The Netherlands Retinopathy of Prematurity Study

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CONTENTS

ABBREVIATIONS

AV	Artificial ventilation
BPD	Broncho-pulmonary dysplasia
BW	Birth weight
CLD	Chronic lung disease
DOB	Date of birth
GA	Gestational age
IGF-1	Insulin-like Growth Factor-1
IQR	Interquartile range (P25-P75)
iNO	inhaled nitric oxide
LOS	Length of stay
Mild ROP	ROP stage 1 and 2
NEDROP study	The Netherlands ROP study
NICU	Neonatal intensive care unit
PNA	Post natal age
PMA	Post menstrual age
PPM	Parts per million
PRN	The Netherlands Perinatal Registry
ROP	Retinopathy of prematurity
Severe ROP	ROP stage ≥ 3
VEGF	Vascular endothelial growth factor


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Chapter 1

Introduction

Retinopathy of Prematurity (ROP) is an important cause of partial sight or blindness in prematurely born infants. Worldwide assessment in 2010 estimated that 21.8% of preterm born infants born has some degree of ROP.[1] Incidence figures for ROP and visual disability due to ROP differ however per country, region or continent. Worldwide ROP accounts for 17.5% of visual impairment in prematurely born babies.

In middle income countries like many Latin American and Asian countries and the Former Socialist Countries of Eastern Europe, ROP is emerging as a major cause of blindness (also referred to as the "third epidemic").[2] Possible reasons for this epidemic are:

- birth rates and rates of premature birth are increasing;
- neonatal care may be compromised as a result of limitation of resources, resulting in higher rates of severe ROP not only in extremely premature infants but also in bigger, more mature infants; and
- no nationwide implementation of screening and treatment programs due to the lack of awareness, skilled personnel and/or financial resources.[3]

For example, a third of all children under the age of ten in schools for the visually impaired in Vietnam and more than 40% of under-5 years of age in similar schools in Mexico are blind as a result of ROP.[4] In lower income countries the incidence of ROP is low as neonatal care is not well developed, so less premature infants survive.[5]

Permanent visual damage will increase with increasing prematurity of the infant. Over the past two decades changes in neonatal care have increased the survival rate of very small and very preterm infants, also in the Netherlands. Significant progress in health care practice like the introduction of surfactant, increased use of antenatal steroids, resuscitation of infants with lower gestational ages, improved nutrition and prophylactic use of indomethacin have contributed to this increased survival. Consequently an increasing number of infants is at risk, not only for visual impairment (VI) caused by ROP or cerebral visual impairment (CVI), but also for non-visual disabilities.[6-10] Termote et al found a significant increase in behavioral abnormalities in infants with visual impairment due to ROP, born between 1994 and 2000.[11]

The last national survey in the Netherlands showed that 8-10 infants per year become visually disabled or blind as a consequence of ROP.[11] Visual impairment due to ROP can be decreased by timely screening, thorough follow up and prompt treatment of neonates who are at risk. So a dedicated screening program is indispensable. However, as reported, incidences of ROP strongly depend on study cohort, level of care and country, so screening guidelines cannot be applied uniformly in different countries. For that reason it is important to define and to inventorize the population at risk for potentially blinding ROP and to provide evidence for a quality guideline per country.

HISTORY

ROP was first reported in 1942 by Terry, who described the histological findings of what would now be considered end-stage, cicatricial disease but back then was called retrolental fibroplasia (RLF).[12]

The first ROP epidemic, occurring in the USA from the 1940s until late 50s, was caused by administering high doses of oxygen to premature infants without monitoring; pulse oximetry was not yet available.[13-19] As a reaction to this, attempts were made to curtail oxygen use in the premature nursery by administering oxygen only at times of clinical need, as short a period as possible and at concentrations less than 40%.[20] Although rates of ROP decreased, cerebral palsy and death increased, blocking the implementation of a restricted oxygen regimen.[17;18]

With the introduction of pulse oximetry in the 1970s, oxygen administration became more controlled and it was anticipated that ROP would disappear. Research by Patz[14] and by Kinsey et al[16], and laboratory experiments by Ashton[21], suggested that ROP could be entirely preventable by thorough oxygen regulation. Unfortunately, this proved not to be the case.

In the 1970's ROP incidence once again increased, referred to as the second epidemic, now as a consequence of increased survival rates of extremely premature babies.[22] In those days ROP screening was performed by neonatologists who performed external examination of the eyes as well as direct ophthalmoscopy. However, by the time pathological retinal changes were evident to the neonatologist the disease was usually very advanced. This called for examination by experienced ophthalmologists. In 1976 the AAP (American Academy of Pediatrics) issued the first screening guideline and recommended that screening examinations for ROP should be performed at the time of discharge from the nursery and at three to six month of age.[23] The median length of stay in the neonatal intensive care unit (NICU) at that time was 61 days (almost 9 weeks) for those with a birth weight (BW) of 751-1000gr, and 30 days for those with BW 1000-1250gr. If there were no fundus abnormalities on discharge from the hospital, no follow-up eye examinations were planned.

Palmer found that the optimal age to detect acute RLF was at age 7-9 weeks and that, for optimal ROP detection, the initial examination should not only occur at about 6 weeks of life but should also be performed by an ophthalmologist.[23] Ideally the fundi should at least twice be classified as normal with an interval of 4 weeks before final discontinuation of screening. Palmer et al[24] also suggested that, if high-risk infants (<1700gr) were discharged or transferred to another hospital prior to an age of 6 weeks, screening should be postponed and not be performed at discharge. He reasoned that parents could have a false sense of security from a normal eye examination and could wrongly decide to refrain from further screening. When this first examination was postponed, the

numbers of infants lost to follow up would be smaller and ROP could still be detected in time to be able to treat infants with severe disease.

In the late '60s treatment of acute ROP with Xenon-arc photocoagulation and cryotherapy were introduced.[25] Cryo-ablation therapy of the avascular retina, freezing from the external ocular surface, affecting the sclera, choroid, and the full thickness of the retina, emerged as the standard treatment for acute phase ROP in the 1980's.[26]

In 1988 the Cryotherapy for Retinopathy of Prematurity Cooperative Group trial (CRYO-ROP) showed the beneficial effect of cryoablation of the peripheral avascular retina and significantly reduced the progression of threshold ROP, which if left untreated carries a risk of blindness up to 50%.[27] The 10-year follow-up showed that 44.4% treated vs 62.1% untreated had visual acuity of 20/200 or worse. At 15 years, the rate of unfavorable outcomes was 30% for treated eyes and 51.9% ($p<0.001$) for eyes that were observed without cryotherapy.[28;29]

In the 1990's Laser (light amplification by stimulated emission of radiation) therapy evolved as the primary modality of treatment, in which a laser is applied through the dilated pupil to the internal retinal surface. Compared to cryotherapy, fewer complications were described. Given the greater ease of treatment with laser a randomized, controlled trial was elaborated in 2003 to prospectively assess the effects of early laser treatment for ROP: The Early Treatment of ROP (ETROP) study.[30] This study confirmed the efficacy of treatment for severe ROP and redefined the indications for treatment.[31] The clock hours and the terminology of threshold and pre-threshold were abandoned and a new categorization of ROP was introduced in which ROP was defined in two types.

Also during the mid-1980s, after decades of discussion regarding the nature of the pathogenesis and the clinical course of ROP, a group of ophthalmologists representing 11 countries and sharing a common interest in ROP, decided that an international classification of ROP was required. They developed the International Classification for ROP (ICROP).[32] Later, in 1988, they added a section on the classification of retinal detachment.[33]

In 2005 the ICROP needed revision as new presentations of ROP occurred in infants with GA of 25 weeks or under and the role of the retinal vessels for the decision to treat had changed as a result of the ETROP study. An extra stage and a definition of (pre-)plus disease were added, clock hours were no longer included.[34]

CLASSIFICATION

The revised ICROP uses the following criteria to score ROP:

- location of retinal involvement specified as zone I-III
- the degree of peripheral vascular abnormalities
  - o stages 1-5, with stage 5 being the most severe (figure 1)
  - o aggressive, posterior ROP (APROP), an aggressive form of ROP, not following the classical stages 1-5
- plus- and pre-plus disease to describe specific features of the retinal vessels. The designation 'plus' is added to the ROP stage number

Zones to define the location of the disease:

Zone I: the area within a circle with a radius of twice the distance from the optic disc to the center of the macula.

Posterior Zone II: the area within the dotted circle with a radius of three times the distance from the optic disc to the center of the macula.

Zone II: extends from the edge of zone I and with the peripheral border the edge of a circle with a radius equal to the distance between optic disc and nasal ora serrata.

Zone III: extends from the edge of zone II. It is only entered with certainty when the nasal retina is fully vascularized.

The zone that is affected by the disease is important because it reflects the extent of the outgrowth of the retinal vessels. The lower the zone, the larger the avascular area resulting in the highest risk for severe ROP. Zone I or posterior zone II are therefore associated with a bigger chance of progression of disease or need of treatment.[35]

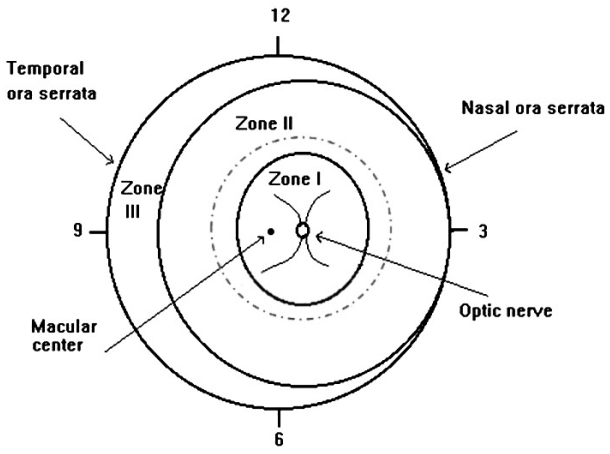

Figure 1 Retinal zones

Stages to classify the severity of the disease:

Stage 1: Characterized by a demarcation line: A thin, flat white line, seen between the vascular and avascular retina.

Stage 2: Characterized by a ridge: an elevation or thickening of the retina in the region of the demarcation line.

Stage 3: Characterized by a ridge with extraretinal fibrovascular proliferation.

Stage 4: Characterized by partial retinal detachment and subdivided in;

Stage 4a: Partial detachment not involving the foveal region

Stage 4b: partial detachment involving the foveal region

Stage 5: Characterized by total detachment of the retina, forming a funnel shape. The funnel is divided in an anterior and posterior part, for descriptive purposes. And both parts can be open or closed.

Anterior	*Posterior*
Open	Open
Narrow	Narrow
Open	Narrow
Narrow	Open

APROP: Characterized by neovascular fronts that lay flat on the retinal surface. No ridge is seen in these eyes, and yet the AV shunting, which occurs within the ridge tissue in more typical ROP, is seen throughout the posterior pole. Vessels are dilated and tortuous in a syncytial pattern. ROP is confined to zone 1 or posterior zone 2.
Most critical feature: may progress directly to severe ROP, without interval findings typical of stage 1 or 2 ROP.

Pre-plus disease: A description of an intermediate level of plus disease (pre-plus) between normal aspect of posterior pole vessels and frank dilation as in plus disease.

Plus disease: Defined as an increased dilation of venules and tortuosity of arteries of the retina in at least 2 quadrants in the posterior pole, whether or not accompanied by engorgement of iris vessels, pupil rigidity and vitreous haze. Plus disease implies that the ROP process is (highly) active and progression may be rapid.

Stages 1 and 2 and any other phase without plus disease are usually considered mild since most cases resolve spontaneously without major visually disabling sequelae.[36] ROP with plus disease and stages 3 - 5 are considered severe, as they have a significant risk of poor visual outcome. Stage 4a eyes that remain stable usually maintain reasonable

vision but progression to stages 4b and 5 (being associated with retinal detachment involving the macular area) always carry a poor prognosis for vision.

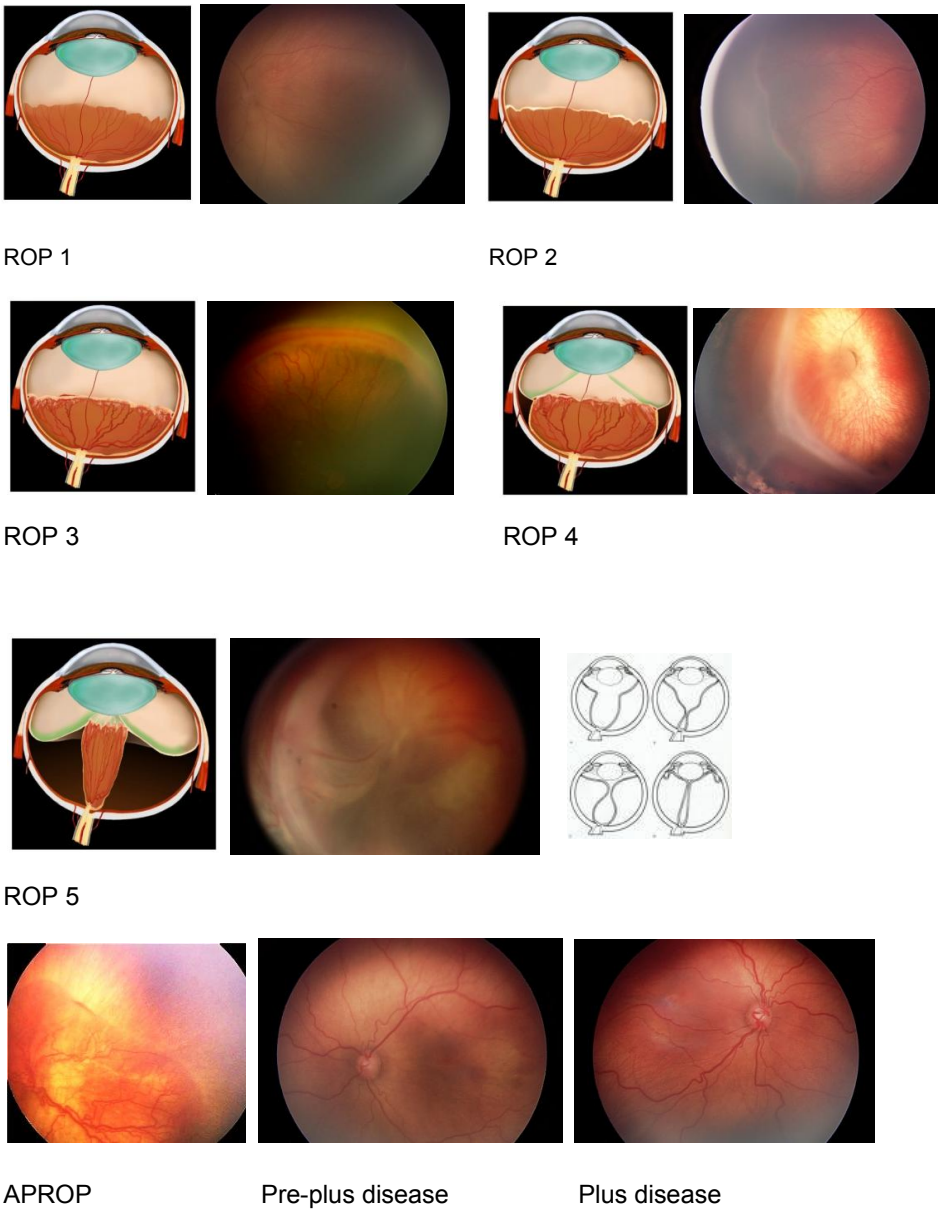

Figure 2 Photo's depicting the different stages of ROP
Schematic pictures are published with approval of ROPARD.
Retcam images from MMC Veldhoven and LUMC.

PATHOFYSIOLOGY

From the 16th week of gestation the retinal vessels start growing from the optic disc to the periphery of the retina. The retina is fully vascularized at the nasal side at 32 weeks and the temporal side around 40 weeks of gestation.[37] Infants born prematurely have incompletely vascularized retinas with a peripheral avascular zone.[38] Two processes underlie vascular development. The first process, termed vasculogenesis, involves the de novo establishment of a rudimentary vascular plexus, and is completed at 21 weeks GA. The second process is termed angiogenesis and involves the development of new vessels from already existing vessels and is initiated by 17–18 weeks GA.[39] When there is a significant disruption in the angiogenesis, ROP may develop.

After premature birth, there is not only a change in oxygenation of the retina but also a loss of maternally derived factors that contribute to normal retinal vessel formation.[40] This may compromise normal vascular development.

Retinopathy of prematurity is a biphasic disease, consisting of an initial phase of vessel growth retardation called the vaso-obliterative phase, followed by a second phase the vaso-proliferative phase. The vaso-obliterative phase is initiated upon birth of the premature infant. The extra-uterine environment is relatively hyperoxic for the infant, and by use of additional oxygen this hyperoxia increases. In response to the elevated levels of oxygen, expression of hypoxia-driven angiogenic factors, like vascular endothelial growth factor (VEGF) and Erythropoietin (EPO) are downregulated: vessel growth ceases and already formed vessels constrict and retract.[41]

The vaso-proliferative phase usually develops after 32 week GA. Because of maturation of the retina, there is an increase in the metabolic activity in the incompletely vascularized areas causing hypoxia. This hypoxia leads to stabilization and translocation of hypoxia-inducible factors (HIFs). HIF-1 is rapidly degraded during normoxia, but in hypoxic conditions, its half-life is prolonged, promoting its nuclear accumulation. Of the hypoxia-inducible factors, HIF-1α is considered the primary hypoxic signaling molecule, leading to stimulation of transcription of angiogenic factors like VEGF and EPO that stimulate new vessel growth.[42] The reduction of HIF-1 is essential for the initiation and progression of the first phase of ROP, whereas its increase is essential for the second phase.[43]

VEGF is necessary for normal vascular development and maintenance of growth. Its production is oxygen-regulated and is found to be important in both phases of ROP.[44] VEGF is likely to be the factor with the strongest influence on vascular activity in ROP eyes.[45]

EPO has a main function in erythrocyte formation in the bone marrow and plays a role in angiogenesis, independent of VEGF.[45] The exact role of EPO in retinal neovascularization is still not well elucidated but it has been reported that it stimulates cell proliferation, migration, tube formation and permeability, just like VEGF.[46]

Hypoxia stimulates overproduction of VEGF and EPO, inducing angiogenesis that can lead to the formation of new vessels of bad quality (neovascularization) at the verge of avascularized and vascularized retina, that can regress if adequate oxygenation is provided to the avascular retina.
Also other molecules with angiogenic or anti-angiogenic properties appear to play an important role either by inter-acting with VEGF or by acting independently as is seen with IGF-1.[47]
Nitric oxide (NO•) and nitric oxide synthase (NOS) are oxidative and nitro-oxidative stress-dependent mediators that are increased in retinal hypoxia. Nitric oxide (NO) is a key signaling molecule that mediates neurotransmission, vasodilatation and host cell defense. NO• triggers the gene expression of several angiogenic, cell-migration and proliferation-inducing factors, including VEGF.[48]
Hypoxic injury increases retinal mRNA and protein expression of endothelial nitric oxide synthase (eNOS), leading to increased NO production and, consequently, vasodilatation and angiogenesis.[49]

Maternally derived factors that play a role in the pathogenesis of ROP are insulin-like growth factor–I (IGF-I) and omega-3 polyunsaturated fatty acids (PUFA).
Insulin-like growth factor (IGF-I) is produced by the placenta and an important factor in normal retinal vascular development.[50] Under normal conditions the concentration of IGF-I in the foetus increases during the third trimester of pregnancy, but in case of preterm birth, IGF-I concentration decreases rapidly, as the placenta can no longer supply IGF-I.[51] As the infant matures, IGF-I levels slowly increase, and metabolic activity of the nonvascularized retina increases, leading to tissue hypoxia. For normal vascular development and outgrowth, concentrations of VEGF and IGF-1 need to be in balance with each other. If the balance is disrupted ROP can develop (fig 3), if the balance is established than regression of ROP can be seen and normal vessel outgrowth can develop.

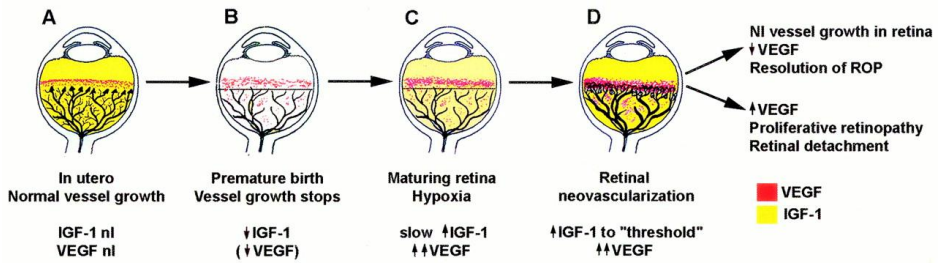

Figure 3 Schematic representation of IGF-I/VEGF control of blood vessel development in ROP.
Adapted from: Hellström et al, Proc Natl Acad Sci USA 2001; 98: 5804-8.

