP with less than threshold disease might benefit from treatment, the Early Treatment for ROP study (ETROP) was undertaken during the period from 2000 until 2002. A risk model based on data from the CRYO-ROP study, including patient demographic characteristics, pace of disease and severity of retinopathy, was used to predict the like-

likelihood of eyes with moderate (pre-threshold) stages progressing to retinal detachment (Hardy et al. 2003). The results of the trial showed a significant reduction in unfavourable structural outcome from 15.6% of eyes treated at threshold to 9.1% for earlier-treated eyes, and also a reduction in unfavourable visual acuity outcomes from 19.5% to 14.5%, respectively (Early Treatment For Retinopathy Of Prematurity Cooperative 2003). The recommendations for earlier treatment were, however, debated, since earlier treatments implied treating a number of infants who might have regressed spontaneously (Good 2004).

In the early 1990s laser photocoagulation was introduced, and since then it has been the method of choice. Trials have shown laser photocoagulation to be at least as good as cryotherapy, and less traumatic (Hunter and Repka 1993; Iverson et al. 1991; McNamara et al. 1991, 1992).

Based on the ETROP data, a clinical algorithm was developed identifying eyes at high risk. Treatment was recommended for eyes with Type I ROP, while it was suggested that eyes with Type 2 ROP should be followed up with continued serial examinations, see illustration below for definitions of Type 1 and Type 2 ROP.

	Type 1 ROP – treatment	Type 2 ROP - close follow-up
Zone 1	Any stage ROP with Plus Stage 3 ROP without Plus	Stage 1 or 2 ROP without Plus
Zone 2	Stage 2 or 3 ROP with Plus	Stage 3 ROP without Plus

There is presently no consensus regarding surgery for eyes with ROP stages 4 and 5. The functional results of surgery on such eyes are often disappointing, even though the structural outcome may be good (Cusick et al. 2006; Repka et al. 2006). However, a positive development in visual acuity has been seen in eyes after lens sparing vitrectomy (Hartnett et al. 2003). In studies of eyes with ROP stages 4A and 4B, between 80 and 90% of the eyes

have achieved retinal attachment after vitrectomy, with better results for stage 4A than for stage 4B (Hubbard 2008). Studies have also shown better results after vitrectomy than after cerclage surgery (Hartnett et al. 2004; Sears and Sonnie 2007). Treatment of eyes with persistent neovascular activity despite laser treatment and eyes with total retinal detachment continues to represent a major challenge (Hubbard 2008).

In recent years there has been increasing interest in anti-vascular endothelium growth factor (anti-VEGF) drugs, especially bevacizumab, in the treatment of ROP (Micieli et al. 2009). Bevacizumab has been shown to have effect on ROP in zone 1 and APROP (Mintz-Hittner and Kuffel 2008), the latter often yielding unfavourable outcomes (Cryotherapy for Retinopathy of Prematurity Cooperative 1990b; Early Treatment For Retinopathy Of Prematurity Cooperative 2003). Furthermore, the drug is cheap and easily administered, which is an advantage in developing countries where ROP is an increasing problem. However, leading neonatologists and ophthalmologists advocate caution before introducing a new, unproven therapy and point out that an understanding of the systemic side effects is essential before wide implementation of new treatment (Darlow et al. 2009). So far, no randomised controlled trials of anti VEGF in infants with ROP have been published, but one study (BEAT-ROP) is now underway in the US. In the meantime, whether a drug that has not been tested and approved for treatment in the eyes should be favoured when alternative approaches are available, is indeed doubtful.

Screening

ROP is a serious but mostly preventable cause of blindness. It is therefore of great importance to detect infants at risk of developing the disease. The World Health Organisation has defined a number of criteria regarding screening for disease and case-finding-programs (Wilson and Jungner 1968). ROP clearly fulfils these criteria since blindness is an important health prob-

lem that should be avoided, not only because this would be cost saving for society but also to prevent many infants from having a lifetime of blindness (Brown et al. 1999; Dunbar et al. 2009; Javitt et al. 1993; Kamholz et al. 2009). The population at risk is easily found in neonatal intensive care units, and treatment is available (Cryotherapy for Retinopathy of Prematurity Cooperative 1988; Early Treatment For Retinopathy Of Prematurity Cooperative 2003).

Following publication of the CRYO-ROP study showing that cryotherapy was an effective treatment (Cryotherapy for Retinopathy of Prematurity Cooperative 1988), the first screening guidelines for ROP were developed in the late 1980s. Such guidelines, however, have to be adjusted to local populations and health care conditions, and should be continuously revised and improved (Gilbert et al. 2005). American and British guidelines have recently undergone such revision and improvement (Section on Ophthalmology American Academy of Pediatrics et al. 2006; Wilkinson et al. 2008).

In Sweden, the first guidelines for ROP were presented in 1993 (Holmström et al. 1993), and were revised in 2002 after a consecutive population-based study in Stockholm County (Larsson and Holmström 2002). In the latter cohort, no infants with a GA >31 weeks at birth developed severe ROP and no infants with a GA >29 weeks were treated for ROP, leading to a lowering of the screening criterion by one week.

Since GA has been difficult to ascertain, prematurity is defined according to birth weight (BW) in many parts of the world. In Sweden, however, studies have found GA at birth to be the most important risk factor for ROP (Holmström et al. 1993), and 95% of the pregnancies are found to be dated by ultrasound (The EXPRESS Group 2009). GA is therefore the major screening parameter in our population.