Another maternally derived factor is PUFA that potently protects against neovascularization. Retinal lipids have a very high content in long-chain poly-unsaturated fatty acids (PUFA). The major PUFA's found in the retina are omega-3 and omega-6. These lipids are essential fatty acids. They have to be of exogenous origin since the human body cannot synthesize their precursors.[48] Omega-3 PUFA is mainly transported in the third trimester of pregnancy and infants born before miss that infusion of specific lipid. Deficiency of omega-3 PUFA causes retardation of retinal vessel growth.[52]
It may be evident that a large number of mediators are involved in the pathogenesis of ROP. Every step in a better understanding of the complex molecular mechanisms underlying the pathogenesis of ROP will hopefully allow the development of new therapies to prevent or treat ROP.

ETIOLOGY

The etiology of ROP is multifactorial, but the most important risk factors are birth weight and gestational age of the premature born infant.[53-57] Other frequently found risk factors are: length of stay on a neonatal intensive care unit (NICU)[58], duration of artificial ventilation (AV)[59;60], administration of postnatal glucocorticoids[59;60], duration of oxygen supplementation and fluctuations in oxygen saturation levels.[57;61] [55] Perinatal infection/inflammation or sepsis and necrotizing enterocolitis (NEC) are published as a risk factor for (severe) ROP.[62-66] Another study found that male gender has a significantly increased risk to develop ROP.[67] More recently published risk factors are hyperglycaemia[68;69], slow weight gain during the first 3-4 weeks after birth[56] or poor growth.[70]
From the 1940s onwards, the toxity of oxygen in relation to ROP has been studied. Hypoxia induced oxidative stress to the developing vessels is not only caused by supplemental oxygen but also mediated by the hypoxanthine-xanthine system generating oxygen radicals. This causes capillary damage through toxic effects on endothelial cells, vaso-obliteration, shunt formation and subsequent neovascularization of vessels.[21;71]
The role of blood transfusions and the association with the development of ROP has been confirmed in several studies.[63,72,73] A Dutch cohort study showed that more than three blood transfusions, given in the first 4 weeks after birth, increased the risk to develop ROP significantly.[74] Red blood cell (RBC) transfusions are associated with an increased risk for ROP as they increase retinal oxygen levels by an increase in oxygen carrying capacity and a decrease in oxygen affinity of the red blood cell. The latter is caused by the fact that infants are usually transfused with adult hemoglobin, which has a reduced oxygen affinity compared to fetal haemoglobin.[75] An additional explanation may be that blood transfusions increase the free, non-protein bound iron load. Non protein bound iron may react with various intermediates of oxygen. It converts less reactive radicals

such as hydrogen peroxide and superoxide to the highly reactive, free hydroxyl radical. Free oxygen radicals are assumed to play an important role in the pathogenesis of ROP as they cause direct, irreversible damage to the developing retinal vessels by damaging the endothelial cell membrane, its mitochondrion and its nucleus.[76] An unintended side effect of RBC transfusions could be the concomitant administration of IGF-1. Hübler et al[77] showed that the IGF-1 load in RBC transfusions is equivalent to a single dose of 1 µg/kg, which is 5-10% of the adult dose. IGF-1 is an important mediator for the development of retinal vessels. Hellström et al showed that in a period of rapid increase of IGF-1 in combination with high levels of VEGF, rapid growth of new vessels takes place.[78] Therefore, supplemental administration of IGF-1 via RBC transfusions may thus trigger a rapid growth of neovascularizations as seen in the development of severe ROP.
Regarding transfusions, infants with twin-twin transfusion syndrome (TTTS) are of interest. Due to severe anaemia, donor infants need high numbers of RBC transfusions facilitating the development of severe ROP.[79]
All above mentioned risk factors have in common that they are indicators for the severity of illness of the infant.[55;80]

PROTECTIVE FACTORS

A few factors are associated with a reduced risk for ROP, and thus related with a lower incidence of ROP: prenatal glucocorticoids, female gender, surfactant and oxygen.[67;81]

Prenatal glucocorticoids
The beneficial role of antenatal glucocorticoids on the severity of ROP is described by Higgins et al.[81] Given before birth, maturation of the fetal lung is stimulated, resulting in a reduction in respiratory distress syndrome (RDS), associated with decreased morbidity and mortality.[82;83]

Female gender
Darlow et al[67] identified gender as a risk factor for ROP finding a significant increase of ROP in boys. The study of Binet et al[84] found no difference in the rates of ROP between the two gender groups. But males had poorer respiratory outcome, were more likely to have an adverse neonatal outcome or had a higher mortality than females. They hypothesize that antenatal glucorticoids do not benefit males as much as females.[84] Several studies describe an advantage in the survival of girls among premature infants supposedly related to differences in hormonal milieu and illness severity.[85;86]

Surfactant

Respiratory distress syndrome (RDS) is caused by a deficiency or dysfunction of pulmonary surfactant. Surfactant lines the alveolar surface and prevents atelectasis by reducing surface tension. Its concentration is often decreased or even lacking in the lungs of very preterm babies and therefore surfactant replacement therapy has been used for the treatment of RDS since the eighties. Beneficial effects on ROP can be explained by earlier stabilization of the RDS, less RDS-related morbidity, a decrease in duration of supplemental oxygen, a decrease in mean fraction inspired oxygen administration and less fluctuations in oxygen saturation. The influence of surfactant therapy on overall incidence and the incidence of severe ROP has been investigated. Some studies found a decrease in severe ROP, others did not find a protective effect.[87-90] To evaluate if the timing of administration of surfactant influences mortality and morbidity a Cochrane review has been performed.[91] Early (within the first two hours of life) versus delayed surfactant administration to infants with established RDS requiring assisted ventilation showed a decreased risk of acute pulmonary injury (decreased risk of pneumothorax and pulmonary interstitial emphysema) and a decreased risk of neonatal mortality and chronic lung disease compared to delaying treatment of such infants until they develop worsening RDS. No difference was found between early versus delayed surfactant administration regarding all stages or stage 3 or more ROP.[92-95]

Oxygen

Although oxygen in general is considered a risk factor for ROP, the role of oxygen to reduce the risk of severe ROP is extensively studied and will be discussed in more detail. The Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP) trial found that higher oxygen saturation levels (96-99%) as compared with lower levels (89-94%) did not significantly reduce the risk of severe ROP, but a subgroup analysis suggested that infants with prethreshold disease without plus disease could benefit from these higher levels.[96] Other studies[61;97;98] describe that lower oxygen saturation levels during the first weeks of life decrease the incidence of ROP and of severe ROP, but are also associated with a higher mortality. To answer the question whether infants should be kept at low or high oxygen saturation in the period after birth, five multicenter randomized trials were recently analyzed in the Neoprom study.[99] The trials included were the SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial)[100;101], the three BOOST trials (Benefits of Oxygen Saturation Targeting) from the UK, Australia and New Zealand[102], and the Canadian Oxygen Trial (COT).[103] A total of 4911 infants with GA < 28 weeks were randomized to low (85–89%) or high oxygen saturation (91–95%) in the first 24 hours after birth and relative risks (RR with 95% confidence intervals) were calculated for mortality and morbidity. A RR>1.0 favored high oxygen saturation. The primary outcome of the SUPPORT was severe ROP / death before discharge, for the BOOST II

death or severe disability at 18-24 months and for the COT death before 18 months or severe neurosensory outcome. The RR for mortality (1.41; 114-174) and necrotizing enterocolitis (1.25;1.05-1.49) was significantly increased and for severe ROP (0.74;0.59-0.92) significantly decreased in low versus high oxygen saturations. No differences were found for bronchopulmonary dysplasia, patent ductus arteriosus and injury to the brain. The conclusion of the Neoprom meta-analysis was that in infants <28 weeks low saturation targets (85–89%) until 36 weeks postmenstrual age (PMA) are associated with more deaths and more NEC and higher saturation targets (91–95%) are associated with more ROP. Based on these figures the final advice of the Neoprom is to target SpO_2 at 90-95% in infants born before 28 weeks until 36 weeks PMA, although this might result in more infants developing ROP.

NATURAL COURSE

ROP is in general a symmetrical disease and both eyes are usually evenly affected. In most infants ROP regresses spontaneously. When ROP develops, it normally progresses with one stage per week, except for APROP.

In studies two different definitions for the age of an infant are used:

- PNA: post natal age: number of days or weeks after birth, and
- PMA: post menstrual age: gestational age plus the days or weeks after birth

The first signs of ROP develop between 5–7 week post natal age (PNA).

In the Natural History Study of Fielder[104] the PMA at which ROP developed ranged from 29.7 to 45.0 weeks. Furthermore it is known that severe ROP does not develop before 31 weeks post menstrual age (PMA) or 4-5 weeks PNA.[105,106]

Comparing the outcomes of the CRYO-ROP and ETROP study onset of the different stages of ROP appears to be consistent: stage 1 at 34.3 vs 34.1 weeks, stage 2 at 35.4 vs 35.1 weeks, stage 3 for both at 36.6 weeks and plus disease at 36.3 vs 36.0 weeks PMA.[107] Larsson et al[105] found a PMA for severe ROP of 36.1 (32–44) weeks. Hains et al[108] found a mean PNA at first diagnosis of stage 3 ROP at 10.8 (4–24.7) weeks and at mean PMA 36.6 (30.8–51.7) weeks.

In most cases, spontaneous regression of ROP usually occurs within 15 weeks from onset[109] without serious secondary damage in eyes with stages 1, 2 and early stage 3 ROP, while serious visual impairment or blindness results from progression to retinal detachment (stage 4 or 5) or severe distortion of the macular area.[110] The incidence of spontaneous regression of ROP stage 1 was between 86.7 - 85%, stage 2 between 57.1-56% and stage 3 between 5.9-6.0%.

With vascular changes in zone III regression was detected in 95-100%, in zone II in 45-46.2% and in zone I in 0-6%.[111;112]

SCREENING

Worldwide different screening criteria are used.
The guideline of the UK developed by the Royal College of Pediatric & Child Health, recommends screening for all infants with a birth weight ≤ 1,500 g or a gestational age of ≤ 31 weeks.[113]
The American guideline advises to screen all infants with a birth weight (BW) <1.500 g or a gestational age (GA) ≤ 30 weeks, as well as selected infants between 1.500 and 2.000 g and selected infants > 30 weeks GA with an unstable clinical course, including those requiring cardiorespiratory support and those who are believed to be at high risk for ROP by their attending pediatrician or neonatologist.[114]
The Canadian guideline recommends screening of infants with a BW ≤ 30 weeks or BW ≤ 1500 g (www.eyesite.ca).
The Guideline of Germany uses the inclusion criterion of GA < 32 weeks or when GA is unsure, a BW < 1500 g.[115] Infants with a GA between 32-36 weeks and > 3 days in need of extra oxygen administration should also be screened.
The screening criterion of Sweden is GA ≤ 31 weeks.[105] The inclusion criteria for screening in the Netherlands, as defined in 1997, were all infants with GA<32 weeks and/or BW< 1500 g and all those needing >40% oxygen for more than 3 days.

The timing for follow-up screening is grossly the same in all the aforementioned countries:
Twice a week: ROP in Zone I including suspected presence of APROP.
Weekly screening: avascular retina in zone I or posterior zone II; with (pre) plus disease; ROP 3 in every zone; ROP 2 in zone II and ROP 1 in zone I.
Every 2 weeks: avascular retina or ROP 1 in zone II; ROP in regression in zone II; avascular retina in zone III with or without ROP.
Every 2-3 weeks: avascular retina in zone II; ROP 1 or 2 in zone III; regression of ROP in zone III; and when regression is seen with follow up examinations.

Last screening
When there is no risk for the development of vision-threatening ROP, screening can be discontinued. If the retina is fully vascularized ROP can no longer develop. When the vessels have grown to zone III the chance of developing severe ROP is minimal.
According to the UK guideline screening may be stopped when apparent regression is seen. The definition of regression has been described in the ICROP.[34] The German guideline advises to end the screening at 40 weeks PMA. When the condition of an infant deteriorates, a reactivation of ROP can be seen and screening should be restarted.

Screening models

Several attempts are made to define risk factor models predicting the chance to develop ROP with the ultimate goal to focus screening on those infants that are really at risk to develop ROP and reduce the overall number of screening examinations.
Preconditions for these models are:

- easy to execute,
- high predictive score so no infants with severe ROP will be missed and
- applicable for different countries.

Four ROP screening models based on postnatal course were developed: WINROP, ROPScore, Cumulative Illness Severity (CIS) and a model based on Clinical Risk Index for Babies (CRIB) score, multiple birth, race and gender.[86;116-119]

WINROP

The WINROP[116] model is an algorithm using postnatal weight measurements, as a tool for the prediction of ROP. Weight measurements are entered into the WINROP database, which triggers an alarm for an abnormal weight gain rate. Infants were classified into categories of no alarm (unlikely to develop type 1 ROP) and alarm (at risk for developing type 1 ROP). Use of WINROP requires that an infant has:

- gestational age less than 32 weeks at birth,
- weekly weight measurements,
- physiologic weight gain, and
- absence of other pathologic retinal vascular disease.

Studies to evaluate the efficacy of WINROP in predicting the need for treatment have been done in different countries: in China the predictive score was 87.5%[120], in Mexico 84.7%[121] and in a Swedish cohort 96%.[122] A retrospective cohort study in South East Scotland emphasizes that WINROP should be used as recommended i.e. using weekly birth weights. They found a sensitivity of 73% when missing BW data were extrapolated and a sensitivity of 87% when BW had been measured weekly.[123]

ROPScore

The ROPScore model is based on risk factors for the onset of ROP and includes data on BW, GA, weight gain proportional to BW measured at 6 weeks of life, the use of oxygen in mechanical ventilation and the need for blood transfusions. ROPScore is calculated automatically when data are inserted. Points are given if risk factors are present. If the score is above 14.5 there will be a higher risk to develop severe ROP than in infants with lower scores. Eckert found a sensitivity of 98% and a specificity of 56% in a cohort of 474 Brazilian infants.[117]

CIS

The third model, Cumulative Illness Severity[118], works with cumulative neonatal illness severity and illness severity fluctuation as predictors of progression from moderate to severe ROP. It is measured using daily Scores for Neonatal Acute Physiology (SNAP) for the first 28 days of life, and illness severity fluctuation as assessed by summing up changes between daily SNAP scores. The physiology-based SNAP score is calculated from 34 biological parameters including vital signs and laboratory values. Cumulative SNAP score for the first 28 days of life (SNAP28) was calculated by addition of daily SNAP scores for each subject. The cumulative SNAP score, turned out to be an independent risk factor for progression from moderate to severe ROP, but after adjustment for different risk factors, it did not enhance assessment of risk for ROP. As it is also time consuming to execute, CIS seems less applicable as easy screening tool.

CRIB

The Clinical Risk Index for Babies score (CRIB)[86] estimates illness severity using data collected in the first 12 hours after birth. The parameters are birth weight, gestational age, congenital malformation, maximum base excess and maximum and minimum appropriate FiO_2 (fraction of inspired oxygen). Yang et al investigated 5 models based on CRIB score, multiple birth, race and gender. Their primary outcome variable was ROP warranting surgery and they found that nonblack race, male gender, and higher CRIB illness severity scores were significant predictors. They also excluded BW and GA from the CRIB score and found that the CRIB-score remained a highly significant independent predictive factor for ROP warranting surgery.

All these prediction models need further validation before they can possibly replace established screening programs. They can however help to reduce the frequency of screening exams in low risk infants.

TREATMENT

The goal of treatment is to decrease the production of angiogenic factors and to stop retinal neovascularization by inactivation of the avascular peripheral retina.
The Cryotherapy for Retinopathy of Prematurity Cooperative Group trial (CRYO-ROP) showed the beneficial effect of cryoablation of the peripheral avascular retina.
Two types of ROP were distinguished, namely threshold and pre-threshold ROP.
Threshold ROP was defined as at least 5 contiguous or 8 cumulative clock hours of stage 3 ROP in zone I or II in the presence of plus disease. Pre-threshold ROP was defined in relation to the location of the disease, for zone I: any stage less than threshold and

for zone II: stage 2 ROP with plus disease, or stage 3 ROP of any amount without plus disease, or stage 3 ROP with less than 5 contiguous or 8 cumulative clock hours with plus disease. When lasertreatment started to replace cryotreatment the Early Treatment of ROP (ETROP) study was performed which confirmed the efficacy of treatment for severe ROP and redefined the indications for treatment.[30;31] The clock hours and the terminology of threshold and pre-threshold were abandoned and a new categorization of ROP was introduced in which ROP was defined in two types, where type 1 needed immediate treatment and type 2 warranted thorough observation:

- Type 1:
  - ROP in zone I, with plus disease;
  - ROP 3 in zone I, with or without plus disease;
  - ROP 2 or 3 in zone II, with plus disease.
- Type 2:
  - ROP 1 or 2, in zone I, without plus disease;
  - ROP 3 in zone II, without plus disease.

The ETROP study was a randomized, prospective multicenter trial comparing the safety and efficacy of earlier vs. conventionally timed ablation of the peripheral retina for the management of moderate to severe retinopathy of prematurity (ROP). Infants with birth weights <1251 g were screened and the total sample size for the randomized trial consisted of 401 infants. Only prethreshold eyes that had a high risk of an adverse outcome were randomized for early treatment. The primary outcome measure was rating visual acuity measured by Teller acuity card. The secondary outcome measure was retinal structure, assessed by ophthalmological examinations conducted at 6 and 9 months post-term.
At six year follow-up an unfavourable outcome was seen in type 1 ROP with early treatment in 25.1% and in type 1 ROP treated at threshold in 32.8% ($p < 0.001$). A visual acuity (VA) worse than 20/200 was found in 24.7% for those treated at pre-threshold vs 29% for those treated at threshold ($p=0.15$).[124]

Definitions of favorable and unfavorable outcome[28] of treatment according to ETROP:

Favorable:

- Essentially normal posterior pole (near periphery and zone I), including angle of vessels
- Abnormal angle of major temporal vascular arcade in the posterior pole
- Macular ectopia
- Stage 4A partial retinal detachment, also including retinoschisis, or fold in the posterior pole (fovea spared)

Unfavorable:

- Stage 4B partial retinal detachment, also including retinoschisis, or fold-all with foveal involvement
- View of macula (and presumably patient's central vision) blocked owing to partial cataract, partial retrolental membrane, or partial corneal opacity due to ROP
- Stage 5 total retinal detachment, or total retinoschisis, or retrolental membrane (blocking all view of fundus)
- Entire view of posterior pole and near periphery blocked by total cataract or total corneal opacity from ROP
- Enucleation for any reason
- Unable to grade or determine or none of the above

To calculate improved vision after treatment according to ETROP criteria vs CRYOROP criteria one has to compare no treatment vs treatment. For the CRYO-ROP study cryo-therapy vs no treatment meant 44.4 vs 62.1% = 17.7% improved vision. In the ETROP study no comparison was made between no treatment and laser as this was considered unethical. So the improved vision in this study is the difference between 25.1% vs 32.8% resulting in 7.7% less infants with VA < 20/200.
The total improved vision is determined by summing the results of CRYO-ROP and ETROP, which would result in 17.7 + 7.7= 25.4% improved vision after early treatment.
With the ETROP classification more emphasis came on the presence of (pre)plus disease, and the extent of avascularity, defined by zone. Nowadays this is the most important treatment algorithm.

With laser and cryo-therapy the treated areas of the retina are permanently damaged and lose their function. Different new possibilities for treatment are being investigated, that might save peripheral retina, the main being treatment suppressing VEGF production by intraocular injections.
To study the efficacy of anti-VEGF drugs, preclinical studies have used models of oxygen-induced retinopathy (OIR) that develop hypoxia-induced intravitreal neovascularization (IVNV).
The Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) study is the first prospective, controlled, randomized, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ ROP compared to conventional laser.[125] The primary ocular outcome was recurrence of retinopathy of prematurity in one or both eyes requiring retreatment before 54 weeks' postmenstrual age. Recurrence of ROP was 4% in the bevacizumab group vs 22% in the laser group (p=0.002). A significant

treatment effect was found for zone I retinopathy of prematurity (P=0.003) but not for zone II disease (P=0.27). The main comment on the study is that laser treatment was not performed according to ETROP criteria, which is common practice nowadays. This might have biased outcomes of laser treated eyes.

Because of this positive result on the short term, other studies have been conducted. Concerning reports of persistent peripheral avascular retina (AVA), recurrent IVNV, and stage 5 ROP retinal detachment, even 1 year following treatment, in some of these treated eyes have been published.[126-129] Furthermore it has been reported that anti-VEGF agents are still measurable in the systemic circulation 8 weeks after treatment possibly causing adverse effects on other developing organs such as kidney, lung and brain.[130]

In an animal study, it was established that even in a controlled model in which external conditions (as for example oxygen levels, body weight, species, number of pups) were kept constant, variability in responses could be seen. The signaling effects following anti-VEGF treatment are complicated by the effects on different retinal cells, timing of anti-VEGF treatment, and dosing. It was concluded that in a human preterm infant the variability is even greater, making it difficult to determine the correct dose. They also found that weight gain was impaired in the pups who received anti-VEGF treatment.[131]

All these side effects of Anti-VEGF treatment therefore call for further investigation in multicenter, randomized controlled trials. Until then, administration of these drugs should only be done by experienced centers and after written informed consent of the parents. After all, we have to keep in mind that VEGF is necessary for normal retinal vessel development.

OUTLINE OF THIS THESIS

Changes in neonatal care have increased the survival of preterm infants and decreased the age at which preterm born infants are kept alive, resulting in an increasing number of infants at risk for ROP. Therefore up-to date information on incidence of ROP and visual impairment (VI) due to ROP was needed.

In Chapter 2 the incidence of VI due to ROP and concomitant disabilities in preterm neonates born between 2000 and 2009 in the Netherlands is reported. Data were retrieved from the Dutch Institutes for the visually impaired. Outcomes were compared with previous Dutch studies resulting in an overview of more than 30 years to determine if changes in neonatal care resulted in a different outcome in incidence of ROP and concomitant disabilities.

The last study on ROP incidence in the Netherlands was conducted in 1952 by Von Winning.[132] As no obligatory national registry for ROP exists, a deficient insight in incidence and risk factors for ROP exists, leaving several Dutch cohort studies as the only source of

information.[60;89;133] A Netherlands Perinatal Registry (PRN) is available, which is used by neonatologists and pediatricians to improve the quality of health care through insight into the perinatal care process and its outcomes. A section on ROP is included, but is often poorly filled out because correct information on ROP is not known or the PRN document is completed in a phase where information on ROP screening is not available yet.
In the Netherlands an increasing number of hospitals provides care to premature born infants, facilitating earlier transfer. Initially most premature infants were admitted to one of ten neonatal intensive care units (NICUs). Nowadays as soon as infants are respiratory and circulatory stable and intensive care is no longer required, they are transferred to one of 16 high care centers (HC) or 77 regional centers (RC).
Before, the initial screening examination was performed by ophthalmologists in a NICU. They screened a large amount of infants and were therefore very experienced in ROP screening. This resulted in careful selection of high risk infants whose transfer to a HC or RC was postponed. Nowadays, transfer from a NICU to a HC or RC often takes place before the first ROP screening has been performed. Therefore, ROP screening has to be performed by an increasing number of Dutch ophthalmologists who have less overall exposure to ROP patients due to a limited number of patients. In addition, transfer of a child can result in unintended loss of clinical information concerning the neonate as well as loss of data concerning start or follow-up of ROP screening.
All the above mentioned issues called for the necessity of an updated insight in incidence and risk factors for ROP, adherence to the screening protocol and treatment policy in our country. Therefore a prospective nationwide inventory on ROP was initialized: the NEDROP study. With these up-to-date data, our final aim was to develop a new quality guideline for screening and treatment that would fit the Dutch situation.

The NEDROP-study

In 2008 we requested pediatricians and neonatologists to report all infants born in 2009 that complied with the inclusion criteria of the then prevailing National Guideline. Furthermore we recruited the screening ophthalmologists to report all children they screened for ROP born in 2009. A code was developed to enable anonymous data transmission and coupling to the National Perinatal Registry (PRN) to link risk factors for ROP with ophthalmological data.
Permission of the Medical Ethical Committee (METC) in Leiden was obtained. Their decision was as follows: *'Since no persons are subjected to a treatment or are required to behave in a certain manner, this proposal does not require a full review by the Medical Ethics Committee according to the WMO (Medical Research involving Human Subjects Act). To protect the privacy the processing of personal data is performed according with the Wbp (Personal Data Protection Act).'*

All personal data were coded and later on further depersonalized by numbering. This discharged us from the obligation to ask permission of METC's of all participating hospitals, enlarging the chance of success enormously.

At the start of this study the active guideline in the Netherlands dated from 1997. [134] The screening criteria included infants with GA < 32 weeks and / or a BW < 1500 grams and /or preterm infants treated with more than 40% oxygen for more than 3 days. Initial screening should be between 5–6 weeks of life (PNA).

Based on these screening criteria we calculated that approximately 1650 premature infants per year would comply and were eligible to enter the NEDROP study. The results of the NEDROP study are reported in chapter 3, 4 and 5. Chapter 3 reports data on the incidence, screening schedules, treatment, transfers and logistics of ROP in the Netherlands. Chapter 4 provides insight in the risk factors found for ROP after coupling the NEDROP database to the PRN database.

With all these data we acquired a good overview of the current situation in our country. As screening for ROP is costly, discomforting for the neonate and time-consuming for the ophthalmologist, the screening guideline was further evaluated. A national ROP guideline working group investigated whether a reduction of our inclusion criteria for screening was possible, on the pre-condition that no infants with severe ROP would be left out. Whether a modification of our national screening guideline is justified is described in Chapter 5. Based on figures from the NEDROP study a cost-effectiveness study was performed, the most efficient strategy is calculated in Chapter 6. Chapter 7 is a case report of two twin pairs with severe retinopathy of prematurity in twin-twin transfusion syndrome (TTTS) after multiple blood transfusions.

Finally a summary of the results is presented and conclusions and recommendations for the future are formulated.

The addendum provides the tangible outcomes of this thesis namely the:

- Summary of the quality screening guideline 2013
- Parents information folder
- The newly developed screening form

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2

Chapter 2

The incidence of visual impairment due to retinopathy of prematurity (ROP) and concomitant disabilities in the Netherlands: a 30 year overview

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ABSTRACT

Aim To determine the incidence of visual impairment (VI) caused by retinopathy of prematurity (ROP) and concomitant disabilities in preterm neonates born between 2000 and 2009 in the Netherlands.

Methods Data were retrieved from the Dutch institutes for the visually impaired. They were compared with similar Dutch studies conducted in 1975-1987, 1986-1994 and 1994-2000.

Results Records of 42 infants with VI due to ROP were included. A gradual decrease of gestational age and birthweight but an increase of duration of artificial ventilation, supplemental oxygen administration, bronchopulmonary dysplasia, developmental delay and behavioural abnormalities was found. Compared with the previous study (1994-2000), significantly fewer children were visually impaired due to ROP (1.84 per 100,000 live births/year vs 3.93 per 100,000 live births/year, $p<0.000$), the incidence of complete blindness decreased from 27.5% to 7.1% ($p<0.05$) and more children were treated (66.7% vs 56.9%, NS). The incidence of concomitant disabilities was high and did not differ greatly from the previous study.

Conclusion This was a retrospective study showing a significant decrease in VI due to ROP in the Netherlands. Changes in neonatal care practices did not result in a decrease in the incidence of concomitant disabilities. More children were treated for ROP, but 33% were not treated.

INTRODUCTION

Retinopathy of prematurity (ROP) is still one of the most important causes of partial sight or blindness in premature infants. In developed countries, ROP accounts for 5.5% to 20% of childhood blindness.[1-4] The pathogenesis of ROP is multifactorial, but the most significant risk factors for ROP are low gestational age (GA) and low birthweight (BW).[5-7] Changes in neonatal care over the past two decades have increased the survival rate of very small and very preterm infants. This was due to introduction of surfactant, increased use of antenatal steroids, resuscitation of infants with lower GA, improved nutrition and prophylactic use of indomethacin. Due to this increased survival rate, many very preterm infants are at risk not only of visual impairment (VI) caused by ROP but also of nonvisual disabilities.[8-10] Apart from changes in neonatal care practices, there have been changes in management of ROP. To reduce the number of adverse outcomes, treatment in the pre-threshold phase was introduced, resulting in an increased number of infants treated for ROP.[11-13] From 1952 onwards, five surveys were carried out in the Netherlands to calculate the number of children visually disabled due to ROP per 100 000 live births per year: 3.24/100 000 from 1952 to 1964 (Schappert-Kimmijser; survey 1),[14] 2.89/100 000 from 1961 to 1973 (van de Pol; survey 2),[15] 4.22/ 100 000 from 1975 to 1987 (Cats and Tan; survey 3),[16] 5.49/100 000 from 1986 to 1994 (Schalij-Delfos; survey 4)[17] and 3.85/100 000 from 1994 to 2000 (Termote et al; survey 5).[18] The last three surveys also included an inventory of concomitant disabilities, showing a marked increase in developmental and behavioural abnormalities. To monitor trends and to determine the incidence of VI caused by ROP, as well as the incidence of associated disabilities in these high-risk, vision-impaired children born between 2000 and 2009, a retrospective study was performed (survey 6). Data from the last three surveys were used for comparison, resulting in an overview of more than three decades.

PATIENTS AND METHODS

Due to privacy regulations and lack of an obligatory registry for children with VI in the Netherlands, access to patient data is limited. Therefore, data retrieval was only possible by collecting the records of all infants with a registered diagnosis of ROP who are known at one of the Dutch institutes for the partially sighted and blind. This information was obtained by one investigator (AJvS). For comparison, the same neonatal and ophthalmological data as in the previous surveys were collected: GA, BW, visual acuity, treatment for ROP, sex, multiple birth, incidence of bronchopulmonary dysplasia (BPD) and duration of supplementary oxygen administration, artificial ventilation (AV) and admission to the neonatal intensive care unit (NICU). With regard to concomitant disabilities the same

definitions and classifications as described by Termote et al were used.[13] We considered children to have multiple disabilities when they had VI caused by ROP plus one or more of the concomitant disabilities that were listed, excluding BPD as pulmonary function usually improves through the years.

To define VI, the recommendations of the International Association for Prevention of Blindness (IAPB) were used (World Health Organization, 1984).[19] Due to limitations in data collection, information on stages of ROP was unreliable and therefore again excluded. As the number of infants with cerebral VI increased over the last decade and became the most important cause of VI in prematurely born infants,20 data on cerebral VI were collected for this survey. However, they could not be compared with the previous studies. Data on the Dutch birth rate were obtained from the Central Bureau of Statistics (CBS). Survival rates of premature infants according to GA were collected from the Netherlands Perinatal Registry (PRN).

Data collected for this study (2000-2009) were compared with data from the previous study (1994-2000). In addition, data from the four surveys conducted from 1975 onwards were compared to identify and evaluate trends in treatments and outcomes.

Statistical analysis

Clinical data from the four surveys (presented in table 1) were evaluated using the independent samples t test. The Poison regression was used to perform calculations on data on VI caused by ROP in relation to Dutch birth rates, and the c2 test was used for all other data. Differences with a p value of <0.05 were considered significant. As all children with

Table 1 Neonatal data of infants with visual impairment caused by ROP in four consecutive periods in the Netherlands.

Period / survey #	1975-1987 / 3	1986-1994 / 4	1994-2000 / 5	2000-2009 / 6
No. Infants	76	87	51	42
Male (%)	47	58	59	74
Mean gestational age (wks)[1]	28.7 ± 2.7	27.5 ± 2.5	27.7 ± 2.4	27.4 ± 2.0
Mean birth weight (gr)[2]	1128 ± 331	1071 ± 385	942 ± 306	912 ± 385
Multiple birth (%)	18.9	20.7	31.4	31.0
Supplemental O_2 administration (days)[3]	43.2 ± 40.7	78.6 ± 88.8	83.2 ±81.6	81.8 ±78.4
Artificial ventilation (days)[4]	13.3 ± 22.0	27.6 ± 27.7	24.6 ±16.6	25.3±17.5
Admission to NICU (days)[5]	-	-	92.1 ± 58.2	97.2 ± 71.1

[1] column 1 vs column 2 p= 0,004, 1 vs 4 p=0.004, 2 vs 3, 3 vs 4 and 2 vs 4 ns

[2] column 1 vs 2 ns, 1 vs 3 p=0.001, 1vs 4 p=0.003, 2 vs 3 p=0.032, 3 vs 4 ns, 2 vs 4 p=0.03

[3] column 1 vs 2 p=0.003, 1 vs 3 p=0.005, 1 vs 4 p =0.004, 2 vs 3, 3 vs 4 and 2 vs 4 ns

[4] column 1 vs 2 p=0.0009, 1 vs 3 p=0.004, 1 vs 4 p=0.004, 2 vs 3, 3 vs 4 and 2 vs 4 ns

[5] column 3 vs 4 ns

VI due to ROP were studied in the subsequent periods, trends could be determined even though the separate values failed to reach significance.

RESULTS

Records of 43 children with VI caused by ROP were found. Informed consent was obtained from 42 parents. No additional infants born between 1994 and 2000 (survey 5) registered with the diagnosis of ROP were found during survey 6.
General data and neonatal data from infants diagnosed with ROP in four consecutive periods in the Netherlands are presented in table 1.
Compared with the previous study (1994-2000) no significant differences were found. However, a gradual decrease of mean GA and BW over the years was seen. For supplemental oxygen and AV a significant increase was found between surveys 3 and 4, but there were no significant changes after the mid 1980s. Not all infants from surveys 3 and 4 were admitted to a NICU, so admission days to a NICU were only analysed for the fifth and sixth survey periods, for which there was no significant difference. Although no significant differences were found in clinical data of children from the present study compared with the previous study, the proportion of infants with VI caused by ROP in relation to Dutch birth rates decreased significantly (table 2).
The average incidence of VI due to ROP is presented column 3 is the result of the fraction of the absolute number of individuals with ROP sequelae (column 1) and the absolute number of individuals born during the study period (column 2). The average incidence of VI due to ROP shows a decrease from the early 1990s.
A decline can be seen starting in the mid 1990s. The incidence of VI due to ROP decreased in the period 1994-2000, but failed to reach significance when compared with the period 1986-1994 (p=0.07). Comparing our study to surveys 4 and 5 a significant

Table 2 Visual impairment caused by ROP in relation to Dutch birth rates.

Period / Number	No. ROP sequelae	No. live births x 10^5 *	ROP sequelae / 100.000 live births
1952 – 1964[14] (survey 1)	100	30.9	3.24
1961 – 1973[15] (survey 2)	89	30.8	2.89
1975 – 1987[16] (survey 3)	97	23.0	4.22
1986 – 1994[17] (survey 4)	79	14.4	5.49
1994 – 2000[18] (survey 5)	46	11.7	3.93
2000 – 2009 (survey 6)	32	17.4	1.84

*Central Bureau of Statistics for the Netherlands
The average incidence of VI due to ROP is presented column 3 is the result of the fraction of the absolute number of individuals with ROP sequelae (column 1) and the absolute number of individuals born during the study period (column 2). The average incidence of VI due to ROP shows a decrease since the early 1990s.

Table 3 Visual acuity in children with ROP in four consecutive periods

Period	1975 – 1987 survey 3	1986 – 1994 survey 4	1994 – 2000 survey 5	2000 – 2009 survey 6
No. Infants	76	87	51	42
Visual acuity unspecified	5.1%			
Not partially sighted or blind (VA>0.3)[+1]	2%	10.3%	9.8%	23.8%
Partially sighted (VA 0.1 – 0.3)	34.3%	31.0%	25.5%	38.1%
Socially blind (VA < 0.1 - ≥ 1/60)	12.1%	10.3%	11.8%	14.3%
Practically blind (VA < 1/60 – LP)	8.1%	21.8%	25.5%	16.7%
Completely blind (VA = 0)[2]	38.4%	26.4%	27.5%	7.1%
Treatment of acute ROP[3]	24.%%	43.9%	56.9%	66.7%

[+] = infants with unilateral blindness and infants whose vision is expected to deteriorate in the future
LP= light perception
VA= visual acuity
[1] column 1 vs4 p= 0.000, 2 vs 4 p= 0.043
[2] column 1 vs 4 p=0.000, 2 vs 4 p=0.010 and 3 vs4 p=0.012
[3] column 1 vs 2 p=0.013, 1 vs 3 p=0.000, 1 vs 4 p=0.000, 2 vs 4 p=0.014

decrease in the incidence of VI caused by ROP was found (p=0.000 for both surveys). More specific data on visual acuity are presented in table 3.

In the current study there were 32 of 42 infants (76.2%) with VI, compared with 46 of 51 children (90.2%) in survey 5, representing a non-significant decrease. In more detail, our survey shows a significant decrease in the number of completely blind children due to ROP compared with the previous period (7.1% vs 27.5%; p=0.012), as well as a significant increase in children who did not fulfill the WHO criteria for VI at the time of inclusion in this study (23.8% vs 9.8%; p=0.043). Eight children (19%) were diagnosed with cerebral VI: two not partially sighted or blind, four partially sighted, one socially blind and one practically blind. The number of children who were treated for ROP increased significantly since survey 3, but there was no significant increase between surveys 5 and 6. Infants were treated with laser (n=16), cryotherapy (n=1), laser + cryotherapy (n=2), cerclage (n=1), cerclage + laser (n=1), cerclage + cryotherapy (n=1), vitrectomy + lensectomy (n=2), vitrectomy + laser (n=2), vitrectomy + laser + lensectomy (n=1) or bevacizumab (n=1). The most commonly used therapy was laser treatment (79%). Fourteen infants (33.3%) in the present study had not been treated versus 22 (43.1%) in the previous study. Four of the untreated children in this study had a final visual acuity >0.3 in at least one eye.

Comparing the incidence of concomitant disabilities in infants with ROP, no significant changes were found except for epilepsy (p=0.007) (table 4).

In the previous study a significant increase in behavioural abnormalities was seen, but this tendency did not extend to the current study. A gradual increase of children with BPD, developmental delay and hearing deficit were observed, but differences did not

Table 4 Concomitant disabilities in infants with visual impairment caused by ROP in four consecutive periods in the Netherlands (%).

Period	1975 – 1987 survey 3	1986 – 1994 survey 4	1994 – 2000 survey 5	2000 – 2009 survey 6
No. Infants	76	87	51	42
BPD[1]	26.3	45.9	60.4	78.3
Behavioral abnormalities and problems[2]	9.2	21.8	46.9	40.0
Epilepsy[3]	5.3	6.9	16.3	0
Hearing deficit[4]	5.3	2.3	8.2	12.5
Developmental delay[5]	35.5	47.1	52.9	65.0
Neurological handicaps[6]	30.3	49.4	45.1	42.5
Multiple disabled[7]	39.5	58.6	68.2	66.7

[1] column 1 vs 2 p=0.009, 1 vs 3 p=0.000, 3 vs 4 p= 0.016
[2] column 1 vs 2 p= 0.028, 1 vs 3 p= 0.000, 1 vs 4 p= 0.000, 2 vs 3 p= 0.000, 2vs 4 p= 0.027, 3 vs 4 ns
[3] column 1 vs 3 p= 0.049 and 3 vs 4 p=0.007
[4] column 2 vs 4 p=0.024
[5] column 1 vs 4 p=0.003
[6] column 1 vs 2 p=0.013
[7] column 1 vs 2 p=0.015, 1 vs 3 p=0.0011 vs 4 p=0.001

reach statistical significance. The number of infants with neurological impairment and a multiple disability increased significantly between surveys 3 and 4 but was stable after this. When the population was subdivided for GA, the incidence of VI caused by ROP based on the estimated number of survivors, as well as the incidence of concomitant disabilities in surveys 5 and 6, was highest in children born under 30 weeks; the incidence of VI increased as GA decreased (table 5). The five infants with unilateral blindness (n=1) or visual acuity >0.3 (n=4) were also included in this analysis because this was also done in the previous studies.

The percentage of children with concomitant disabilities was again high in this survey, but did not differ greatly from survey 5. In survey 5 there were 35 children with concomitant disabilities (68.6%) versus 31 (73.8%) in our survey.

Table 5 Visual impairment caused by ROP in relation to estimated number of survivors and concomitant disabilities.