Ethical considerations

This study is part of a national quality-assuring project, the EXPRESS study, initiated by the Swedish Association of Perinatology and the Swedish National Board of Health and Social Welfare. The aim of the investigation is to study mortality and morbidity and long-term follow-up in infants born before 27 weeks of gestation. Earlier studies of preterm infants in Sweden showed differences in neonatal outcome among hospitals (Finnström et al. 1997; Håkansson et al. 2004), as has also been reported in Australia and New Zealand (Darlow et al. 2005a). These findings have resulted in debate regarding neonatal care and quality and, more specifically, neonatal intensive care at the margins of viability. These issues have recently been discussed at Australian, Italian, Dutch, American and British conferences, contributing to development of national recommendations (Committee on Fetus and Newborn 2007; Lui et al. 2006; Pignotti et al. 2007; Verhagen and Sauer 2005; Wilkinson et al. 2009). Good evidence-based data is crucial when considering these questions, not least because of the long-term medical consequences for these infants and their families. This is the kind of data that has been collected in the neonatal part of the EXPRESS study, and ROP is one of the major neonatal morbidities. The results of an ongoing follow-up of the infants at age 2.5 years and planned later follow-ups will provide information regarding the long-term outcome in this population of extremely preterm infants.

This project is a quality-assuring project and health register. The Ethics Committee at Lund University approved the study (no. 42/2004), and decided that no informed consent was necessary. The parents were, however, informed about the data collection. When analysing the data, the patients

were de-identified to protect those involved. Further, ethical aspects regarding data collection and protection have been continuously considered throughout the study, not least regarding safe handling of sensitive information on its way from hospitals to the data register.

Aims

During the past decade, improved neonatal care has resulted in increased survival of prematurely born infants, yielding a growing population of extremely preterm infants. We hypothesized that this new population differs from the population of less immature infants and might be more susceptible to ROP. We wanted to investigate various aspects of ROP in a national population of extremely preterm infants born with a gestational age of <27 weeks. The aim of the project was thus to study and evaluate:

- The incidence of ROP and its relation to GA at birth (**Paper I**).
- Different aspects of treatment for ROP, including treatment in relation to GA at birth and treatment routines (**Paper II**).
- The natural history of ROP with focus on time and site of onset and progression of the disease (**Paper III**).
- Screening routines for ROP with special emphasis on the start, frequency and termination of screening examinations (**Paper IV**).

Material and Methods

This study is part of a national project in which mortality and morbidity are studied in extremely preterm infants (The EXPRESS Group 2009). The study includes all infants with a GA of less than 27 weeks who were born in Sweden between April 1, 2004, and March 31, 2007. Terminations of pregnancies and infants born outside of Sweden and transferred to Sweden for neonatal care were excluded. Infants with congenital anomalies involving the eyes were excluded.

A group of paediatric ophthalmologists in charge of screening for ROP was organised throughout Sweden. The group was assembled and informed about the study procedures and protocols, and the diagnoses and indications for treatment were discussed before onset of the study and regularly during the study. Information and advice were also given at annual meetings of the Swedish Ophthalmologic Society and the Swedish Society of Medicine, as well as at regional ophthalmological meetings. Regional ophthalmologic coordinators met regularly in order to ensure the quality of the study.

After birth, all infants in Sweden fulfilling the study criteria were immediately reported to the study coordinator and the responsible ophthalmologist at the infant's hospital. The tracking of infants and mothers was facilitated by the Swedish system of personal identification numbers given at birth. When infants were transferred to another hospital, the new ophthalmologist was to be contacted by phone or fax to avoid any delay in the screening program.

According to our protocol, eye examinations were to start the fifth postnatal week and the infants were thereafter to be examined weekly, enabling study of the course and severity of ROP. In infants with no or mild ROP

(stages 1 and 2), without progression during the latest examinations, further examinations were performed each week or every other week from PMA 35 weeks. The infants were to be followed until complete retinal vascularisation or until regression of ROP. Retrospectively, if the regression of ROP and the peripheral vascularisation were prolonged, a time interval between examinations of 1 month or more was regarded as the end of screening.

We used the International Classification of Retinopathy of Prematurity revisited to categorise ROP (International Committee for the Classification of Retinopathy of Prematurity 2005), and followed the Early Treatment for Retinopathy of Prematurity Cooperative Group recommendations concerning criteria for treatment (Early Treatment For Retinopathy Of Prematurity Cooperative 2003).

The following variables were reported: date of first and last examination, number of examinations, ROP at first examination, maximal stages and zone of ROP in each eye, site of onset of ROP, date at onset of ROP and of various stages of ROP in each eye, number of treatments, type of treatment, date of treatment, aggressive ROP or plus disease at treatment in each eye. Further, it was noted if the infant died before the retina was fully vascularised or before regression of ROP.

The pupils were dilated twice with combined cyclopentolate hydrochloride 0.5% and phenylephrine hydrochloride 0.5% 45 and 30 minutes before examination. Indirect ophthalmoscopy was recommended. When needed, topical anaesthesia, an eyelid speculum and scleral indentation were used to visualize the border between vascularised and nonvascularised retina. Infants who did not tolerate screening for ROP as scheduled were examined as soon as permitted by the neonatologist.