GA (wks)	% VI caused by ROP (n) related to estimated survivors*				% Concomitant disabilities (n)	
	'75 – '87 survey 3	'86 – '94 survey 4	'94 – '00 survey 5	'00 – '09 survey 6	'94 – '00 survey 5	'00 – '09 survey 6
24 – 25	10.4 (11)	12.5 (11)	3.1 (9)	2.4(10)	67 (6)	70 (7)
26 – 27	3.3 (40)	4.3 (36)	1.3 (23)	0.9(19)	65 (15)	79 (15)
28 – 29	0.8 (26)	0.4 (10)	0.3 (10)	0.2(9)	80 (8)	78 (7)
30 – 31	0.2 (13)	0.2 (8)	0.1 (6)	0.03(2)	66 (4)	50 (1)
>32 - <37	0.01 (12)	0.01 (7)	<0.001 (2)	<0.002 (2)	100 (2)	50 (1)

* Numbers of estimated survivors were derived from the Netherlands Perinatal Registry

DISCUSSION

We performed a retrospective study on the incidence of VI due to ROP in preterm infants born between 2000 and 2009 in the Netherlands. The incidence presented in this study must be considered as a minimum incidence because there is no obligatory national registry for VI, children may be missed and there is always a possibility that children born in the study period will become visually impaired at a later age. However, the same caveats apply to earlier studies and no additional infants from the previous periods were found during our current search. Data were compared with three earlier Dutch studies starting in 1975 (surveys 3, 4 and 5), thus providing an overview of more than 30 years.
Over the years there has been an increase in the survival rate of smaller and more immature infants due to changes in neonatal care practices.[21] From 1975 until the present time mean GA and BW of infants with VI due to ROP in the Netherlands has gradually decreased. Although we found no significant changes in neonatal data in infants with VI in the present study compared with the previous study of Termote et al[18], we found a decrease in VI due to ROP. It seems reasonable to assume that improvement in neonatal care might contribute to a better visual outcome in these preterm neonates. An important limitation is that we were unable to gain detailed information about the neonatal period. From other Dutch studies covering approximately the same period we can learn more about general changes that have taken place. Two Dutch cohort studies from Hoogerwerf et al[22] and Groenendaal et al[23] demonstrated an improvement in outcome. Groenendaal et al analysed two cohorts of inborn preterm neonates (1997-2001) and (2002-2006) with a GA of 25-29.9 weeks and found an improved survival rate but no increase in the number of infants treated for severe ROP. The study from Hoogerwerf et al focused on changes in the incidence and risk factors responsible for the development of ROP and compared two cohorts of premature infants born in the time periods of 1991-1995 and 2001-2005.
They found an increase in the use of antenatal steroids and surfactant and a decrease in the duration of AV, supplemental oxygen administration and NICU admission, as well as a decrease in incidence of ROP. Most of these changes were not reproducible in our study. However, we included only those infants that were referred to one of the Dutch institutes for the visually impaired and were supposedly the most critically ill neonates. We speculate that more subtle improvements in neonatal care are responsible for the decrease in the incidence of VI caused by ROP and of completely blind children. Furthermore, there was an increase in infants treated for ROP (from 56.9% to 66.7%). The Early Treatment of Retinopathy of Prematurity criteria (ETROP) were introduced in the early phase of this survey resulting in a larger number to treat and an expected reduction of adverse outcomes.[3,11,12] In addition, the study of Termote et al[18] resulted in a campaign for more awareness of necessity to treat timely and for potential visual problems on the

long term. Earlier referral to the Dutch institutes for partially sighted and blind together with changed treatment criteria could be an additional explanation for the significantly higher number of infants with a visual acuity >0.3 found in the current study and the significant decrease in VI due to ROP. Although more infants received treatment in the current study, 33% (n=14) did not, of which 10 had a visual acuity of <0.3. Haines et al[24] also described that, even after implementation of screening guidelines, some children developed VI because of non-adherence to the screening protocol.

Studies from the UK on VI due to ROP as a proportion of childhood VI, covering the same period,[4,25] show a tendency that compares favourably with our surveys. A study by Schiariti et al[1] demonstrated an increase in ROP as well as severe ROP without changes in the incidence of VI when comparing neonates born in 1992-1996 and 1997-2001. Slidsborg et al[5] found a more than twofold increase in the incidence of treated ROP cases born in Denmark from 2001 to 2005 compared with 1996-2000. This increase was most pronounced for the smallest infants. The number of infants with VI or blindness caused by ROP was stable. These studies also attribute the decline of VI due to ROP to a more complete ophthalmic surveillance, earlier treatment and improvement in neonatal care. Similarly to the earlier Dutch surveys, most children with VI caused by ROP were surviving preterm neonates <30 weeks of gestation. This group of infants also showed the highest incidence of concomitant disabilities. Although a substantial number of infants had one or more concomitant disabilities (73.8%), no significant changes were found compared with the study of Termote et al. Inexplicably, no children with epilepsy were registered in the present study. The incidence of BPD, developmental delay and hearing deficit gradually increased whereas behavioural abnormalities, multiple disabilities and neurological impairment decreased minimally. A Dutch study by van Baar et al[26] showed a clear association between preterm birth and multiple disabilities at 5.5 years of age in 157 children born before 30 weeks GA. One or more disabilities were found in 75% of the children. Several other studies have concluded that the survival rate for extremely preterm born infants has improved over the past decade, but that the overall prevalence of neurodisability after preterm birth has not fallen, thus supporting the findings in our study.[8-10] This overview of more than 30 years shows a decrease in GA and BW and a gradual increase in AV and supplemental oxygen administration, with a turning point in the early 1990s when novel treatments such as surfactant treatment, high frequency oscillation (HFO), postnatal steroids and inhaled NO were introduced. The incidence of VI caused by ROP has decreased over the past 30 years with the most obvious change seen in the last survey period. Additional changes in neonatal care practices such as treatment with antenatal steroids and antenatal antibiotics together with earlier treatment for ROP could be an explanation. However, these changes did not result in a decrease of concomitant as well as multiple disabilities. Although more children were treated, 33% were not treated.

Therefore, it can not be emphasised enough that timely screening, follow-up and treatment, as well as close collaboration by all professionals involved in the care of these at-risk neonates should be our aim to enable a further decrease the number of children with VI caused by ROP. While the GA and BW of survivors continue to decrease, it seems a more difficult task to diminish the number of children with multiple disabilities.

Competing interests

None. Patient consent Children were included in the study when informed consent was obtained from their parents.

Ethics approval

This study was conducted with the approval of the medical ethics committees of all participating institutes for the partially sighted and blind.

Provenance and peer review Not commissioned; externally peer reviewed.

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3

Chapter 3

Outcome and quality of screening in a nationwide survey on retinopathy of prematurity in the Netherlands

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ABSTRACT

Purpose

Provide insight in natural history, screening and treatment policy of Retinopathy of Prematurity (ROP) in the Netherlands.

Methods

A multicenter, prospective, population based study (NEDROP) included all preterm infants born in 2009 in the Netherlands fulfilling the inclusion criteria for ROP-screening. Anonymized data from ophthalmologists, neonatologists and pediatricians were merged on identification number.

Results

Of 2033 reported infants, 1688 (83%) were screened for ROP. ROP stage was reported in 100%, zone in 94.4% and plus disease in 83%. ROP developed in 324 (19.2%), mild ROP (stage 1-2) in 294 (17.4%), severe ROP (stage 3 or more) in 30 (1.8%) and 17 (1%) were treated. The initial screening examination was not performed within the required 42 days in 641 (38%). Date for follow up was recorded 1973 times and accomplished within 3 days from the planned date in 1957 (99.2%). The chance of not being screened increased from 12.9% without transfer to another hospital to 23.5, 18.5 and 25% after respectively 1, 2 or 3 transfers.

Conclusion

The incidence of severe ROP and infants treated was low. NEDROP emphasizes that timing of initial examination and transfer to another hospital are issues of concern within the screening process.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vision threatening disease in prematurely born infants. Over the years, our knowledge about the disease has improved and its management is evolving. At the same time, advances in neonatal care result in survival of an increasing number of infants with an extremely low gestational age (GA) which are the most susceptible to develop severe ROP.[1] Careful screening and timely treatment play a key role in the reduction of the number of infants left with a permanent visual disability. Several countries have developed evidence-based guidelines for screening and treatment of ROP.[2–6] The last ROP guideline in the Netherlands, based on a national retrospective study by Schalij–Delfos et al[7], is dated from 1997. Additionally, the International Classification for ROP (ICROP) was revised in 2005, and the Early Treatment for ROP (ETROP) study changed the treatment algorithm.[8,9] Therefore, revision of the Dutch guideline was imperative. A 30-year overview on visual impairment due to ROP in the Netherlands showed an increased risk of ROP among infants with decreasing GA and birth weight (BW), a relative reduction of visual impairment due to ROP but also an indication that not all infants at risk might have been seen or treated in time.[10] So, before releasing a new ROP guideline, the necessity for insight in incidence and risk factors for ROP, adherence to the screening protocol and treatment policy in our country, called for a nationwide inventory on ROP: the NEDROP study.

METHODS

The NEDROP study is a multicentre, prospective, population-based study, and includes all preterm infants born in 2009 in the Netherlands that fulfilled the inclusion criteria for ROP-screening according to the prevailing guideline: GA <32 weeks and/or BW <1500 g, and preterm infants that needed ≥40% supplemental oxygen for more than 3 days. Neonatologists and paediatricians provided coded information on all those who were eligible to enrol in the study: initials (first letter of first name and surname), zip code, date of birth, GA and BW. Multiple births were numbered consecutively (1/2, 2/2, 1/3, etc). Ophthalmologists reported the same coded information of all infants that were actually screened for ROP. On a specially designed form, they reported the date of first examination, the suggested and executed dates of follow-up examinations, the date and reason for discontinuation of screening, ROP classification, presence or absence of plus disease and need for treatment. According to the prevailing guideline, the first screening examination should be scheduled at 5 weeks (before 42 days) postnatal age (PNA). For study purposes, infants were categorised as mild (ROP stages 1 and 2) or severe (ROP stage ≥3) ROP. However, some data will be presented by stage of ROP. In

retrospect, infants were classified in Type 1 and Type 2 ROP, according to the ETROP criteria. At transfer, the next hospital's name was noted. Data input for the NEDROP database was centralised and handled by one investigator (AvS).

Statistical analysis

Data files on patient characteristics and screening were merged on identification number. Numerical values are presented as medians with 25–75% IQR in brackets. Data about screening examinations and transfers are presented with minimum-maximum range. Data management and statistical calculations were done with the SAS V.9.2 package (SAS Institute, Cary, North Carolina, USA).

RESULTS

Population

All 103 hospitals involved in ROP screening (10 neonatal intensive care units (NICU), 16 high-care centres (HC) and 77 regional centres (RC)) participated in the study. Neonatologists and paediatricians reported 2033 infants eligible for screening of which 556 were part of twins or triplets. Infants were born at a NICU (1735; 85.3%), a HC (177; 8.7%) or a RC (121; 6%). Of the reported infants, 1688 (83%) were screened for ROP (figure 1). Their median BW and GA are presented in table 1. Of the reported infants, 164 died, of which four were fully screened and, therefore, included in the study. For several other reasons, infants were not screened or lost to follow-up: the ophthalmolo-

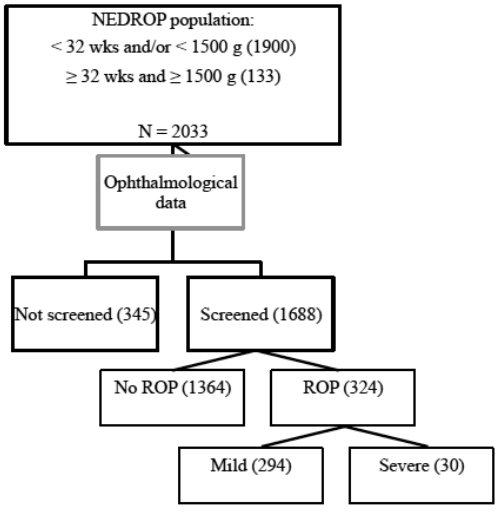


Figure 1 Flowchart

Table 1 Study population characteristics

	Screened for ROP	No ROP	Overall ROP	Mild ROP	Severe ROP
Patients (N)	1688	1364	324	294	30
GA	30.1 (28.6-31.4)	30.7 (29.3-31.7)	28.0 (26.4-29.4)	28.1 (26.6-29.6)	26.3 (25.4-27.0)
BW	1320 (1050-1560)	1400 (1150-1620)	950 (780-1212)	960 (790-1225)	890 (730-1060)
Examinations (N)	3891	2402	1489	1250	239
median	2 (1-3)	1 (1-2)	4 (3-6)	4 (3-6)	6 (5-10)
1st exam PMA	35.4 (33.7-37.0)	35.9 (34.4-37.1)	33.1 (31.4-34.9)	33.4 (31.6-34.9)	31.7 (31.0-34.1)
1st exam PNA	5.6 (5.0-6.4)	5.6 (5.0-6.4)	5.4 (5.0-6.1)	5.4 (5.0-6.1)	5.7 (5.1-6.7)
1st exam >42 days (N)	592	513	79	74	5
1st detection ROP PMA	NA	NA	34.1 (32.4-36.0)	34.3 (32.4-36.0)	34.0 (32.3-35.6)
1st detection ROP PNA	NA	NA	6.3 (5.3-7.7)	6.3 (5.3-7.6)	7.3 (6.0-8.0)

Number (N) of infants, screening examinations and initial examinations > 42 days after birth.
Median values with 25-75 IQR for gestational age (GA), birth weight (BW), number of examinations, 1st screening examination and first detection of ROP.
PMA = postmenstrual age, PNA = post natal age, NA = not applicable, exam = examination

gist was not summoned (126), different inclusion criteria for screening were used (23), transfer of the infant to another hospital before the first screening (12), no show at the outpatient appointment (10), and transfer abroad (4). For 10 infants, the reason was unknown. Due to the anonymous data retrieval, it is not known if those not screened developed ROP.

ROP

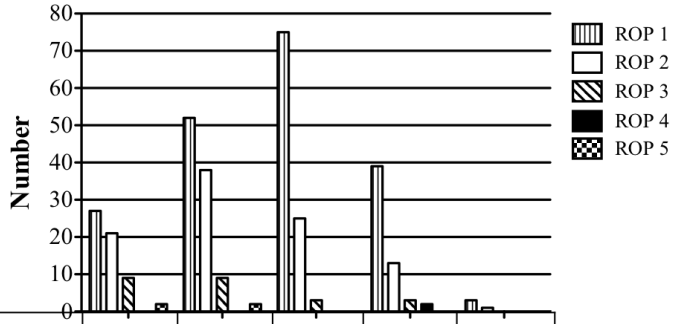
Of the 1688 infants screened, 324 (19.2%) developed ROP, of which 294 were mild and 30 severe (tables 1 and 2). The absolute numbers of infants with ROP increase with decreasing GA (figure 2). At time of detection, ROP was located in Zone I in 7, Zone II in 133 and Zone III in 166 cases. The zone was not noted in 18 (5.6%) infants. Plus disease was present in 32, absent in 237 and not noted in 55 (17%) infants. Treatment was performed in 17/324 infants with ROP (5.2%): three with ROP stage 2, 12 with ROP stage 3 and 2 with ROP stage 4.

In retrospect, infants were divided in Type 1 and Type 2 ROP, according to ETROP criteria: of the 324 infants 21 could be classified as Type 1 ROP, 10 as Type 2 ROP, 280 did not fit the criteria, and 13 could not be categorized due to incompleteness of data. Of the 21 infants with Type 1 ROP, 11 were treated (9× ROP 3, 2× ROP 2) and 10 regressed sponta-

Table 2 Characteristics of infants with ROP specified per stage

	N	GA	BW	Examinations (N)
ROP 1	196	28.4 (23 6/7-33)	1030 (440-2040)	3 (1-9)
ROP 2	98	27.4 (24 2/7-34)	890 (530-1660)	6 (2-12)
ROP 3	24	26.4 (24 2/7-31 3/ 7)	913 (600-1880)	6 (3-23)
ROP 4	2	30.7 (30-31 3/7)	1223 (975-1470)	4 (1-6)
ROP 5	4	25.7 (25 3/7-26 2/7)	675 (520-806)	13 (10-20)

Median gestational age (GA), birth weight (BW) and number of screening examinations with minimum-maximum range in brackets.



Weeks	23-25	26-27	28-29	30-31	≥32
ROP1	27	52	75	39	3
ROP2	21	38	25	13	1
ROP3	9	9	3	3	0
ROP4	0	0	0	2	0
ROP5	2	2	0	0	0

Figure 2 Number of infants with retinopathy of prematurity (ROP) and their distribution of gestational age (GA)

neously. Six treated infants could not be categorized, two with stage 4 and four because notification of zone or plus disease lacked.

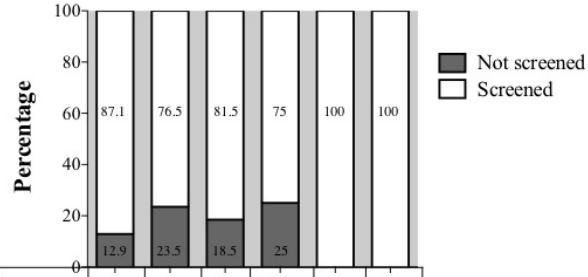
Screening

Ophthalmologists performed 3891 funduscopies. Infants that developed ROP were screened 1489 times, those without ROP2402 times. Roughly, the number of screening examinations increased with severity of disease (tables 1 and 2). Of the screened infants

544 (32.2%) had a BW ≥1500 g and 252 (14.9%) a GA ≥32 weeks. Data about initial screening and detection of ROP are displayed in table1. The initial screening was performed at a median age of 39 (11–334) days. At the first examination, 1480 had no ROP, 202 mild and six severe ROP. In 641 (38%) infants, the first screening examination was performed >42 days after birth. Three of these infants already had mild and five severe ROP. The date for follow-up screening was recorded 1973 times and accomplished within 3 days from the planned date in 1957 (99.2%). For five infants, the follow-up examination was outside this interval (range 1–8 weeks) without consequences for the outcome.

Transfer

More than half the population (59.6%) was born and cared for in the hospital of birth. The others were transferred once or more times, with a maximum of six (figure 3) times. Infants that had more than three transfers had been moved to and from a treatment centre. Of the non-transferred infants, 12.9% (156/ 1211), and of the infants with one or more transfers, 23% (189/822) had not been screened (p<0.001). However, no significant relation was found between the number of infants that were not screened, and the absolute number of transfers (p=0.64).



Transfers	0	1	2	3	4	6
Number of patients	1211	736	65	16	4	1
Screened	1055	563	53	12	4	1
Not screened	156	173	12	4	0	0

Figure 3 Number of transfers and percentage screened. Number of transfers and percentage of screened / not screened infants are presented in the graph. Absolute numbers are presented in the adjoining table.

DISCUSSION

This prospective, population-based study was conducted with participation of all centres involved in ROP screening, thus providing insight in natural history, screening and treat-

ment policy adherence in the Netherlands. This resulted in a large cohort of 2033 infants. The number of infants screened was high (83%) and comparable with a large cohort (n=13 282) described by Bain et al[11] who found an overall rate of missed ROP screening of 18.6% in 2005 and 12.8% in 2007. Comparison of results on incidence of ROP is complicated as most studies are retrospective and not nationwide, and inclusion criteria vary. There are a number of studies with inclusion criteria similar to ours. Hoogerwerf et al[12] studied a cohort retrospectively in the central part of the Netherlands, from 2001 to 2005. They found similar incidences for overall ROP (23.3%) and severe ROP (1.2%). Ho et al[13] found an incidence of 19.2% ROP (36/187), 9.6% severe ROP and 8.6% treatment in a retrospective study from 1996 to 2003 in a tertiary centre in the South Glasgow region. Larsson et al[5] performed a population-based study in Stockholm County, Sweden, from 1 August 1998 to 31 July 2000, and found ROP in 25.5% (100/392), severe ROP in 12.2% and treatment of 8.1%. Isaza et al[14] reported ROP in 40.4% (171/423), severe ROP in 9.2% and treatment in 5.7% in a retrospective study in a NICU in Canada from July 2006 to July 2010. A prospective study by Dhaliwal et al[15] performed in Lothian, Scotland, from 1990 to 2004 found ROP in 17%, severe ROP in 8.5% and 5% treatment in 474 infants born during 2000–2004.