When the eye examinations were finished, the protocols were completed by the ophthalmologist in charge and sent to Gerd Holmström and Dordi Austeng at Uppsala University. The data were registered in an already existing data base, the perinatal quality register, PNQ, where the obstetrical and

neonatological data were also registered. The data were collected from both obstetricians and neonatologists and no dropouts are registered.

Gestational age (GA) denotes time from the last menstrual period to birth, and was estimated by ultrasound examination at 17 or 18 postmenstrual weeks (The EXPRESS Group 2009). The postmenstrual age (PMA) was calculated as the sum of GA at birth plus the postnatal age (PNA), i.e. the number of weeks (and days) after birth. ROP stages 1 and 2 were defined as mild ROP and stages 3 to 5 as severe ROP.

Statistical analyses were performed using a commercially available software program (Gauss; Aptech Systems Inc., Maple Valley, WA, USA).

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using multiple logistic regression analyses. The GA was analysed using class variables or, if specified, it was entered in the models as a linear continuous variable. If specified, adjustments were made for BW (continuous variable).

The Spearman correlation coefficient was determined when evaluating the correlation between rank transformed data (e.g. assessment of the correlation between severity of ROP and GA at birth, and when estimating the degree of symmetry between the stages of ROP in the right and left eyes).

The relations between site of onset and age of onset, respectively, and severe ROP, i.e. stage ≥ 3 (dichotomous outcome variable), were investigated using simple logistic regression analyses or, when specified, multiple logistic regression analyses adjusting for GA as a continuous linear variable.

Age at onset (PNA and PMA) in relation to severity of ROP (stages 1, 2 and 3) and GA was investigated using MANOVA analyses.

All objectives regarding GA at birth (divided into groups 22w, 23w, 24w, 25w, and 26w, respectively) in relation to the continuous variables considered in the current study were investigated using non-parametric tests (Kruskal-Wallis).

Results

Background data

During the three-year study period, 305 318 infants were born in Sweden and of those, 1011 were born before 27 weeks of gestation (incidence 3.3/1000 infants). Of 707 live-born infants with GA < 27 weeks, 200 infants died before the first ROP examination (189 died before postnatal week 5, i.e. when screening should have started, and 11 died after the 5th postnatal week but before the first eye examination). One infant was excluded because of chromosome anomaly. Hence, the study cohort screened for ROP comprised 506 infants (229 girls (45.4%) and 277 boys (54.7%); 410 single births (81.0%) and 96 multiple births (19%)). Mean GA and BW were 25.4 weeks (range 22.1-26.9) and 777 grams (range 348-1315).

The infants were examined at 27 hospitals throughout the country, 64 ophthalmologists participated in the screening, and 19 ophthalmologists treated the infants at the seven university hospitals.

Start of the screening

The first eye examination in the total population of 506 infants was performed at a mean and median PNA of 5.8 and 5.3 weeks (range 4.0-13.6 weeks) and a mean and median PMA of 31.1 weeks (range 27.4-38.1). Forty-two infants had ROP at the first eye examination. Twenty-nine infants had ROP 1, 10 had ROP 2 and, of clinical importance, three had ROP 3 at the first examination. Further details on the start of the screening and the proportions of infants screened at the different post natal and post menstrual ages are given in Paper IV.

Frequency of the eye examinations

The mean and median number of days between examinations in the total cohort was 8.6 and 7.9 days (range 1-27.8). The mean and median number of examinations in the total population (503 infants with available information) was 11.6 and 10 examinations (range 1-30). The number of examinations decreased significantly with increased GA at birth ($p < 10^{-6}$).

Termination of the screening

Six infants died before the screening was terminated and were excluded from these analyses. Ninety-nine infants were treated for ROP. The last eye examination in the remaining 401 infants was performed at a mean and median PNA of 18 and 16 weeks (range 7.6-42.6) and a mean and median PMA of 43.6 and 41.6 weeks (range 34.4-67.4). In 99% of the infants, the last examination was performed in the 36th postmenstrual week or later.

Five infants had their last examination before the 36th postmenstrual week. One infant was discharged from further screening by mistake at PMA 34 weeks and was examined later, with no visible sequelae after ROP. The other four had a GA at birth of 26 weeks, developed no ROP, and had their last examination at a PMA of 34 - 35th weeks.

Further details are given in Paper IV.

Incidence of ROP and relation to GA at birth

Of the 506 infants, 73% (368/506) developed ROP; 37.9% (192/506) developed mild ROP (stages 1-2) and 34.8% (176/506) developed severe ROP (stages 3-5). The incidence of ROP in relation to GA at birth is illustrated in Table 1. The severity of ROP showed a negative correlation with GA at birth (Spearman $\rho = -0.25$, $p < 10^{-6}$).

ROP stages	22w (n=5)	23w (n=53)	24w (n=99)	25w (n=171)	26w (n=178)	Total (n=506)
No ROP	0%	10%	14%	23%	44%	27%
Mild ROP (stage 1-2)	20%	28%	36%	45%	36%	38%
Severe ROP (stage 3-5)	80%	62%	50%	32%	20%	35%

Table 1. Incidence of retinopathy of prematurity (ROP) in relation to gestational age at birth (weeks).

Three logistic regression analyses were performed (Figure 1). In the first, GA was entered as a class variable, with 26 completed weeks as a reference. In the second analysis, GA was entered as a continuous variable in a linear model. In the third analysis, GA and BW were entered as continuous variables in a multiple linear model. In Figure 1, the class variable ORs were almost the same as the estimates obtained from the linear univariate model using GA as a continuous variable. The series of ORs for severe ROP were 16, 7, 4 and 2 for the classes during weeks 22, 23, 24 and 25, respectively, compared with 26 weeks. This corresponds to an OR of 0.51 (CI 0.42–0.62) for each additional gestational week obtained from the model using GA as a continuous variable.

When adjustment was made for BW, the association between GA at birth and severe ROP declined but remained statistically significant. Both GA at birth and BW were independently associated with severe ROP, but GA at birth was a stronger predictor for severe ROP than BW ($p=0.0001$ and $p=0.004$, respectively).

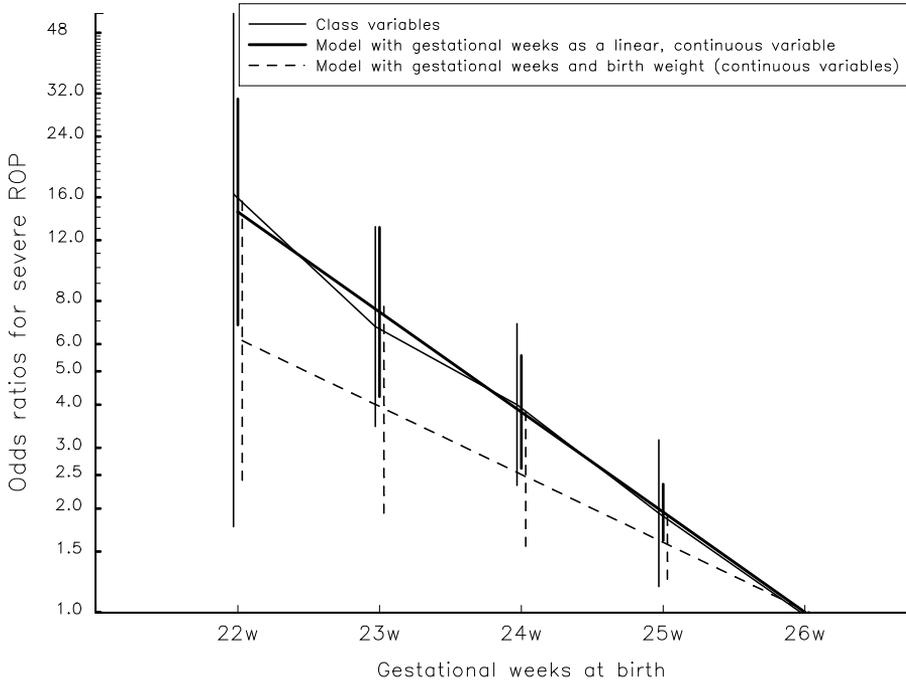


Figure 1. Odds ratios (with 95% confidence intervals) for severe retinopathy of prematurity (ROP) ($ROP \geq 3$) in relation to gestational age at birth and birth weight (univariate and multivariate logistic regression analyses).

Onset of ROP

In analysing the onset of the disease, eyes with ROP at the first examination were excluded. Twenty-nine infants had ROP 1, ten had ROP 2 and three had ROP 3 at the first examination. The infants with ROP 3 had their first examination at PMA 32+4, 33+1 and 34+6 weeks, respectively. In the remaining 326 infants with ROP, the mean and median PNA and PMA at onset of ROP were 8.9 and 8.6 weeks (range 4.7 – 16.3) and 34 and 33.6 weeks (range 30.1 – 41.7), respectively.

Symmetry of ROP

Symmetrical stages of ROP in the right and left eyes were found in 424/506 infants (83.8%). There was a significant correlation between the right and left eyes regarding maximal stage of ROP ($p < 0.001$), and thus we performed the following analyses only on the 352 right eyes with ROP.

Site of Onset and relation to severe ROP

The site of onset of ROP was recorded in 308 of 352 right eyes. In 85 (27.6%) of the eyes ROP was first localized in the nasal retina, in 73(23.7%) both nasally and temporally simultaneously, and in 150 (48.7%) eyes ROP was first localized temporally. The site of onset was significantly related to GA at birth ($p < 0.001$). The risk of nasal onset was nearly doubled for every week of decrease in GA at birth (OR 1.8, CI 2.3-1.5). Nasal onset was also related to severe ROP, even after adjustment for GA at birth ($p < 0.001$).

Onset of ROP stages 1, 2 and 3 and of Plus disease

Onset of the different stages of ROP and of Plus disease is presented in Table 2. PMA at onset of stages 1, 2 and 3 and of Plus disease was found to be significantly lower in the most immature infants ($p < 0.05$). No correlation with PNA was found.

ROP stage	Excluded	Included	PNA (weeks)					PMA (weeks)				
			Min	5%	50%	95%	Max	Min	5%	50%	95%	Max
ROP1	26	179	5.7	6.3	8.6	13.1	16.4	30.3	31.3	34.1	38.3	42.0
ROP2	9	229	5.9	6.9	9.4	14.4	19.4	29.9	31.9	34.6	39.6	44.3
ROP3	3	157	6.6	7.7	11.1	19.1	24.7	31.6	32.6	35.9	43.3	50.6
Plus	0	82	7.4	8.4	11.3	17.7	29.3	31.7	32.7	35.9	41.6	54.1

Table 2. Postnatal age (PNA) and postmenstrual age (PMA) at onset of the different stages of retinopathy of prematurity (ROP) and of Plus disease (Plus) in the 352 right eyes (median, 5th and 95th percentile, range). For every stage of ROP, eyes with that particular stage at the first examination were excluded.