The incidence of ROP in the current study (19.2%) is similar to most studies, but low for infants with severe ROP and those treated. The NEDROP population is large, covers the whole nation and includes all infants screened for ROP in 2009, also those ≥32 weeks and ≥1500 g (7.5%). This is reflected in a mean GA (30 weeks) and BW (1435 g) that is relatively high compared to the other studies, not including infants >32 weeks gestation. Only Isaza[14] also included those judged at risk.

Furthermore, only one NEDROP infant had a GA <24 weeks, probably due to the contemporary Dutch policy not to resuscitate infants at birth with a GA <24 weeks.

We found a low number of treated infants. Retrospectively, 21 infants were classified with Type I ROP of which 11 were actually treated. If all Type 1 ROP infants would have been treated (27/1688=1.6%), the difference with the studies above would still be substantial. In 17%, plus disease was not recorded. It is unknown if plus disease was not recorded because it was absent or whether the implication of plus disease was not appreciated by the ophthalmologist. An inventory on visual impairment due to ROP by van Sorge indicated that not all infants with severe ROP might have been treated in time.[10] This inventory again suggests that ETROP treatment criteria were not implied at large in 2009, and not all infants are treated in time. The old guideline did not include a section about treatment supporting the necessity for guidelines to include rules for screening and also for treatment. This has been effected in the new national ROP guideline.

This study provides useful information about the screening process. The main deviation of the protocol was a delay in the initial screening examination. According to the prevailing guideline, the first screening examination should take place at PNA 5 weeks

(<42 days). The median PNA at initial screening was 5.6 weeks. Figures about postmenstrual age (PMA) (median 35.4 weeks) are not well comparable with others due to the substantial number of infants with GA >32 weeks in this study. For unknown reasons, 641/1688 infants were screened >42 days of age. Eight of these infants already had ROP at the initial examination, of which five were severe. In a population-based study on severe ROP, Haines et al[16] also found that 31/221 (14%) infants already had severe ROP at first screening in contrast with 0.4% in our study. Gupta et al,[17] investigating 23 Canadian centers, found that eight different criteria were in use for timing of screening, and only 40% initiated screening at 4–6 weeks.

PMA and PNA for the development of ROP and severe ROP was similar to other studies.[18,19] A date for follow-up was recorded 1973 times and executed within 3 days of the intended date in 99%. This suggests that written recommendations increase the rate for follow-up.

Transfer has been reported as an important weak link in the screening process.[20] Reynolds et al[21] described 13 ROP malpractice cases of which eight were related to failure to refer or follow-up. Attar et al[20] found that the risk of not being screened at all was associated with transfer or discharge of the NICU before the initial eye examination, no written recommendation in the discharge summary, and no scheduled appointment at discharge to home.[22] We anticipated that transfer could be a bottle neck in our screening process as policy of transfer changed. In the past, at least the initial screening examination was performed in a NICU resulting in a careful selection of high-risk infants whose transfer was postponed. Currently, infants are transferred to a HC or RC as soon as they are respiratory and circulatory stable, often before the first screening examination. As lack of screening or delay in follow-up can have devastating consequences, we should direct our efforts towards optimisation of communication and distribution of information. A recent study by Barry et al[23] showed that the attendance rates for initial outpatient examinations and fulfilment of the screening programme significantly increased after they introduced parent education forms, streamlined scheduling and introduced a log book for follow-up monitored by the attending ophthalmologist. As a result of the NEDROP study, several indicators were added to our National Monitoring System for Quality in Health Care to improve the screening process. Shortly after births, parents should receive a ROP brochure, and the week for initial screening is defined and noted in the patient's medical record. The neonatologist is obliged to include information about ROP screening in the letter of transfer (including ophthalmological data and a week number for first or planned follow-up screening), or infants get a scheduled appointment before discharge to home. Although the anonimysed data admission facilitated participation of all centers involved, it was also a limitation as neonatal and ophthalmological data were available for each individual patient, but could not be linked directly to the centre of care. For example, for individual infants, we do not know the reason they were not

screened, or the reason for discontinuation of screening after transfer. Furthermore, this study covered only 1 year of screening. There is, however, no reason to assume that this year would deviate much from other years. Finally, we should consider variability in the judgment of different examiners for staging and treatment of ROP. As the group is large, this observer bias is expected to level out in the final results.

Gilbert et al[24] emphasized that each country should adjust its screening guidelines based on characteristics from its own population. The shortcomings in the execution of the 1997 guideline emphasize the need for evaluation of the implementation of guidelines even in well-structured healthcare systems. Ideally, this should be done in an obligatory national registry but the complexity to organize this as well as local privacy and legal regulations might prevent countries from institutionalizing such a register. The alternative is a national inventory on a regular basis. The NEDROP study resulted in a new guideline[25] for screening and treatment of ROP. Oral communication at regional and national meetings, quality indicators and an online e-learning should second all-encompassing implementation, the results of which will be evaluated in the next national inventory.

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Competing interests

None.

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Chapter 4

Nationwide inventory of risk factors for retinopathy of prematurity in the Netherlands

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ABSTRACT

Objectives

To study the incidence and risk factors for retinopathy of prematurity (ROP) in the Netherlands.

Study design

Prospective, approximating population-based study that included infants with gestational age (GA) <32 weeks and/or birth weight (BW) <1500 g born in 2009. Pediatricians and ophthalmologists of all hospitals involved in care for premature infants reported data that were matched with the national perinatal database for risk factor analysis.

Results

Of 1380 infants, median GA 29.8 weeks (IQR 28.1-31.1) and median BW 1260 g (IQR 1020-1500), ROP developed in 21.9%. Logistic regression identified GA and BW as risk factors for ROP ($P < .001$). After adjustment for GA and BW, additional risk factors were inhaled nitric oxide (iNO; OR 2.6, 95% CI 1.1-6.2, $P = .03$), stay at a neonatal intensive care unit >28 days (OR 1.6, 95% CI 1.1-2.6, $P = .03$), and artificial ventilation >7 days (OR 1.6, 95% CI 1.1-2.5, $P = .02$). Prenatal glucocorticoids (OR 0.6, 95% CI 0.4-0.8, $P < .001$) and female sex (OR 0.7, 95% CI 0.5-0.99, $P = .04$) showed a lesser incidence of ROP. iNO remained significant after correction for all significant factors (OR 2.6, 95% CI 1.1-6.2, $P = .03$).

Conclusion

In addition to established risk factors (GA, BW, stay at a neonatal intensive care unit >28 days, and artificial ventilation >7 days), treatment with iNO as risk factor for ROP is a novel finding.

INTRODUCTION

Retinopathy of prematurity (ROP) accounts for 5.5%-20% of childhood blindness in developed countries.[1] Improvement in neonatal care during the past 2 decades has increased the survival of prematurely born infants and lowered the gestational age (GA) and birth weight (BW) of survivors.[2] Several studies demonstrated that this decrease in mortality was accompanied by an increase in significant neonatal morbidities such as severe ROP.[3,4] ROP is a condition confined to the developing retinal vasculature in the prematurely born infant and develops in 2 phases. Vascularization of the retina begins at 16 weeks' and reaches the peripheral retina at 40 weeks' gestation. When infants are born prematurely, the growth of vessels ceases, leaving an incompletely vascularized peripheral retina. Insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are crucial to the normal development of retinal vessels. IGF-1 is produced by the placenta, and preterm birth results in decreased levels of serum IGF-1. Very prematurely born infants cannot produce sufficient IGF-1, and its concentration may be further reduced by sepsis, acidosis, and poor nutrition, which are frequent conditions in those infants. These low levels of IGF-1 are coresponsible for the cessation of retinal vessel outgrowth. The expression of VEGF is regulated by oxygen. ROP can be initiated immediately after premature birth by relative hyperoxia, as supplemental oxygen but also room air increases retinal oxygen saturation to levels far greater than those in utero. Most preterm infants do not get ROP, but in those who do, this hyperoxia suppresses the production of VEGF, resulting in a hypoxic, avascular retina. Subsequently, chronic hypoxia leads to compensatory, excessive VEGF synthesis, causing pathologic neovascularization.[5,6]
Because oxygen and the extent of the avascular peripheral retina play a key role in the pathogenesis of ROP, factors influencing oxygen levels as well as factors responsible for large areas of avascularity are expected to be associated with an adverse outcome. Low GA, low BW, and factors related to general illness such as length of stay (LOS) on a neonatal intensive care unit (NICU), duration of artificial ventilation, and the administration of supplemental oxygen are established risk factors.[7]
Screening and treatment protocols vary by country and may result in differences in incidence and risk factors for ROP. To provide optimal care for premature infants at risk, a nationwide inventory was conducted to provide up-to-date insight on the incidence and potential risk factors for ROP in the Netherlands.

METHODS

The Netherlands ROP (NEDROP) study is a multicenter, prospective, approximating population-based study in which investigators analyzed all infants born in 2009 eligible

for screening of ROP according to the prevailing guideline: GA <32 weeks or BW <1500 g or preterm birth and treatment with >40% supplemental oxygen for more than 3 days. Pediatricians and ophthalmologists of the 103 Dutch hospitals involved in care for premature infants reported all infants entitled for ROP screening to the study center. Ophthalmologists reported all infants actually screened for ROP as well as ROP classification, the presence of "plus disease" (additional signs of active disease), screening schedule, and whether there was need for treatment. ROP was classified according to the International Classification of ROP, the highest stage in either eye being reported.[8] Data entry in the NEDROP database was coordinated, centralized, and handled by one investigator (A.v.S.). To comply with patient privacy regulations, infants were reported anonymously with initials, zip code, date of birth (DOB), GA, and BW. The NEDROP database was merged with the already-existing Netherlands Perinatal Registry, which is a medical, professional-based registry where pediatricians and neonatologists report their data of neonates born in the Netherlands. Contribution to the Netherlands Perinatal Registry is obligatory for NICUs and high-care centers and voluntary for regional centers of which 50% participate.

All infants born with a GA <30 weeks and 85%-90% of infants with GA 30-32 weeks are admitted to a NICU. Yearly, more than 95% of infants born <32 weeks' gestation are reported to the Netherlands Perinatal Registry.

To combine the NEDROP and the Netherlands Perinatal Registry databases, DOB and/or zip code and/or BW were applicable. Clinical data were classified according to the definitions of the Netherlands Perinatal Registry; for bronchopulmonary dysplasia (BPD), the new definition was used (need of supplemental oxygen at 36 weeks' postmenstrual age); artificial ventilation meant ventilation via an endotracheal tube (synchronized intermittent mandatory ventilation or high-frequency ventilation). Longer stay at a NICU and duration of artificial ventilation were regarded as indicators for severe illness and defined as stay at a NICU for more than 28 days and artificial ventilation more than 7 days (http://www.perinatreg.nl/wat_wordt_geregistreerd). All neonatologists provided their 2009 inhaled nitric oxide (iNO) protocol. No interventions in practice and screening, to reduce the rate of ROP, were undertaken throughout the study. The study was approved by the Institutional Review Board (Medical Ethical Committee of Leiden University Medical Center, the Netherlands).

Statistical Analyses

GA and BW are presented as median values with the IQR (25th-75th percentile). The occurrence of risk factors in the study population and the incidence of ROP were tabulated as numbers and percentages. Some of the characteristics such as sex, small for gestational age, duration of artificial ventilation, duration of O2, and LOS on NICU were not filled out for every patient in the Netherlands Perinatal Registry.

We handled them as missing data. A logistic regression model was used to investigate the association between a risk factor and the development of ROP, corrected for possible confounders. Because part of the data consisted of observations on multiple births, risk factors and probability of ROP for these neonates were correlated. To take into account this dependency of the data, a generalized estimating equation approach was used to estimate the coefficients of the logistic regression model (proc GENMOD in SAS; SAS Institute, Cary, North Carolina). For each potential risk factor, the OR and the 95% CI, adjusted for GA and BW, were calculated. The final adjusted OR was obtained from the model that included all the significant factors. $P < .05$ was considered statistically significant.

RESULTS

In the NEDROP database, 1900 infants with GA <32 weeks and/or BW <1500 g were reported, of which 1561 (82.2%) were screened for ROP. The NEDROP and the Netherlands Perinatal Registry database were merged by DOB and zip code, resulting in a

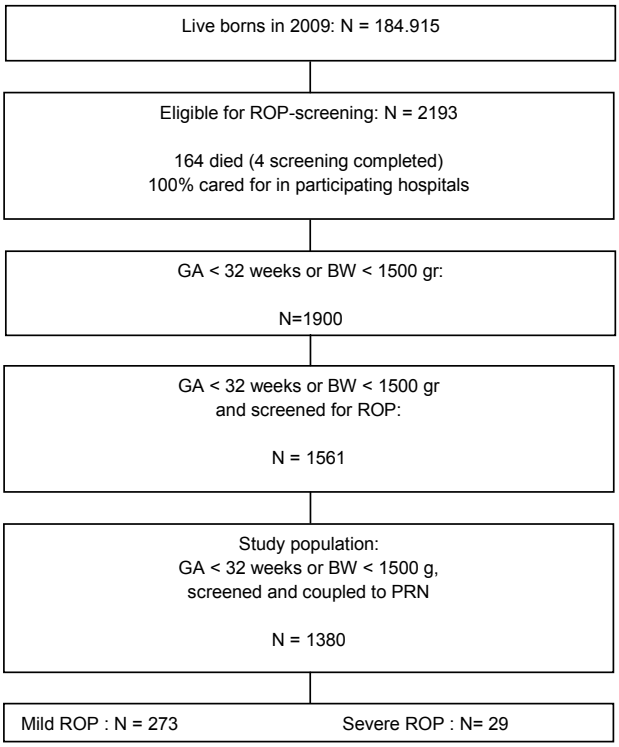

Figure 1 Flowchart of the study.

Table 1 Descriptive statistics

		N	ROP %	
N		1380	302 (21.9)	
Characteristic		N (%)	characteristic +	characteristic –
Female gender		527 (44.7)	20.5	21.7
Extremely low BW (<1000g)		323 (23.4)	51.1	13.0
Small for GA (<P10)		106 (9.0)	23.6	25.9
Multiple birth		404 (29.4)	19.3	23.0
Duration of AV	yes, ≤7 days	360 (30.5)	21.4	
	yes, >7 days	169 (14.3)	53.3	
	No	650 (55.1)	12.6	
Duration of O_2	yes, ≤28 days	484 (44.9)	16.3	
	yes, >28 days	210 (19.5)	50.9	
	No	383 (35.6)	13.8	
LOS NICU	yes, ≤28 days	789 (67.1)	12.2	
	yes, >28 days	259 (22.0)	51.0	
	No	128 (10.9)	14.1	
BPD		65 (4.7)	58.5	20.1
Patent ductus arteriosus		235 (17.0)	40.9	18.0
Sepsis		404 29.3)	31.7	17.8
IVH / PVH		207 (15.0)	30.9	12.2
iNO		23 (1.7)	47.8	21.4
Prenatal glucocorticoïds		622 (45.1)	19.6	23.7
Postnatal glucocorticoïds		78 (5.7)	57.7	19.7
IRDS		663 (48.0)	26.7	17.4
NEC with perforation		27 (2.0)	63.0	21.1
Hyperglycaemia (>8mmol/l)		139 (10.1)	45.3	19.3
Packed cells		549 (39.8)	33.9	14.0

ELBW, extremely low birth weight; IVH/PVH, intra- periventricular hemorrhage; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; SGA, small for GA.
The denominator is 1380 except for some characteristics with missing data: female sex (n = 1180), small for GA (n = 1176), multiple birth (n = 1372), duration of artificial ventilation (n = 1179), duration of supplemental O2 (n = 1077), and LOS at NICU (n = 1176).

complete set of combined perinatal and ophthalmologic data of 1380 of 1561 infants (88%). A detailed flow chart of the study population is presented in Figure 1, and clinical characteristics are shown in Table 1. All ophthalmologists involved in ROP screening participated in the NEDROP study.

The incidence of ROP in the study population was 302 of 1380 (21.9%); 273 infants (19.8%) developed mild ROP (stage 1 and 2) and 29 infants (2.1%) severe ROP (>stage 3). The infants had a median GA 29.8 (IQR 28.1-31.1) weeks and median BW 1260 (1020-

1500) g, those with ROP 28.0 (26.4-29.4) weeks and 950 (780-1212) g and with severe ROP 26.3 (25.4-27.0) weeks and 890 (730-1060) g. Logistic regression analysis identified GA and BW as significant risk factors for ROP (P < .0001).

After adjustment for GA and BW, additional risk factors were as follows: iNO (OR 2.6, 95% CI 1.1-6.2, P = .03), NICU stay >28 days (OR 1.6, 95% CI 1.1-2.6, P = .03), and artificial ventilation >7 days (OR 1.6, 95% CI 1.1-2.5, P = .02). Prenatal glucocorticoids (OR 0.6, 95% CI 0.4-0.8, P < .001) and female sex (OR 0.7, 95% CI 0.5-0.99, P = .04) showed a significantly lower incidence of ROP (Table 2).

Twenty-three infants were treated with iNO. Of these, 47.8% developed ROP and 8.7% severe ROP. In 2009 iNO was administered in the first weeks of life in dosages of 5-20 parts per million (ppm), the vast majority of the hospitals starting with 20 ppm. Because of the potential confounding effect of other risk factors on the association of iNO and ROP, a final adjusted OR for iNO was estimated from the model that included all factors found to be significant in this study. iNO continued to be a significant risk factor for

Table 2 Risk factors associated with the development of ROP corrected for GA and BW.

	OR	p-value	95% CI
Obstetric characteristics and interventions			
Prenatal glucocorticoids	*0.6*	*0.0002*	*0.4-0.8*
Multiple birth	1.1	0.59	0.8-1.6
Infant characteristics			
Female Gender	*0.7*	*0.04*	*0.5-1.0*
Neonatal morbidity			
Sepsis	1.3	0.13	0.9-1.7
IVH / PVH	1.0	0.90	0.7-1.5
PVL	1.0	0.99	0.3-3.0
Patent ductus arteriosus	1.0	0.99	0.7-1.4
IRDS	1.1	0.66	0.8-1.4
BPD	1.3	0.35	0.7-2.3
NEC with perforation	2.3	0.09	0.9-5.9
Hyperglycaemia (>8 mmol/l)	1.2	0.53	0.7-1.8
Neonatal interventions			
Packed cells	1.1	0.50	0.8-1.5
iNO	*2.6*	*0.03*	*1.1-6.2*
Postnatal glucocorticoïds	1.6	0.08	0.9-2.8
NICU admission (weeks)	*1.2*	*0.0002*	*1.1-1.2*
AV (weeks)	*1.2*	*0.0016*	*1.1-1.4*
Oxygen administration (weeks)	1.1	0.08	1.0-1.1

IRDS, infant respiratory distress syndrome; PVL, periventricular leukomalacia.
Significant risk factors are in italic.

ROP (OR 2.6, 95% CI 1.1-6.2, P = .03). Because of the small number of infants treated the confidence interval is wide.

DISCUSSION

This nationwide inventory of infants born in 2009 in the Netherlands yielded a very large database because of the participation of all Dutch pediatricians, neonatologists, and ophthalmologists from hospitals involved in care for premature infants. Treatment with iNO for hypoxic pulmonary failure was found to be a risk factor for the development of ROP. Other already-known risk factors confirmed by this study were GA, BW, LOS in the NICU, and duration of artificial ventilation. A cohort study of Hoogerwerf et al[3] performed in the central Netherlands during 2001-2005 supported the results of this study. Comparable incidences of overall ROP (23.3% vs 21.9%), mild ROP (22.2% vs 19.8%), and severe ROP (1.2 vs 2.1%) were found and duration of artificial ventilation was found to be a significant risk factor for ROP. This study did not include data on iNO. Prenatal glucocorticoids and female sex were, as reported in other studies, related with a lower incidence of ROP.[9,10] Seiberth and inderkamp[11] demonstrated artificial ventilation for >7 days to be a risk factor for ROP. Amultivariate logistic regression analysis in a Chinese cohort study by Huang et al[12] showed that low BW and mechanical ventilation were significantly associated with ROP. Furthermore, Martinez-Cruz et al[13] performed a prospective study in their National Institute of Perinatology in Mexico and found several risk factors associated with the development of ROP, among which were GA, LOS on a NICU, mechanical ventilation, and oxygen therapy. The beneficial role of antenatal glucocorticoids on the severity of ROP is described by Higgins et al.[9] Given before birth, maturation of the fetal lung is stimulated, resulting in a reduction in respiratory distress syndrome, associated with decreased morbidity and mortality.[14,15] Darlow et al[10] identified male sex as a risk factor for ROP. Binet et al[16] found no difference in the rates of ROP between the two sexes, but male infants were more likely to die or have an adverse neonatal outcome than female infants and have poorer respiratory outcomes. The authors hypothesized that antenatal corticosteroids do not benefit male infants as much as they do premature female infants. Several studies describe an advantage in the survival of girls among premature infants supposedly related to differences in hormonal milieu and severity of illness.[17,18] The fact that administration of antenatal glucocorticoids and female sex both reduce morbidity can be an explanation for the reduced risk of ROP. iNO was found to be a risk factor for ROP. iNO may help to reduce hypoxic respiratory failure in preterm infants. It vasodilates the pulmonary vasculature through relaxation of smooth muscle cells, thereby improving oxygenation. Models in animals indicate that hyperoxia affects microvascular development in the lung and reduces the expression of VEGF. Currently

iNO is the treatment of choice for term infants with persistent pulmonary hypertension who do not respond to mechanical ventilation with high fractions of inspired oxygen and treatment with vasopressor-drug therapy.

In preterm infants, the use of iNO is a relatively new treatment modality.[19] It has been given as rescue therapy for severe acute respiratory failure, as prophylaxis to prevent BPD, and as treatment for severe BPD.[20] The influence of iNO on survival, chronic lung disease (CLD), and adverse neurologic events has been evaluated in a Cochrane systematic review and more recently in a systematic review by Donohue et al.[20,21] These reviews included 14 randomized controlled trials of iNO therapy in preterm infants and reported a reduction of 7% in the combined outcome of death or CLD. No evidence was found that iNO influenced the rate of other complications of prematurity such as severe ROP. Askie et al[22] performed an individual-patient data analysis in which raw data from 3298 individual participants of 12 randomized controlled trials were re-evaluated. There was no evidence that iNO therapy had a statistically significant effect on the primary end points of death, CLD, or severe neurologic sequelae. The use of a greater starting dose (>5 ppm) seemed to be associated with a better outcome, but the differences in the design of the included trials were substantial, making it difficult to draw strong conclusions.

In the current study, iNO treatment and development of ROP were found to be significantly associated. A possible explanation for this discrepancy may be that, contrary to previous studies, iNO treatment in the Netherlands, at the time of the NEDROP study, was only used as rescue therapy for preterm infants with a very high oxygenation index and not routinely in preterminfants with pulmonary disease. It was administered in dosages 5-20 ppm, the majority starting with 20 ppm, whereas other studies report maximum doses of 5-10 ppm and even treated infants routinely for pulmonary disease.[22]

There might be doubt whether iNO is correlated to supplemental oxygen use, artificial ventilation, or just following the severity of disease reflected in the time spent at a NICU. However, in this study, iNO continued to be significant after correction for such variables.

It is postulated that VEGF is an important mediator in the development of ROP. The relationship between iNO and ROP may be explained by the acutely increased oxygen saturation after the initiation of iNO treatment. This hyperoxia is also present in the retina. High oxygen tensions damage immature retinal capillary endothelial cells, thereby preventing complete vascularization, and cause further downregulation of VEGF, which compromises outgrowth of retinal vessels, thus facilitating the vaso-obliterative first phase of ROP. Because of its rapid effects, iNO therapy is also associated with large fluctuations in arterial pO2, another known risk factor for ROP.[23] These fluctuations may cause an imbalance of VEGF and therefore additionally enhance the negative effect on outgrowth of retinal vessels.

The strength of this national study is the extent and the completeness of the database, providing a realistic picture of the situation in our country. The anonymized data fa-

cilitated participation of all centers involved in care for the prematurely born. On the other hand, this anonymized data retrieval is also one of the limitations of the study as neonatal and ophthalmologic data were available for each individual patient but could not be linked directly to the center of treatment. Although the data retrieved were extensive, they did not provide information specific enough to calculate the relation between severity of illness and iNO bymeans of the oxygenation index or the Clinical Risk Index for Babies score, both measures of general illness.[24,25] For example, data per infant about start of treatment, doses administered, duration of treatment and targeted oxygen saturation during treatment with iNO are not available.

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Chapter 5

Reduction in screening for retinopathy of prematurity through risk factor adjusted inclusion criteria

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ABSTRACT

Aims

To develop a new national screening guideline for retinopathy of prematurity (ROP).

Methods

Included were infants of the 2009 prospective ROP inventory in the Netherlands with gestational age (GA) <32 weeks and/or birth weight (BW) <1500 g. Five models were studied, based on GA and BW in combination with no, one or a set of five risk factors for ROP. Risk factors were determined by logisticregression. In MEDLINE and EMBASE, additional risk factors were searched. A precondition was that no infants with severe ROP would be missed. Receiver operating characteristic curves or classical measures were used to determine diagnostic accuracy.

Results

The model including all infants with severe ROP comprised screening of infants with GA <30 weeks and/or BW <1250 g and a selection of infants with GA 30–32 weeks and/or BW 1250–1500 g, with at least one of the following risk factors: artificial ventilation (AV), sepsis, necrotising enterocolitis (NEC), postnatal glucocorticoids or cardiotonica. This model would not detect 4.8% (95% CI 2.5% to 8.0%) of infants with mild ROP and would reduce infants eligible for screening by 29%.

Conclusions

In the Netherlands, screening may be safely reduced using a new guideline based on GA, BW, AV, sepsis, NEC, postnatal glucocorticoids and cardiotonica.

INTRODUCTION

Retinopathy of prematurity (ROP) is a serious vasoproliferative disease of the retina of the very premature infant, which may lead to visual impairment or blindness. Treatment is possible and laser therapy is still preferable. As treated eyes have a better visual outcome than untreated eyes, timely detection of ROP through screening is important.[1] Different screening criteria are used worldwide and depend mainly on national incidences of ROP, which in their turn mainly depend on socioeconomic factors and local neonatal care. However, highly developed countries vary in their criteria also. The current UK guideline recommends screening of all infants with a birth weight (BW) ≤1500 g or a gestational age (GA) ≤31 weeks.[2] The American guideline advises screening all infants with a BW <1500 g or a GA ≤30 weeks and selected infants between 1500 g and 2000 g with an unstable course.[3] The screening criterion of Sweden is GA ≤31 weeks.[4] The Dutch guideline dating from 1997 advises screening infants with a BW <1500 g and/or a GA <32 weeks or preterm infants treated ≥3 days with ≥40% oxygen.[5] These guidelines have in common that they screen infants with GA ≤30 weeks, and most screen infants with GA 30–32 weeks. In the past decade, the incidence of ROP has altered. In Central Netherlands, a significant decrease in the incidence of overall and severe ROP was seen in infants with BW <1000 g in the period 2001–2005 compared with 1991–1995.[6] Also, Tan et al[7] found a reduction in the incidence of severe ROP in southeast Scotland from 1990 to 2009.

As screening for ROP is uncomfortable for the neonate, and costly and time consuming for the ophthalmologist, the aim of this study was to evaluate whether our inclusion criteria for screening could be reduced on the condition that no infant with severe ROP would be missed.

METHODS

The study group consisted of patients included in the NEDROP study, a prospective inventory of ROP in preterm infants born in the Netherlands in 2009. Paediatricians and neonatologists of the 103 Dutch hospitals involved in the care of premature infants reported all infants eligible for ROP screening according to the national guideline to the study centre.[5] Ophthalmologists reported all infants actually screened for ROP, any ROP classification, presence of 'plus disease', screening schedule and treatment. The NEDROP study was approved by the institutional review board (medical ethics committee of Leiden University Medical Centre, the Netherlands).

To extend the clinical data of the study infants, coupling to the national perinatal registry (PRN) was performed. This database contains data of more than 95% of all infants

with GA <32 weeks and/or BW <1500 g.[8] Because of the lack of data for older and heavier infants, only infants with GA <32 weeks and/or BW <1500 g screened for ROP were included. Infants were categorized into two groups: infants with GA <30 weeks and/or BW <1250 g (high risk (HR) group) and infants with GA 30–32 weeks and/or BW 1250–1500 g who do not fit into the HR group (moderate risk (MR) group). Clinical data, such as infant respiratory distress syndrome (IRDS), bronchopulmonary dysplasia (BPD), sepsis, intra-/periventricular haemorrhage (IVH/PVH), necrotising enterocolitis (NEC) and pre- and postnatal glucocorticoids were classified according to the definitions of the PRN.[8] In those cases where one or more characteristics were not recorded, we considered these data as missing. ROP was classified following the International Classification of ROP.[9] ROP was categorised as mild (stages 1–2) or severe (stages 3–5). A thorough search of the literature for risk factors of ROP was performed in MEDLINE and EMBASE from 2006 to December 2011 using the search terms ROP, risk factor(s), prematurity, screening and guideline. Papers were limited to English, Dutch, French and German language. Reference lists of selected manuscripts were examined for additional relevant publications. Only those factors registered in our PRN, easily accessible and available at the time of the first screening were selected.

To improve the efficacy of our current screening programme, several models were studied and compared with regards to reduction in the number of infants to be screened and the number of infants with ROP that would not have been detected on the precondition that no infant with severe ROP would be missed. A second precondition was that the model should be easy to use clinically and would be implementable. First we investigated if screening could be reduced to infants in the HR group (model 1). Secondly, a prediction model for all infants of the study group was developed, based on GA and BW model 2). Then one additional risk factor was added to the model based on GA and BW for all study group infants (model 3).

Risk factors investigated were pre- and postnatal glucocorticoids, length of stay (LOS) on a neonatal intensive care unit (NICU), duration of artificial ventilation (AV), inhaled nitric oxide (iNO), gender, sepsis, IVH/PVH and NEC. In model 4 we investigated combining screening of the HR group with infants in the MR group with one specific risk factor, apart from GA and BW. Therefore, for infants in the MR group, a model based on BW, GA and one additional risk factor was developed. Risk factors included were those of model 2, as well as patent ductus arteriosus, IRDS, BPD, supplemental oxygen, cardiotonica and erythrocyte transfusions. In model 5, screening of the HR group was combined with screening of infants in the MR group with at least one risk factor of a selected set of risk factors, including AV, postnatal glucocorticoids, cardiotonica, sepsis and NEC.

Statistical analysis

To calculate the probability that a child will develop mild or severe ROP based on GA or BW, a multinomial logistic regression model was applied. Additional risk factors for the development of ROP were explored with logistic regression. As some of the data consist of observations on multiple births, risk factors and probability of ROP for these neonates will be correlated. To take into account this dependency of the data, a generalised estimating equation approach was used to estimate the coefficients of the logistic regression model.

For each risk factor, a logistic regression model, including GA and BW, was explored. The ability of the model to discriminate between no ROP and ROP was quantified by the area under the receiver operating characteristic curve (AUC). For a model to be clinically useful, the predicted probabilities have to be low for children who do not develop ROP, intermediate for children with mild ROP and high for children with severe ROP. This was assessed graphically by plotting histograms of the predicted probabilities in the three groups.Classic measures for the diagnostic accuracy of model 1 and model 5 were calculated with 95% CIs.

RESULTS

Neonatologists and paediatricians reported 2193 infants, of whom 160 (7.3%) died before screening was completed. Of the remaining 2033 infants, 1688 (83%) were screened for ROP, of whom 1561 infants had GA <32 weeks and/or BW <1500 g.

After coupling to the PRN, 1380 infants were eligible to enter the study (81.8% of the screened population). Among these infants were 352 multiple births to 173 mothers. Infants had a median GA of 29.8 weeks and median BW was 1260 g. Clinical data are shown in table 1. The incidence of overall ROP was 21.9% (302/1380); the incidence of mild ROP was 19.8% (273/1380) and severe ROP, 2.1% (29/1380). A gradual decline in predicted probability for mild as well as severe ROP with increasing GA is seen in figure 1.

In the HR group (n=871), 246 infants (28.2%) developed mild and 28 infants (3.2%) severe ROP. If screening was confined to the HR group (model 1), a sensitivity of 0.91 (274/302) (95% CI 0.86 to 0.94), specificity of 0.45 (481/1078) (95% CI 0.41 to 0.48) and a reduction of infants to be screened of 36.9% (509/1380) was found. However, 10% (27/273) with mild and 3.4% (1/29) with severe ROP would have been missed.

In model 2, a prediction model for all infants of the study group was developed based on GA and BW. GA and BW were the most important risk factors for ROP in our study group (GA, $p<0.0001$; BW, $p<0.0001$). The AUC for this model was 0.80. Figure 2 shows the predicted probability of ROP using this model.

Table 1 Clinical characteristics of the study group, and incidence of (severe) ROP for each Characteristic

Characteristics	Study group (%)	Infants with ROP (%)*	Infants with severe ROP (%)*
N	1380	302 (21.9)	29 (2.1)
Median gestational age (wks) (P_{25}-P_{75})	29.8 (28.1-31.1)	28.0 (26.4-29.4)	26.3 (25.4-27.0)
Median birth weight (g) (P_{25}-P_{75})	1260 (1020-1500)	950 (780-1212)	890 (730-1060)
Extremely low Birth weight (<1000g)	345 (25.0)	178 (51.6)	6 (1.7)
Small for gestational age (<P_{10})	106 (7.7)	25 (23.6)	1 (0.9)
Female gender	527 (38.2)	108 (20.5)	13 (2.5)
AV	529 (38.3)	167 (31.6)	20 (3.8)
Supplemental O_2 administration	694 (50.3)	186 (26.8)	22 (3.2)
NICU Admission	1048 (75.9)	228 (21.8)	21 (2.0)
BPD	65 (4.7)	38 (58.5)	8 (12.3)
Sepsis	404 (29.3)	128 (31.7)	15 (3.7)
IVH / PVH	207 (15.0)	64 (30.9)	8 (3.9)
iNO	23 (1.7)	11 (47.8)	2 (8.7)
Prenatal glucocorticoïds	622 (45.1)	122 (19.6)	11 (1.8)
Postnatal glucocorticoïds	78 (5.7)	45 (57.7)	14 (17.9)
IRDS	663 (48.0)	177 (26.7)	20 (3.0)
NEC with perforation	27 (2.0)	17 (63.0)	5 (18.5)
Erythrocyte transfusion	549 (39.8)	186 (33.9)	20 (3.6)

AV = artificial ventilation
NICU = neonatal intensice care unit
BPD = bronchopulmonary dysplasia (extra O2 need at 36 weeks of gestation)
IVH/PVH = intra-or periventricular haemorrhage
iNO = inhaled nitric oxide
IRDS = infant respiratory distress syndrome
NEC= necrotising enterocolitis
P= percentile
*percentages: fraction of patients in this group with ROP or severe ROP, unless indicated otherwise

For infants without ROP, prediction was good, as the predicted probability was ≤0.20 for 71.7% of infants with no ROP. For patients with mild and severe ROP, prediction was less accurate. Only 36.2% of infants with mild ROP had a predicted probability between 0.35 and 0.65, and only 24.1% of infants with severe ROP had a predictive probability ≥0.70.
In model 3, the following risk factors were added to GA and BW, one at a time: pre- and postnatal glucocorticoids, LOS on NICU, duration of AV, iNO, gender, sepsis, IVH/PVH and NEC. None of these risk factors resulted in improvement in AUC.
In the MR group (n=509), 27 infants (5.3%) developed mild and one infant (0.2%) severe ROP. The AUC of the model, based only on GA and BW, was moderate in the MR group (0.69). Addition of any of the following risk factors gave no improvement in AUC: pre- and postnatal glucocorticoids, gender, sepsis, IVH/PVH, patent ductus arteriosus, IRDS,

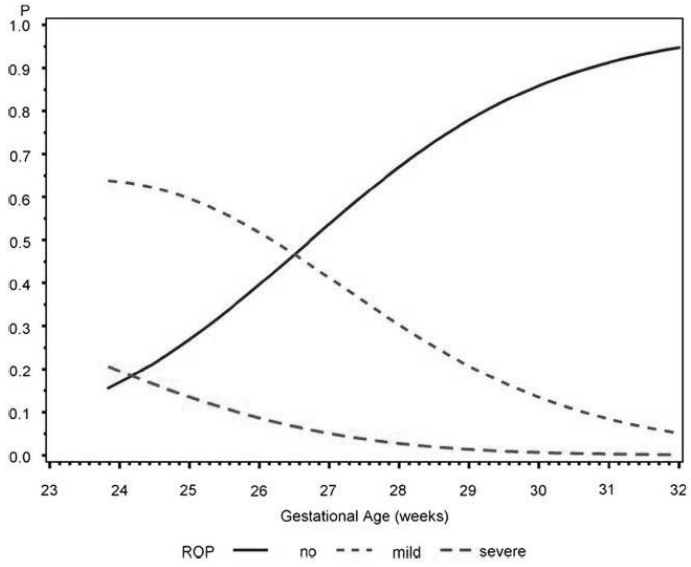

Figure 1 Predicted probability of no, mild and severe ROP in relation to gestational age for preterm infants born in 2009 in the Netherlands.

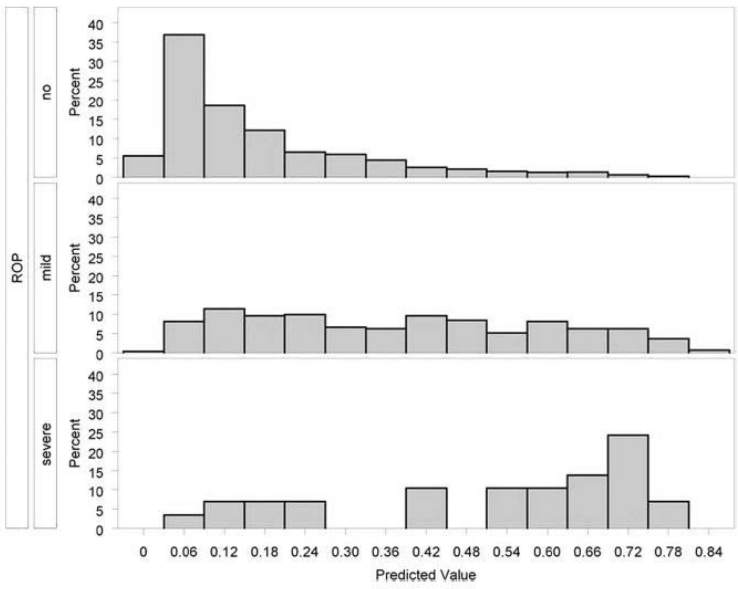

Figure 2 Predicted probability of ROP based on GA and BW for infants in the study group classified by observed ROP.

Table 2. Reduction in number of infants that need to be screened and in number of fundus examinations for different screening criteria in comparison with the old guideline.

Inclusion criteria	Infants (N)	Exam (N)	Reduction infants (%)	Reduction exam (%)
< 32 wks and/or < 1500g	1561	3705		
< 32 wks and/or < 1500g (study group coupled to PRN)	1380	3339	11.6	9.9
< 30 wks and/or < 1250g (HR Group)	871	2539	44.2	31.5
< 30 wks and/or < 1250g and 30-32 wks and/or 1251-1500g with ≥ 1 risk factor or unrecorded risk factors	1109	2919	29.0	21.2

BPD, duration of AV, LOS on NICU, iNO, supplemental oxygen, cardiotonica, NEC and erythrocyte transfusion (range of AUCs 0.68–0.72) (model 4). For model 5, a set of risk factors was selected. Of the risk factors found through the literature search, AV, postnatal glucocorticoïds, cardiotonica, sepsis and NEC met our selection conditions.

Of the 509 infants in the MR group, 107 needed AV, four postnatal glucocorticoïds, 28 had cardiotonica, 105 had sepsis and 10 had NEC. No risk factors were found in 271 infants (53.2%) and ≥1 risk factors in 177 infants (34.8%); data for 61 infants (12.0%) were incomplete. The true positive rate (TPR) of model 5 was 0.26 (289/1109) (95% CI 0.23 to 0.29) and the true negative rate (TNR) was 0.95 (258/271) (95% CI 0.91 to 0.98), assuming that children with missing data were also screened. The TPR of this model was low but no infant with severe ROP, and only 13/273 infants with mild ROP, were missed. Introduction of model 5 would result in exclusion from screening of at least 19.6% (271/1380) of infants in the study group, again assuming that infants with missing data are also screened. In comparison with the old guideline, this model would have resulted in a reduction of 29.0% (452/1561) of infants and 21.2% (786/3705) of examinations (table 2).