Onset of ROP in relation to GA at birth

PMA at onset of ROP was significantly lower in the most immature infants ($p < 0.001$) while PNA at onset was significantly higher in those who were most immature ($p < 0.05$). Figure 2 illustrates PMA at onset of ROP and Table 3 presents onset of ROP 3, both in relation to GA at birth.

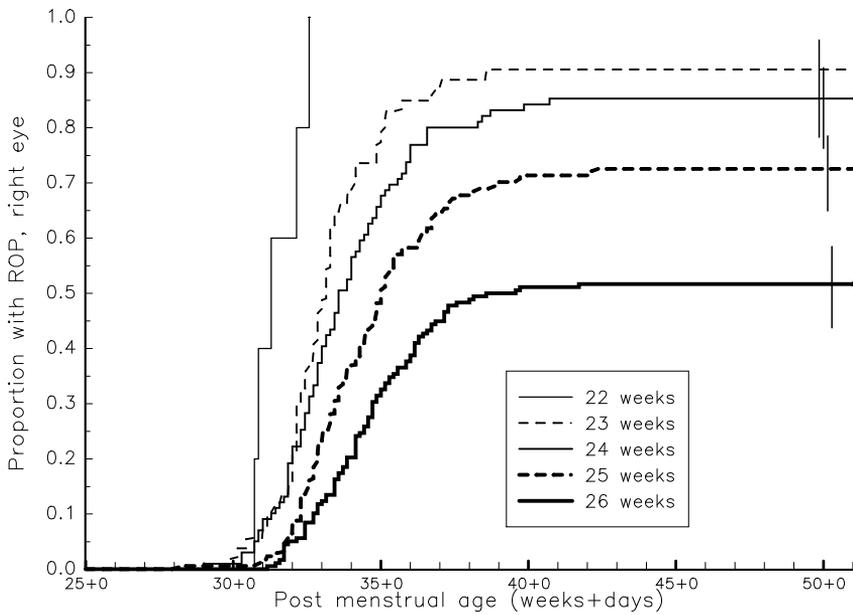


Figure 2. Onset of retinopathy of prematurity (ROP) in the right eyes in relation to gestational age at birth (with 95% confidence intervals at 50 weeks as vertical bars).

GA at birth	No. of eyes	PMA (weeks) at onset of ROP 3				
		1%	5%	50%	95%	99%
22	4	32.3	32.3	36.2	40.9	40.9
23	29	31.6	32.0	34.4	39.9	42.7
24	46	31.7	32.9	35.9	45.4	48.6
25	49	32.0	32.9	36.6	42.3	50.6
26	29	33.4	33.7	37.4	42.1	46.1
Total	157	31.7	32.6	35.9	43.3	48.6

Table 3. Postmenstrual age (PMA) at onset of ROP 3 in 157 right eyes in relation to gestational age at birth.

Onset of ROP in relation to severity of ROP

PMA at onset of ROP was significantly related to severity of ROP ($p < 0.001$), i.e. the lower the PMA the more severe the final stage of ROP. This relation remained after adjustment for the GA at birth ($p < 0.05$).

Progression of ROP

Time from onset of ROP to onset of ROP 3 was significantly shorter in infants reaching treatment criteria (median time 14 days) compared to those who did not (20.5 days) ($p < 0.05$). No correlation was found between rate of progression from onset of ROP to ROP 3 and GA at birth.

Treatment and relation to GA at birth

Of the 506 infants screened for ROP, 99 infants (19.6%) were treated. GA and BW were significantly lower in infants treated for ROP than in those not treated ($p < 0.001$). Multiple logistic regression analyses showed a significant relation between treatment and GA at birth ($p < 0.001$). Table 4 presents percentages of infants treated in relation to GA at birth.

GA at birth (weeks)	22 (n=5)	23 (n=53)	24 (n=99)	25 (n=171)	26 (n=178)	Total (n=506)
Infants treated	80%	43%	31%	16%	7%	20%
Infants not treated	20%	57%	69%	84%	93%	80%

Table 4. Relation between infants treated for ROP and gestational age at birth.

The risk of reaching the criteria for treatment was reduced by 56% for each week of increase in GA at birth (OR 0.44, CI 0.35-0.55). Adjustment for BW only slightly affected this relation (OR 0.58, CI 0.44-0.76, $p < 0.001$).

The risk of progression from ROP 3 to treatment criteria also declined with increase in GA at birth ($p < 0.001$), and the ORs for requiring treatment for ROP 3 were nearly halved for each additional week of GA at birth (OR 0.58, CI 0.43-0.79).

Age at first treatment

The first treatment was given at a mean and median PMA of 37.6 and 36.4 weeks (range 32.1 – 46.9). Three infants were treated at a PMA of between 49 and 54 weeks because of local vessel anomalies in eyes with regressed ROP. PMA at the first treatment was significantly lower in infants with lower GAs ($p < 0.05$). Table 5 presents PMA at treatment in relation to GA at birth.

GA at birth	No. of eyes	PMA (weeks) at first treatment				
		1%	5%	50%	95%	99%
22	4	32.9	32.9	38.1	41.4	41.4
23	21	32.1	32.9	35.6	38.6	39.1
24	30	32.1	32.9	36.3	45.7	46.9
25	28	34.0	34.1	37.1	41.3	46.7
26	13	34.3	34.3	38.3	46.3	46.3
Total	96	32.1	32.9	36.4	42.9	46.9

Table 5. Postmenstrual age (PMA) at treatment in 96 right eyes in relation to gestational age (GA) at birth.

Discussion

Strengths and limitations

This is a population-based study containing data on all infants born before 27 weeks of gestation in Sweden during a three-year period. Most studies on the incidence and treatment of ROP are based on single and multicentre studies, and only a few studies have been designed to achieve an unbiased sampling within a given geographic area (Allegaert et al. 2004; Darlow et al. 2005b; Larsson et al. 2002; Markestad et al. 2005; Tommiska et al. 2007; Weber et al. 2005). More specifically, the main advantage in population-based studies is that all infants living within the geographically defined borders are included. This is in contrast to hospital-based studies, where a selection of the population might partly reflect the economic situation of participating families (private contra public hospitals) as well as travel distances and the level of neonatal care at the hospital.

A major bias in any study involves infants lost to follow-up. The group followed will often differ from the group lost to follow-up, but it might be difficult to predict how the groups will vary (Lagerberg 2001). In the present study none of the 506 infants initially included were lost during the study period.

Another important advantage pointed out by Good, is that ROP is a primary outcome, i.e. the main result, not only an adjunct to other studies (Good 2008). The ophthalmological part of the study was designed and organised by ophthalmologists, who were also responsible for all data collection and input during the study. The data were collected prospectively on standard study protocols, and missing data were tracked until the ophthalmologist in charge concluded that the data were unobtainable.

As in most national studies, a weakness of the present study was that there were many ophthalmologists involved in the examinations. In a recent study, Darlow et al. question the considerable variation in the incidence of ROP at centres within the Australia and New Zealand Neonatal Network (Darlow et al. 2008). They conclude that observer bias likely contributes to the variation and that there should be a certification process for studies in which ROP is an outcome. However, variability among the observers was also present in the CRYO-ROP study in which the participating examiners underwent certification (Reynolds et al. 2002). In the present study we tried to reduce this problem with observer bias by initially giving standardized instructions to the participating ophthalmologists and by repeating information and discussing classification and diagnostics throughout the study.

Incidence of ROP and frequency of treatment

This national, population-based study of infants with a GA of less than 27 weeks at birth shows that 73% develop ROP and that 20% reach treatment criteria. The high incidence of ROP in the present study is in accordance with previous studies reporting no significant reductions in major morbidities such as ROP, visual impairment and cognitive disabilities, despite improvements in the treatment of neonates in recent decades (de Kleine et al. 2007; Larsson et al. 2002; Msall 2007; Serenius et al. 2004). The incidence seems to be higher than in other population-based studies of extremely pre-term infants (Allegaert et al. 2004; Darlow et al. 2005b; Markestad et al. 2005; Tommiska et al. 2007; Weber et al. 2005). This is probably explained by the high proportion of infants in our study who were born in the earliest weeks of gestation as compared to the above-mentioned studies (The EXPRESS Group 2009). Furthermore, these extremely premature infants, who previously did not survive, are probably especially vulnerable and prone to develop complications such as ROP.

The present study showed a log-linear relationship between severe ROP and GA at birth. Darlow et al. have observed a log-linear trend in the effect of GA on infants with a gestational age of 25 to 28 weeks (Darlow et al. 2005b). Considered together, these studies suggest that the log-linear relationship between GA at birth and the risk of severe ROP is also true for the entire extremely premature period, including all infants born before 28 gestational weeks.

During the past decade several authors have reported an increase in the frequency of extremely preterm infants treated for ROP (Slidsborg et al. 2008; Todd et al. 2007). Our analyses confirm these results and show an even higher frequency than in a Danish population of infants born during the period 2001 to 2005 (Slidsborg et al. 2008), 26% (in our study) vs. 21% (in the Danish study) of infants with a GA < 26 weeks. It seems reasonable that our higher frequency is due to the higher percentage of infants born in the earliest weeks of gestation (The EXPRESS Group 2009).

Natural history of ROP in extremely preterm infants

Understanding the natural history of ROP provides us with clues about the underlying mechanisms of the disease and is important for the management of ROP, regarding both screening and treatment. Risk factors for reaching treatment criteria and elements of importance in terms of screening are discussed in the following paragraphs.

ROP has been found to develop over a relatively narrow range of PMAs and to be linked more to the developmental stage of the infant (PMA) than to neonatal events (PNA) (Fielder et al. 1986, 1992a; Holmström et al. 1993; Palmer et al. 1991; Quinn et al. 1992). This was also true for the present population, where the most immature infants developed ROP within a narrower range than found in earlier population-based studies (Fielder et al. 1986, 1992a; Holmström et al. 1993). This is not surprising, since the infants

in our population were all born within a narrower range of gestational weeks than reported in previous studies. The development of ROP in the present population was highly symmetrical in the two eyes, which has also been observed previously (Fielder et al. 1992a; Quinn et al. 1995).