DISCUSSION

The aim of this study was to develop a new guideline for ROP screening in the Netherlands, on condition that restriction of the inclusion criteria for screening would not lead to infants with severe ROP being missed. For development of the guideline, a predictive ROP model was evolved for which ROP and clinical data for all infants with GA <32 weeks and/or BW <1500 g born in the Netherlands in 2009 and completely screened for ROP were used. Five different models were investigated. The model which included all infants with GA <30 weeks and/or BW <1250 g as well as infants with GA 30–32 weeks and/or BW 1250–1500 g with one or more of the risk factors AV, NEC, sepsis, postnatal glucocorticoids or cardiotonica, predicted the risk of ROP best (TPR 0.26 and TNR 0.95).

Using this model, no infant with severe ROP was missed and 4.8% with mild ROP were missed. We performed a literature search to find the most established risk factors for ROP and compared these with those available in our database and found in our study. Apart from being easily accessible, they should be available before the age of 5 weeks postpartum, as this is the time at which ROP screening for many infants already starts. Seiberth et al, Karna et al and Hoogerwerf et al demonstrated that duration of AV is a risk factor for (severe) ROP.[6,10,11] Treatment with dopamine was a risk factor for (severe) ROP in studies of Mizoguchi et al and Liu et al.[12,13] Hoogerwerf et al, Smolking et al and the systematic review of the Cochrane database showed that (late) treatment with postnatal steroids is a risk factor for ROP.[6,14,15] Lee, Chen et al, Weintraub et al and Jensen et al demonstrated perinatal infection/inflammation or sepsis to be a risk factor for (severe) ROP.[16–19] Arrøe proved this for NEC.[20] Most national ROP guidelines are based on GA and/or BW, the major risk factors for ROP. Another important risk factor, postnatal illness, is seldom considered. Recently, four ROP screening models based on postnatal course were developed: WINROP, ROPscore, cumulative illness severity and a model based on Clinical Risk Index for Babies score, multiple birth, race and gender.[21–24] All predicted proliferative ROP requiring treatment appropriately.

The former mentioned models could not be applied to our study as the PRN contains only limited information. Due to privacy regulations, data were also not accessible. In order to reflect the postnatal course, we added the risk factors AV, cardiotonica, postnatal steroids, sepsis and NEC, to GA and BW as selection criteria in our new screening guideline.

Our new guideline has two important advantages. First, compared with the old one, this model reduced the number of infants who required eye examinations by 29%, whereas 4.8% of infants with mild ROP and no infants with severe ROP would have gone undetected. This corresponds with a reduction of 21% of fundoscopies. As screening is stressful for the neonate, this decrease is important. On the other hand, we should also consider that screening can be made less uncomfortable for the infant and more efficient for the ophthalmologist by swaddling of the infant, use of a pacifier and/or sucrose, and by good positioning of the infant. Secondly, our guideline takes several pathological conditions into account that might occur within the first 4 weeks of life and predispose to the onset of ROP.

Our model also has two disadvantages. First, a small percentage of infants with mild ROP will go undiagnosed. Secondly, for the group of infants with GA 30–32 weeks and/or BW 1250–1500 g, who do not fit into the HR group, our model contains five items which have to be assessed. This implies extra work for the attending neonatologist or paediatrician. All items are, however, easily accessible and should be present in the letter of transfer, if patients are already discharged from the NICU before the first screening. If risk factors are not properly recorded, the old criteria (GA <32 weeks and/or BW <1500

g) should be used. External validation is essential for a new guideline.[25] Validation of the new guideline is currently underway in the Netherlands since September 2012. Future studies will be necessary for monitoring the accuracy of the model, as it was based on an ROP inventory study in 2009. In conclusion, in the Netherlands, ROP screening may be reduced by adding risk factors representative for each patient's postnatal course to the well known risk factors of GA and BW.
Although this implies an additional effort on the part of the neonatologist, it will reduce the number of infants exposed to these stressful examinations and will allow ophthalmologists to focus on those infants with the highest risk for ROP.
Monitoring of the new guideline is necessary.

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Competing interests
None.

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6

Chapter 6

Cost and effects of risk factor guided screening strategies for retinopathy of prematurity

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Submitted

ABSTRACT

Purpose

To investigate the cost and effects of risk factor guided screening strategies for retinopathy of prematurity.

Methods

Clinical data from the Netherlands ROP study (NEDROP study), that included all infants screened for ROP and born in 2009 were used to assess the cost and effects of several screening strategies for ROP using different criteria: (1) Gestational age(GA), (2) Birth weight(BW), (3) combined GA-BW and (4) combined GA-BW and presence of risk factors.

Results

The most efficient screening strategy to include all infants treated for both treatment strategies is to screen all infants with a GA of 30 weeks or less and a BW of 1250 g or lower together with infants with a GA of 30-32 weeks and a BW of 1250-1500 g with at least one risk factor. The marginal cost ranged from €43,848 to € 226,914 per additional infant with improved vision.

Conclusion

The current Dutch guideline may be improved: the same effectiveness can be obtained for lower costs. Also releasing the precondition that no infants with severe ROP might be missed, will lead to lower costs, but this will also lead to a lower number of infants with improved visual acuity. However, the costs of detecting all infants with severe ROP seems acceptable for society when also including the QALY gain and savings from a societal perspective resulting from improved vision.

INTRODUCTION

Retinopathy of Prematurity (ROP) is still one of the most important causes of partial sight or blindness in premature born infants. Various studies showed that early detection and treatment of ROP improve visual outcome.[1]
As younger and sicker infants are surviving, the number at risk for (severe) ROP increases. We conducted a prospective population based study, the NEDROP study, to inventorize the incidence and risk factors for ROP in the Netherlands. Based on these data the former ROP-guideline was adjusted to focus screening on those infants with the highest risk of ROP and reduce the infants exposed to stressful screening examinations. The new screening guideline included all infants with gestational age (GA) < 30 weeks and/or birth weight (BW) < 1250 gram (g) as well as infants with GA 30-32 weeks and/or BW 1250-1500 g with one of the following risk factors: artificial ventilation (AV), necrotising enterocolitis (NEC), sepsis, postnatal glucocorticoids or treatment with cardiotonica in the period between birth and the first screening examination.[2] A precondition for adjustment of the inclusion criteria was that no infants with severe ROP would be missed. As costs become more and more important in health care, the aim of this study is to compare the effects and costs of the Dutch screening strategy with other risk factor guided screening strategies, including strategies in which not all infants with severe ROP are detected.[3]

MATERIAL AND METHODS

Data

Clinical data were retrieved from the Netherlands ROP study (NEDROP study), that included all infants screened for ROP and born in 2009. Eligible to enter this study were infants with GA < 32 wks and/or BW < 1500 gram. The incidence of blind and visually impaired children was obtained from retrospective data from the Dutch institutes of the visually impaired.[3]
ROP was classified according to the International Classification of ROP (ICROP), the highest stage in either eye being reported.[4] For risk factor analysis the NEDROP database, encompassing all ophthalmological data, was merged with the Netherlands Perinatal Registry (PRN) which is a medical, professional based registry where pediatricians and neonatologists report their data of neonates born in the Netherlands.

In the NEDROP database 2193 infants were reported, of which 164 died (4 screening completed). Of the remaining infants, 1888 infants had a registered GA < 32 wks and/or BW < 1500 gram, of which 1551 (82.2%) were screened for ROP. ROP developed in

323 (20.8 %) infants, mild ROP (stage 1 and 2) was found in 294 (19.0%) and severe ROP (stage ≥ 3) in 29 (1.9%) infants. Seventeen (1.1%) infants were treated.

Data analysis

Several screening strategies for ROP were studied using different criteria: (1) GA, (2) BW, (3) combined GA-BW and (4) combined GA-BW and presence of risk factors. An overview of the strategies studied is presented in table 1.

Merging of NEDROP- and PRN database was possible for 1380 infants of the 1551 that are included in the present study. Missing data on risk factors were substituted using multiple imputation by chained equations[5], with 10 iterations for the switching regression model. For each missing data item, an imputation regression model was used that included GA, BW, treatment, presence of risk factors and ROP classification.

Using complete data the number of infants eligible for screening, severe ROP and treated were assessed for all screening strategies (table 1). This table was used to identify the strategies that screened the least number of infants for different numbers of

Table 1 Number of infants eligible for screening, diagnosed with severe ROP and treated for ROP for the different screening strategies

Nr	Criteria*	Eligible	Treated for ROP	Severe ROP
	GA, weeks			
1	<26	85	7	11
2	<27	179	13	21
3	<28	313	13	22
4	<29	477	13	22
5	<30	750	15	25
6	<31	1053	16	26
7	<32	1430	17	29
	BW, g			
8	< 700	72	5	6
9	< 1000	342	13	19
10	< 1100	465	15	22
11	< 1200	644	15	27
12	< 1250	726	15	27
13	< 1300	806	16	28
14	< 1400	956	16	28
15	< 1500	1134	17	29
	Combined, GA and BW			
16	< 29/<1200	382	13	22
17	< 29/<1250	407	13	22

Table 1 Number of infants eligible for screening, diagnosed with severe ROP and treated for ROP for the different screening strategies (continued)

Nr	Criteria*	Eligible	Treated for ROP	Severe ROP
18	< 29/<1500	456	13	25
19	< 30/<1200	485	14	24
20	< 30/<1250	529	14	24
21	< 30/<1500	672	15	25
22	< 31/<1200	572	15	25
23	< 31/<1250	628	15	25
24	< 31/<1500	871	16	26
25	< 32/<1200	610	15	27
26	< 32/<1250	678	15	27
27	< 32/<1500	1013	17	29
	Combined, GA and/or BW			
28	< 29/<1200	739	15	27
29	< 29/<1250	796	15	27
30	< 29/<1500	1155	17	29
31	< 30/<1200	909	16	28
32	< 30/<1250	947	16	28
33	< 30/<1500	1212	17	29
34	< 31/<1200	1125	16	28
35	< 31/<1250	1151	16	28
36	< 31/<1500	1316	17	29
37	< 32/<1200	1464	17	29
38	< 32/<1250	1478	17	29
39	< 32/<1500	1551	17	29
	Combined GA-BW-risk factor			
40	<30 wks and <1250 g and at least a risk factor	436	12	20
41	<32wks and <1500 g and at least a risk factor	687	15	25
	Combined GA-BW-risk factor			
42	<30 wks and/or <1250 g and at least a risk factor	666	14	24
43	<32 wks and/or <1500 g and at least a risk factor	899	15	25
44	< 30 wks and 1250 g OR 30-32 wks and/or 1250-1500 g and at least a risk factor	866	17	29
45	< 30 wks and/or 1250 g OR 30-32 wks and/or 1250-1500 g and at least a risk factor (current Dutch strategy)	1180	17	29

*Light grey: efficient strategies using the outcome of the NEDROP study (17 infants treated); Dark grey: efficient strategies using severe ROP as treatment strategy; Medium grey: efficient strategies for both the current treatment strategy and the severe ROP treatment strategy.

treated infants found (efficient strategies).[6] Two treatment strategies were evaluated: the infants actually treated in the NEDROP study (n=17) and the infants that would have been treated when early treatment guidelines would have been used (n=29).

Cost-effectiveness analysis

The efficient strategies were included in the cost-effectiveness analysis, in which the costs and effects of the different strategies were compared.

Cost of Screening

The costs resulting from the different strategies were estimated from a healthcare perspective. Costs are expressed in 2013 Euros. We used expert opinions to assess the personnel time and costs of equipment and disposables. Personnel time was valued using the salary costs increased with employers' costs.[7] Costs consisted of screening and treatment costs.

Costs of screening were assessed by multiplying the number of screening examinations per infant with the costs per screening. The mean number of screening examinations per infant was obtained from the NEDROP study[8] for infants diagnosed with no ROP (1.2), mild ROP (4.3) and severe ROP (8.0). Costs per screening consisted of nursing costs (40 minutes), costs of ophthalmologist (30 minutes), eyelid speculum and eye drops, resulting in €109 per screening.

Costs of treatment consist of ambulance transport costs, necessary for transfer to the treatment center, and costs of surgery. Ambulance transport cost amount to € 2282. Laser treatment was performed in 82.5% of the infants and the remaining part underwent vitrectomy. Cost of laser treatment amount to €2,755 (costs of operating theatre use, 2 surgery assistants, an anesthesiologist and an anesthetic nurse, an ophthalmologist (vitreoretinal surgeon), in 30% also a neonatologist during 105 minutes, and equipment costs of €31 per laser treatment) and cost of vitrectomy which amount to €5178 (costs of operating theatre, 2 surgery assistants, an anesthesiologist and an anesthetic nurse, ophthalmologist (vitreoretinal surgeon), in 30% also a neonatologist during 180 minutes, and equipment and disposable costs of €540).[9]

Effects

The effects of screening in terms of improved visual acuity depend on the improvement of visual acuity of early laser treatment compared to no treatment. However, only some smaller studies are available comparing the effects of early laser treatment with no treatment.[10-12] We therefore obtained the effect of laser treatment from the CRYO-ROP en ETROP study. The CRYO-ROP study[13] compared treatment with cryotherapy with no treatment and the ETROP compared the improved vision of early laser treatment with late treatment with cryotherapy.[14] Using the adjusted indirect comparison method[15;16],

we combined the improved vision of the CRYO-ROP study of 17.7% with an improved vision of 7.7% resulting from the ETROP study, giving an estimated improved vision of 25.4% of laser treatment versus no treatment.[13;14]

RESULTS

Table 1 presents the number of infants eligible for screening, diagnosed with severe ROP and treated for ROP for the different screening strategies.

Table 1 shows that the most efficient screening strategy to include all infants treated for both treatment strategies is to screen all infants with a GA of 30 weeks or less and a BW of 1250 g or lower together with infants with a GA of 30-32 weeks and a BW of 1250-1500 g with at least one risk factor. This requires screening of 866 children in the screening cohort.

The other shaded strategies are the most efficient strategies when detection of a lower number of children that need treatment would be accepted. In Table 2 the cost-effectiveness of the efficient screening strategies are shown. The strategies are presented by ascending order of persons with improved vision. In table 2a the efficient strategies are shown for the infants that were treated in the NEDROP study and in table 2b for treating all severe ROP. Also the cost and effects of the current and previous Dutch guidelines, respectively screening infants with GA <30 weeks *and* BW <1250 g and a selection of infants with GA 30-32 weeks and/or BW 1250-1500 g with at least one risk factor and screening infants with a BW <1500 g and/or a GA <32 weeks are presented for comparison.

The total costs per year of the different screening programmes (including treatment costs) range from €58,208 for the efficient strategy detecting 5 of the 17 infants that were treated in the NEDROP study (strategy nr 8) to €359,106 for the efficient strategy that detects all 17 infants (strategy nr 44). Detecting all 17 infants will on average lead to an improved vision in 4.3 infants. The average cost per person with improved vision (AC/PIV) ranges from €43,848 per person with improved vision when screening all infants with a GA of 26 weeks or less (strategy nr 1) to €82,953 for the efficient screening strategy that will detect all infants that were treated in the NEDROP study (strategy nr 44). Some efficient strategies were dominated by other strategies, i.e. there was an alternative strategy or combination of alternative strategies resulting in more infants with improved vision for lower costs.

The marginal cost per additional PIV is the most important outcome in the cost-effectiveness analysis. It indicates the additional cost of a unit of improved outcome of a dominant screening strategy compared to the next less intensive dominant screening strategy.

Table 2a Costs, effects and cost-effectiveness of efficient screening strategies for ROP (based on treatment practice determined in NEDROP study) compared to the current and previous Dutch strategy

Cost derivation	Screening strategy									
	BW <700	GA<26	GA<30 and BW <1250 and risk factor	GA<27	GA <30 and BW <1200	BW <1100	BW <1300	(GA < 30 and BW < 1250) OR GA 30-32 and/ or BW 1250-1500 and risk factor	Current NL strategy (GA < 30 and/or BW < 1250) OR GA 30-32 and/or BW 1250-1500 and risk factor	Previous NL strategy (GA<32 and/or BW<1500)
Infants to be treated for ROP detected	5	7	12	13	14	15	16	17	17	17
Number of screenings	267	341	1355	677	1497	1426	2214	2375	2997	3707
Total cost	58,208	77,692	220,067	149,563	244,843	242,918	334,824	358,190	426,080	503,563
No of PIV	1.3	1.8	3.1	3.3	3.6	3.8	4.1	4.3	4.3	4.3
AC/PIV	45,833	43,848	69,871	45,295	68,854	63,758	82,388	82,953	98,675	116,620
MC/APIV	Dominated	43,848*	Dominated	46,982	Dominated	183,769	Dominated	226,914	Dominated	Dominated

*compared to a situation without screening

(A)PIV: (additional) persons with improved vision; AC: average cost; MC: marginal costs

Table 2b Costs, effects and cost-effectiveness of efficient screening strategies for ROP (using severe ROP as criterion for treatment) compared to the current and previous Dutch strategy

Cost derivation	Screening strategy													
	BW <700	GA<26	BW <1000	GA <30 and BW<1250 and risk factor	GA <27	GA < 28	GA <30 and/or BW<1250 and risk factor	GA < 31 and BW<1200	GA < 31 and BW<1500	GA <32 and BW<1200	BW <1300	(GA < 30 and BW < 1250) OR GA 30-32 and/ or BW 1250-1500 and risk factor	Current NL strategy (GA < 30 and/ or BW < 1250) OR GA 30-32 and/ or BW 1250-1500 and risk factor	Previous NL strategy (GA<32 and/or BW <1500)
Infants to be treated for ROP detected	**6**	11	19	20	21	22	24	25	26	27	28	29	29	29
Number of screenings	267	341	1131	1355	677	1045	2214	1685	2347	1785	2214	2375	2997	3707
Total cost	64,023	101,224	233,971	266,591	196,087	242,017	350,222	329,319	407,403	351,955	404,611	427,976	495,866	573,349
No of PIV	1.5	2.8	4.8	5.2	5.3	5.6	6.2	6.4	6.6	6.9	7.1	7.4	7.4	7.4
AC/PIV	42,010	36,229	48,481	51,450	36,762	43,310	56,509	51,861	61,690	51,320	56,891	58,102	67,318	77,837
MC/APIV	Domi-nated	36,229*	Domi-nated	Domi-nated	37,348	Domi-nated	Domi-nated	Domi-nated	Domi-nated	102,276	Domi-nated	149,647	Dominated	Domi-nated

*compared to a situation without screening

(A)PIV: (additional) persons with improved vision; AC: average cost; MC: marginal costs

Detecting 7 or 13 children that need treatment, lead to marginal costs less than €100,000 per infant with improved vision (respectively €43,848 in strategy nr 8 and €46,982 in strategy nr 2). However, detecting also (some of) the other children that need treatment leads to higher marginal costs ranging from €183,769 (strategy nr 10) to € 226,914 (strategy nr 44) per additional infant with improved vision.
Total costs treating all infants with severe ROP are higher (table 2b), but as also the number of persons with improved vision will be higher, average and marginal cost per (additional) person with improved vision are lower, ranging respectively from €36,229 (strategy nr 1) to €61,690 (strategy nr 24) and from €36,229 (strategy nr 1) to €149,647 (strategy nr 42).

DISCUSSION

We found that even if we do not want to miss infants with severe ROP, there is a more efficient screening guideline than the current Dutch guideline, namely screening infants with GA <30 weeks *and* BW <1250 g and a selection of infants with GA 30-32 weeks and/or BW 1250-1500 g, with at least one risk factor. This screening strategy reduces the number of infants to be screened with 27% ((1180-866)/1180). In determining the current Dutch guideline a safety approach was chosen. Based on the results of 2009 stricter inclusion criteria for screening could be chosen to reduce the number of infants screened while still detecting all infants with severe ROP, as illustrated by the results of our economic evaluation. The current guideline has led to a reduction in yearly costs of €77,500 compared to the previous Dutch guideline dating from 1997 advising screening infants with a BW <1500 g and/or a GA <32 weeks[17], however further savings of €67,900 each year might be obtained by the more stringent screening strategy resulting from this study.
However, the probability that in another year infants with severe ROP will be missed will be higher if a more stringent screening strategy is used. Therefore, it is interesting to investigate the stability of the current results in follow-up studies of the NEDROP, using data from other calendar years or in large cohorts from other countries.
If we release the precondition that no infants with severe ROP should be missed, there are other strategies having lower costs per infant with improved vision (see table 2). To decide whether we accept missing children with severe ROP, we have to determine which costs per additional infant with improved vision are acceptable for society. For the current treatment strategy these marginal costs range from €43,848 to €226,914. These costs should be compared to the benefits of improved vision. These benefits include both gains in quality of life and societal cost savings, for example due to lower educational costs as these infants don't need special education. Assuming a mean visual acuity

of 0.20 in non-treated eyes and 0.48 in treated eyes[18], a yearly gain in utility of 0.10 can be obtained according to the formula of Sharma et al.[19] For an average life expectancy around 80 years[20] and applying a discount rate of 3% over this period, this amounts to 3.3 quality adjusted life-years (QALYs) for an infant with improved vision during lifetime. Relating this to the marginal costs of €226,914 results in a cost-utility ratio of €70,000 QALY, which is high compared to the acceptable range of €20,000-€40,000 per QALY in the Netherlands. To reach this acceptable range, improved vision should also lead to cost savings of more than €100,000 during lifetime. This may be attained by savings in special education which amount to about €6,000 per year (personal communication). With an average of 15-20 years of education in the Netherlands, these cost savings will be attained. Next to savings in special education, also other savings may be attained for example in home modifications and devices and costs for carers.