Earlier natural history studies based on more mature infants born about 20 years ago found that PMA at onset of ROP was closely related to GA at birth, with the most immature infants developing ROP at an earlier PMA than the more mature infants (Fielder et al. 1986; Holmström et al. 1993; Palmer et al. 1991; Quinn et al. 1992). The age at onset of ROP and its relation to GA at birth and the severity of the disease, together with the zone/site of onset and the progression/regression of the disease, are discussed further below.

Risk factors for reaching treatment criteria

In the CRYO-ROP study, Schaffer et al found that infants ran a lower risk of reaching threshold with an increase in GA at birth (Schaffer et al. 1993). They reported that for each additional week of GA at birth, the odds ratios of reaching threshold were reduced by 19%. Our study revealed that the risk of reaching the criteria for treatment was reduced by 56% for each additional week of GA at birth. In the ETROP recommendations a multiple logistic risk model was used, integrating risk factors for unfavourable outcome in eyes that reached prethreshold ROP in the CRYO-ROP study. GA at birth is one of the risk factors integrated in this model. The natural history data in the present study revealed three other risk factors for reaching treatment criteria: 1) PMA at onset of ROP, 2) rate of progression of ROP and 3) site of onset of ROP. Regarding PMA at onset of ROP, we found a significant relation to GA at birth and to severity of ROP. The relation between PMA at onset and GA at birth, as well as the rate of progression of ROP, were also found in the CRYO-ROP study, and integrated in the risk model on which the ETROP study was based. However, two findings have not been reported previously:

the significant relations between PMA at onset of ROP and severity of ROP, and between site of onset of ROP and severe ROP. Risk factors for reaching treatment criteria are discussed in more detail below:

1) PMA at onset of ROP was closely related to GA at birth, with the most immature infants developing ROP at an earlier PMA than the more mature infants, i.e. infants with a GA of 23 weeks would on average develop ROP two weeks earlier than infants with a GA of 26 weeks. This corresponds to earlier natural history studies based on more mature infants born about 20 years ago (Fielder et al. 1986; Holmström et al. 1993; Palmer et al. 1991; Quinn et al. 1992), and was also integrated in the first risk model based on the CRYO-ROP data (Hardy et al. 1997). However, analyses of time at onset of ROP as a risk factor for progression to severe ROP revealed relations that were not found earlier. PMA at onset of ROP was significantly related to severity of ROP, even when controlling for GA, i.e. the earlier the onset of ROP, the higher the risk of developing severe ROP. This is clearly in contrast to findings in the CRYO-ROP study (Hardy et al. 2003; Schaffer et al. 1993) and might be explained by several factors. Firstly, the study designs were different, as the CRYO-ROP study was hospital-based as opposed to our national population-based EXPRESS study (The EXPRESS Group 2009). Secondly, and more likely, the advances in neonatal care in recent decades have provided us with a population of preterm infants at the limit of viability (Louis et al. 2004), and a shift in infants susceptible to ROP from more mature preterm infants towards the extremely preterm infants (Larsson et al. 2002; Todd et al. 2007).

2) Rate of progression of ROP. In the natural history cohort of the CRYO-ROP study, there was a higher risk of unfavourable macular outcome in infants with a rapid rate of progression of ROP to prethreshold disease (Schaffer et al. 1993). Further, in the multiple logistic risk model for prethreshold ROP by Hardy et al. (Hardy et al. 2003), the interval of ROP progression from onset to prethreshold level played a major role in the progno-

sis, and was least unfavourable for eyes with an interval of more than three weeks. Our results are in accordance with these findings, revealing a mean time of progression of two weeks between onset of ROP to ROP 3 in infants who reached treatment criteria, compared to three weeks in those who did not reach treatment criteria. Although the studies and treatment criteria differ and the population of infants reaching these criteria has changed during the past 20 years, we conclude that the rate of progression nevertheless predicts a risk.

3) Site of onset of ROP is another factor not included in the risk model on which the ETROP study was based, and not included in the subsequent treatment recommendations of today (Hardy et al. 2003). In our cohort of extremely immature infants, nasal onset was significantly related to the lowest GAs at birth. In addition, we found that nasal onset was related to severe ROP, even after adjustment for GA at birth. These findings confirm the tendency previously reported by Fielder et al. (Fielder et al. 1992a, 1992b) and thus, according to our results, site of onset is an additional risk factor for clinicians to consider.

Screening

In evaluating the ROP screening in this study of extremely preterm infants in Sweden, we found good compliance among participating colleagues, i.e. concerning the start, frequency and termination of screening.

Regarding the start of screening, we believe that the first examination should be done in due time to detect severe ROP and before reaching treatment criteria. The most immature infants in the present study had an earlier onset of ROP 3 than the less immature infants, but not before a PMA of 31 weeks. Because three infants with ROP 3 were found at delayed first examinations, we cannot be sure that ROP 3 did not develop before PMA 31 weeks. However, all three infants had the first examination within time for

successful treatment. Treatment was also performed earlier in the most immature infants, but not before 32 weeks.

British guidelines recommend that ROP screening should start at a PMA of 30-31 weeks in infants below 27 weeks of gestation at birth and at a PNA of 4-5 weeks in infants born at 27 to 32 weeks of gestation (Wilkinson et al. 2008). Moreover, American guidelines recommend that the first screening examination should be performed at PMA 31 weeks or PNA 4 weeks, whichever is later (Section on Ophthalmology American Academy of Pediatrics et al. 2006). However, the authors point out that the recommendations for the most immature infants (GA 22-23 weeks) should be considered tentative rather than evidence-based because of the small number of survivors (Reynolds et al. 2002). In the present study with a high proportion of infants born in the earliest weeks of gestation, we confirm that it should not be necessary to start ROP screening of infants born before 27 weeks of gestation earlier than at a PMA of 31 weeks, which would also enable timely treatment of the ROP, see Table 4.

GA at birth (weeks)	American guidelines		Present study
	PMA	PNA	Onset ROP 3 PMA
22	31	9	32.3
23	31	8	31.6
24	31	7	31.7
25	31	6	32.0
26	31	5	33.4
27	31	4	
28	32	4	
29	33	4	
30	34	4	
31	35	4	

Table 4. American guidelines (Section on Ophthalmology American Academy of Pediatrics et al. 2006) (99% confidence interval for developing serious ROP*) and Onset of ROP 3 in the present study (lower range). *Serious ROP is defined as conditions that indicate a risk of poor outcome: Prethreshold, Threshold, Any Stage of ROP with Plus disease, Stage 3 ROP with Plus disease.

At present, there is no consensus in the literature on the termination of screening for ROP. This study was not designed to study the regression of the disease and therefore we cannot draw extensive conclusions from our findings. Nevertheless, our data are in line with the American and British guidelines stating that in cases of no previous ROP, the risk of sight-threatening ROP is minimal once the retinal vessels have entered zone III. Regarding infants with ROP 2, we believe that they should be followed until regression or at least until the risk of developing treatment requiring ROP has passed. In our study, all infants had been treated by PMA 46.9 weeks.

This is in accord with findings of Reynolds et al. who reported that 99% of eyes that develop serious ROP (defined as prethreshold ROP, threshold ROP, any stage of ROP with plus disease and stage 3 ROP with plus disease) will have done so by 46.3 weeks PMA (Reynolds et al. 2002). Hence, the risk of progression to treatment criteria should be minimal after PMA 46 weeks.

The importance of screening intensity is illustrated by the limited window of time when treatment criteria are fulfilled, see Figure 4. No infant reached treatment criteria before PMA 32 weeks and 50% of the infants were treated between PMA 35 and 39 weeks (i.e. the 25th and 75th percentiles).

Further, and as shown below, the infants in the present population had a high risk of developing severe ROP and reaching treatment criteria, and the risk was closely related to GA at birth, with the most immature infants at highest risk. Consequently, screening intensity is particularly important in the most immature infants up to a PMA of at least 39 weeks. Efficient screening intensity is crucial during this time period, and we recommend that the examiner consider both the GA at birth and the PMA of the infant when deciding upon the time for the next examination. This view is in accordance with suggestions by Donahue (Donahue 2002) and Elder (Elder 2008).

We also believe that these risk factors should be included in screening guidelines to avoid intervals between examinations that are too long, leading to increased risk of treatment failure and poor visual outcome. For the time being, neither the American nor the British guidelines consider the degree of immaturity at birth or the PMA at the time of examination in the recommendations for screening intervals (Section on Ophthalmology American Academy of Pediatrics et al. 2006; Wilkinson et al. 2008).

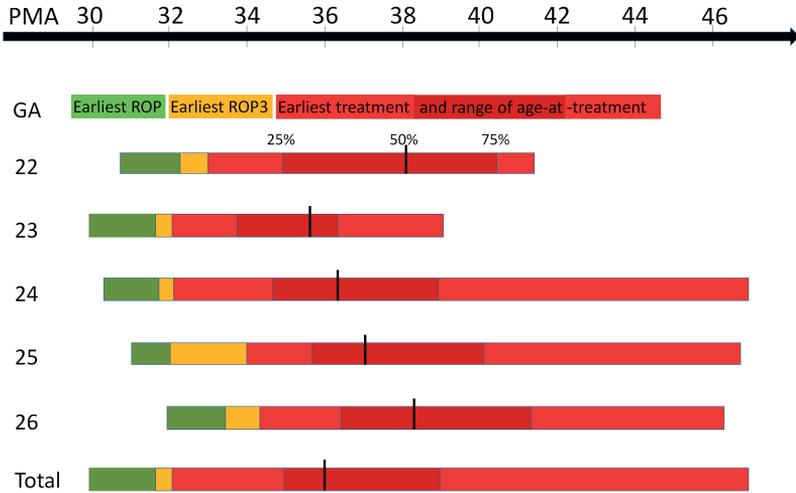


Figure 4. Postmenstrual age (PMA) at onset of earliest retinopathy of prematurity (ROP) (green bars), earliest ROP 3 (yellow bars) and earliest treatment for ROP (red bars, including the range of age-at-treatment with 25th, 50th and 75th percentiles) in relation to gestational age (GA) at birth.

Conclusion

In summary, the present population-based study of infants born extremely preterm showed a high risk of ROP and of reaching treatment criteria. The risk was significantly related to GA at birth. The natural history of ROP in this population of infants born before 27 weeks of gestation did not differ much from less immature populations. However, the study clearly revealed some new findings which should be taken into account when screening extremely preterm infants, i.e. both the time and site of onset of ROP were significantly related to the severity of the disease. We believe that the present study contributes to the knowledge of ROP in extremely preterm infants born at the limit of viability. Further, it emphasises the importance of efficient screening programs to detect and treat severe ROP and to reduce future visual handicaps.

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