Infants with improved vision will also have a higher chance of getting a paid job. Goertz et al evaluated unemployment among 500 clients of Royal Visio, a large institute for the visually disabled, and found that 36.8% had a job.[21] However, when using the friction cost method to assess productivity costs, which is the preferred method in economic evaluations in the Netherlands [22;23], this will not lead to additional cost savings. Finally, infants born prematurely are at greater risk to have concomitant disabilities in later life.[3;24;25] To preserve as much vision as possible in infants with ROP is important for lifelong independency.

In the NEDROP study not all infants with severe ROP were treated, we therefore not only calculated the costs and effects of the treatment practice determined in the NEDROP-study (table 2a), but also the costs and effects if all infants with severe ROP were treated (table 2b), as it is expected that further implementation of the treatment guidelines according to ETROP will lead to the treatment of all infants detected with severe ROP. As shown in our analyses the efficient strategies of both treatment strategies largely overlap indicating that further implementation of treatment guidelines will not change which screening strategies are efficient in the Netherlands, but will lead to lower average and marginal cost per (additional) person with improved vision.

Several cost-effectiveness studies in retinopathy of prematurity are performed previously.[6;18;26-31] Part of them compared different treatment methods[26;31] or screening methods[27;28], a single screening strategy with no treatment[18] or different screening frequencies.[30] Lee et al 2001[6] and Yanovitch et al[29] compared different screening strategies, comparable with our analysis. Lee et al[6] found a screening strategy of screening only infants having a BW of 1200 g and less to be the most cost-effective strategy for routine ROP screening. In our cohort, we would have missed 2 infants treated for ROP using this strategy. Yanovitch et al [29] found a screening strategy with a BW <1500 g and a selection of infants with BW 1501 to 2000 g and greater than or equal to two significant risk factors to have the most favourable cost-benefit per infant screened. For our cohort,

this strategy would have detected all infants treated for ROP but at the expense of 1292 children to be screened, which is 49% more than in the most efficient strategy to detect all infants treated for ROP.

This study has some limitations. First, the analyses are based on the outcomes of ROP screening of a single year (2009), repeating the analysis for another year may lead to different results. Secondly, the results are assessed for the Dutch situation and may not be directly applicable to other countries. This is illustrated by the fact that Lee et al [6] and Yanovitch et al[29] found different screening strategies to be efficient for their study population. In future studies the stability of the current results over time and place have to be assessed.

Furthermore, we used the same percentage of improved vision due to early laser treatment for all children with severe ROP, independent of the ROP stage (3, 4 or 5). Also the use of the adjusted indirect comparison method to assess the improved vision, may be less reliable than a direct estimate.

In conclusion, based on our economic evaluation, the current Dutch guideline may be improved: the same effectiveness can be obtained for lower costs. Also releasing the precondition that no infants with severe ROP might be missed, will lead to lower costs, but this will also lead to a lower number of infants with improved visual acuity. However, the marginal costs of detecting all infants with severe ROP seems acceptable for society when also including the QALY gain and savings from a societal perspective resulting from improved vision.

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7

Chapter 7

Letter to the editor

Severe retinopathy of prematurity in twin–twin transfusion syndrome after multiple blood transfusions

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Retinopathy of Prematurity (ROP) is a potentially blinding disease in premature infants. Several risk factors associated with the development of ROP have been reported such as gestational age (GA), birth weight (BW), duration of artificial ventilation, sepsis and blood transfusions, whereas prenatal glucocorticoids would be protective. Vascularisation of the retina starts at 16 weeks and is completed around 40 weeks of gestation. Outgrowth of vessels is defined in 3 Zones, Zone I being the most central one.[1] Vascular Endothelial Growth factor (VEGF) and Insuline-like Growth Factor-1 (IGF-1), produced by the placenta, play a crucial role in vascularisation of the retina.[2] ROP is defined as abnormal vessel growth in the developing retina. In the first phase of ROP down regulation of VEGF together with a decrease of IGF-1 causes an arrest in vessel outgrowth. In the second phase of ROP IGF-1 levels slowly and VEGF-levels more rapidly increase causing plus disease (tortuosity and dilation of retinal vessels) and neovascularizations. Twin-Twin Transfusion Syndrome (TTTS) complicates 10-15% of monochorionic diamniotic twin pregnancies. This is a second report of TTTS accompanied by severe ROP and describes the history of two twins.[4] GA, BW, risk factors and specifications about ROP are presented in table 1. Both donor twins showed normal weight gain and catch-up growth. The course of development of ROP was remarkable as it developed rapidly although the outgrowth of retinal vessels had already progressed to peripheral zone II. In the first donor twin ROP stage 1 without plus disease was seen up to 39 weeks Post Menstrual Age (PMA) then rapidly progressing to stage 5. The second donor twin presented with stage 3 ROP with plus disease at the first examination.

Multiple births are unique because of the confounding effect of certain risk factors, such as GA and maternal risk factors, on incidence and severity of ROP. Both donor twins had several mild risk factors for ROP. The most striking difference between the donor and the recipient twins however is the number of blood transfusions given within 3 weeks postnatal age.

Red blood cell (RBC) transfusions are associated with an increased risk for ROP as they increase retinal oxygen levels by an increase in oxygen carrying capacity and a decrease in oxygen affinity of the red blood cell, caused by transfusing infants with adult hemoglobin having a reduced oxygen affinity as compared to fetal hemoglobin. A second explanation may be that blood transfusions increase the free, non-protein bound iron load leading to the production of free oxygen radicals that can cause irreversible damage to the developing retinal vessels.[5]

Last, an unintended side effect of RBC transfusions could be the concomitant administration of high doses of IGF-1. Hübler et al[6] reported that the IGF-1 load in RBC transfusions is equivalent to a single dose of 1 µg/kg, which is 5-10% of the adult dose. Hellström et al showed that a rapid increase in IGF-1 together with high levels of VEGF induces rapid growth of new vessels.[2] Based on this model, we hypothesize that artificial administration of IGF-1 via RBC transfusions causes a misbalance in IGF-1 and VEGF levels, resulting

Table 1 Characteristics of the twins

	Twin 1		Twin 2	
	Donor	**Recipient**	**Donor**	**Recipient**
Birth weight (g)	771	900	1270	1590
Gestational age (wks)	28+1	28+1	31+1	31+1
Prenatal glucocorticoïds	Yes	yes	Yes	yes
AV (days)	8	0	7	0
RDS (grade 2-3)	Yes	no	No	no
Inhaled NO	Yes	no	No	no
Transfusions	9	0	12	0
ROP				
ROP stage	5	no ROP	3	no ROP
Plus disease	Yes	no	Yes	no
First screening	33+4	33+4	37+4	37+4
PMA ROP	35+3		37+4	
PMA severe ROP	41+5		37+4	
ROP treatment	Laser Vitrectomy Lensectomy		Laser Vitrectomy Lensectomy	

in instant growth of neovascularizations in case of concomitant high levels of VEGF or postponement of neovascular growth when VEGF levels are low.

With this letter we want to create more awareness for those infants delivered after TTTS who need high numbers of RBC transfusions. Although their peripheral retina may be largely vascularized, they can develop potentially blinding ROP in a rapid and progressive way and should therefore be monitored closely so treatment can be in time and blindness can be prevented.

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Summary

Despite intensive research retinopathy of prematurity (ROP) is still an important cause of visual impairment or blindness in prematurely born infants. The number of infants susceptible for severe ROP continues to rise as the gestational age of infants continues to decrease due to improvements in perinatal care.

It is well established that early detection and timely treatment of ROP diminishes the chance of developing a permanent visual disability. An evidence-based screening guideline is an important tool to improve early detection. However, screening guidelines cannot be applied universally, as level of care and risk factors differ per nation. The aim of this thesis was to develop a new screening guideline for the Netherlands. To minimize the likelihood that an infant with severe ROP would be missed, this guideline required easy and widespread implementation and a high predictive value..

Before any new guideline can be developed, it is vital to assess current, nationwide practices regarding neonatal care, ROP screening and treatment. We performed a national, prospective observational study on incidence of ROP, risk factors, ROP screening coherence, influence of transfers between hospitals, treatment criteria and practices: the NEDROP study.

First we investigated the incidence of infants with a visual disability due to ROP that were registered in the Institutes for the visually impaired in the Netherlands. Chapter 2 describes a follow up study of three earlier Dutch studies and presents a 30 year overview of visual impairment due to ROP in the Netherlands. In addition to the incidence of visual impairment (VI) caused by ROP, concomitant disabilities in preterm neonates born between 2000 and 2009 were evaluated using data obtained from the Dutch Institutes for the visually impaired. In the study group of 42 infants with ROP (or visual impairment), we observed a gradual decrease of gestational age (GA) and birth weight (BW), an increase of duration of artificial ventilation (AV), supplemental oxygen administration, bronchopulmonary dysplasia (BPD), developmental delay, and behavioral abnormalities. Compared with the previous study (1994-2000), significantly fewer children were visually impaired due to ROP and the incidence of complete blindness significantly decreased. Although more children received treatment, one third did not. The incidence of concomitant disabilities remained remained unchanged (73.8 vs 68.6%).

Screening logistics and ophthalmological data of the NEDROP study are presented in Chapter 3. Participation in the NEDROP study was high: all screening ophthalmologists, neonatologists, and pediatricians of the neonatal intensive care units (NICU's) and high care centers (HC's) and one third of pediatricians of regional centers participated. All infants born with a GA <30 weeks and 85%-90% of infants with GA 30-32 weeks are admitted to a NICU. Therefore, our study provided good insight into screening logistics and incidence of ROP in the Netherlands. In total, 2033 infants were reported of which 1688 (83%) were screened. ROP developed in 324 infants (19.2%), with a low incidence of severe ROP (30 infants (1.8%)) of which only 17 infants (1%) were treated. Difficulties with

retrospective classification of infants in type 1 and 2 ROP suggested that ETROP criteria for treatment were not universally implemented at the time of the NEDROP study. The median post menstrual age (PMA) when ROP was first detected was 34.1 weeks. In 641 cases (38%), the initial screening examination was not performed within the required 42 days. In 99.2% of all cases, the date for follow up was accomplished within 3 days of the planned date. Transfer to another hospital increased the chance of not being screened from 12.9% to 25% in case of three transfers.

The reported data by neonatologists and pediatricians (GA, BW, date of birth, zip code and numbered multiple births), enabled coupling of our NEDROP database to the already existing perinatal registry. Yearly, more than 95% of infants born <32 weeks' gestation are reported to the Netherlands Perinatal Registry. Of the 1561 infants with GA <32 weeks and/or BW <1500 g reported in the NEDROP study, 1380 could be linked (88%) to the perinatal registry. Based on these data, a risk factor analysis was performed (Chapter 4). Similar to previous studies, a lower incidence of ROP was observed in females and after prenatal administration of glucocorticoids. We also confirmed previously reported risk factors including GA, BW, length of stay at a NICU > 28 days and Artificial Ventilation (AV) > 7 days. In addition, we found that treatment with inhaled nitric oxide (iNO) presented a risk factor for ROP development. Inhaled NO is commonly administered to the most severely ill neonates, and is a relatively new rescue therapy.

We then developed a new guideline with the aim to reduce the number of infants that require screening (Chapter 5), since screening is stressful to the neonate and time-consuming for the care-giver. Screening criteria were developed to assure that no infants with severe ROP were missed: GA <30 weeks and/or BW <1250g and a selection of infants with GA 30-32 weeks and/or BW 1250-1500g, with at least one of the following risk factors: AV, sepsis, necrotizing enterocolitis (NEC), postnatal glucocorticoids or use of cardiotonics. Applying these new criteria to our study group resulted in a 29% reduction in screening, at the cost of not detecting 4.8% infants with mild ROP but without missing any infants with severe ROP. This reduced the number of fundoscopies by 21%.

The final analysis conducted with the NEDROP data represents a cost-effectiveness study (Chapter 6). With increasing awareness for costs in health care, the aim was set to compare the effects and costs of the Dutch screening strategy with other risk factor guided screening strategies, including also strategies in which not all infants with severe ROP are detected. It proved possible to improve the cost effectiveness of the current Dutch guideline by screening infants with GA <30 weeks *and* BW <1250 g, and infants with GA 30-32 weeks and/or BW 1250-1500 g with one of the previously described risk factors. This screening strategy reduced the number of infants to be screened by 27%. Compared to the previous Dutch guideline dating from 1997, the current guideline has reduced yearly costs by €77,500. However additional yearly savings of €67,900 might be obtained by even more stringent screening strategy as shown in this study.

Even lower costs would be achieved by leaving out the requirement of not missing out on infants with severe ROP. However, this will increase the chance of missing infants with severe ROP and may therefore reduce the number of infants with improved visual acuity. As this poses ethical questions and infants with improved vision have a higher chance of getting a paid job and live independently, a safety approach was chosen when the criteria for the current Dutch guideline were set.

In Chapter 7, a special subgroup at risk for severe ROP is highlighted. Donors with twin-twin transfusion syndrome (TTTS) developed severe ROP, in contrast with the receiver twin who does not develop ROP at all. A large number of blood transfusions convene a possible deleterious effect by simultaneous suppletion of IGF-1 administered via these blood transfusions. Although their peripheral retina may be largely vascularized, they can develop potentially blinding ROP in a rapid and progressive way and should therefore be monitored closely, so treatment can be performed in time, and blindness can be prevented.

Conclusions and recommendations for the future

The overall goal of our study was to establish a guideline to optimize care for infants at-risk for development of retinopathy of prematurity (ROP). Before we started our prospective inventory, a retrospective study was performed to evaluate the number of infants with permanent visual disability due to ROP in the Netherlands. Three previous studies performed a similar assessment. We combined all data to provide an overview of more than thirty years of ROP in the Netherlands, reflecting changes in neonatal care and treatment policies in our country. A decrease was observed in children with visual impairment due to ROP, the percentage of concomitant and multiple disabilities remained high. One third of at-risk infants was not treated.

To obtain insight in the current status of ROP and the logistics involved in screening and care for premature born infants, we initiated a national prospective inventory: the NEDROP-study. In this study, which included 2033 infants, 83% of the population was screened and ophthalmological data could be coupled to perinatal data in 88%. The incidence of ROP was 19%. Transfer to another hospital increased the risk for loss to follow-up. In addition, ETROP criteria for treatment turned out to be not well applied since 12 out of 29 infants with severe ROP were not treated. By coupling the NEDROP database to the existing perinatal registry, we identified treatment with inhaled nitric oxide as a new risk factor for ROP in addition to already established risk factors as BW, GA, stay at a NICU > 28 days and AV > 7 days. Based on this risk factor analysis, an overview of the literature and the precondition that no infants with severe ROP should be missed, a new screening guideline for the Netherlands was developed. Using this new guideline the number of infants who require eye examinations can be reduced by 29% and more focus can be put on those infants with the highest risk for ROP. Cost effectiveness analysis showed that our new screening criteria are efficient, the marginal cost ranging from 43.000–226.000 euro per additional infant with improved vision. These costs are acceptable for society when also the QALY gain and savings from a societal perspective are included, resulting from improved vision obtained through treatment in time after timely detection.

RECOMMENDATIONS FOR THE FUTURE

Two recent changes in neonatal care are expected to increase the number of infants at risk to develop (severe) ROP in the Netherlands: 1) the change in resuscitation policy in our country: since the end of 2010 the advised resuscitation level was lowered from 25 weeks GA to 24 weeks GA[1], and 2) the new oxygen saturation level recommendations from the Neoprom meta-analysis.[2] These changes in treatment in neonatal care are also expected to increase the number of infants needing treatment and might have consequences for our screening and treatment strategy. Therefore, close monitoring of our data in future is mandatory, as well as monitoring the incidence of blind- and poor-

sighted infants known at the Dutch Institutes for the visually impaired. To ensure that the number of infants with visual impairment will continue to decrease over the coming years, it is required that at-risk neonates are screened, followed-up and treated in a timely manner. This also includes the twins with TTTS. These infants need to be investigated on larger scale. In addition, close collaboration between all professionals involved in the care and screening for ROP in premature infants is critical. Implementation of our newly developed guideline should facilitate good ROP practice, and should be evaluated within a few years. We also need to monitor if the reduction in screening, achieved with our new guideline, is safe or even can be reduced further. We therefore are engaged in the implementation of a (web-based) database to provide and retrieve up-to-date information about infants screened for ROP in the Netherlands. This will facilitate the detection of changes in incidence of ROP and severe ROP and call for modification of the guideline when required. Also, education and information about ROP is of prime importance. To provide such support, we developed an app that will be instrumental in delivering information about need of screening for an infant for neonatologists. An app that will facilitate import of data to the aforementioned web-based database for ophthalmologists is under construction.
Furthermore, an e-learning was developed to implement the current guideline, yielding CME credits for ophthalmologists.

Even though not covered by my thesis, it will be of great importance to investigate prevention and new treatment modalities.
As treatment in any form is substantial to prevent blindness, but not addressing the underlying cause, the possibility of preventing ROP should be further investigated. Several studies are underway to evaluate the effect of possible preventing factors, with the primary endpoint to get a reduction or elimination of severe ROP.
A pharmacokinetic and dosing study of intravenous IGF-1–IGFBP3 complex in preterm infants, showed no adverse effects and an increase in serum IGF-1 to in-utero concentrations.

Furthermore, granulocyte colony-stimulating factor (GCSF) a biologic cytokine to increase leukocyte counts, has been shown to increase levels of IGF-1, which supports normal vasculogenesis. So, GCSF may promote angiogenesis in ischemic retina without any known negative effect on VEGF.

Supplementing ω-3 long-chain polyunsaturated fatty acids reduces the risk of ROP in mice. An increased retinal omega-3 and omega-6 PUFA ratio had 50% protective effect against pathologic neovascularization due to increased regrowth of vessels after vessel loss.

More knowledge needs to be gained through preclinical studies regarding anti-angiogenic treatment in ROP, including dose, type, and safety. Not only do we need more knowledge about treatment with bevacizumab, also other anti-VEGF agents like pegaptanib (Macugen®) for partial blockage of VEGF-A, or drugs such as ranibizumab (Lucentis®) and aflibercept (Eylea®) for pan-VEGF-A blockage, need to be investigated.

Gene therapy shows promising results in mice, by targeting and regulation of various cytokines and growth factors known to be involved in the pathogenesis of ROP. However the safety of gene application therapy and its possible effects to a developing preterm infant are uncertain and have yet to be fully evaluated.

Improvement of screening as well as treatment together with better prevention of ROP will hopefully result in a decrease of visual impairment in preterm infants in the Netherlands. This will improve their quality of life and contribute to their independence. It would be of much importance if this could be demonstrated in NEDROP-2.

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Nederlandse Samenvatting

Bij veel te vroeg geboren kinderen blijft prematurenretinopathie (ROP) een belangrijke oorzaak van blind- en slechtziendheid. Dit ondanks uitgebreid onderzoek. De oorzaak hiervan is, dat de leeftijd, waarop deze kinderen geboren en in leven gehouden kunnen worden daalt door een betere neonatologische behandeling. Het aantal kinderen, dat ernstige ROP kan oplopen neemt hierdoor toe. Een vroege opsporing en behandeling van ROP kan de kans op het ontwikkelen van een visuele beperking en de ernst daarvan verminderen.

Een evidence-based richtlijn is een belangrijk hulpmiddel om de zorg voor deze hoogrisico prematuren te optimaliseren. Er is echter geen universeel screeningsprotocol op te stellen, omdat het niveau van de neonatologische zorg per land erg kan verschillen. Het doel van deze studie was om een nieuwe screeningsrichtlijn op te stellen voor Nederland die voldoet aan de volgende voorwaarden: relatief eenvoudig te implementeren en een hoog voorspellende waarde heeft zodat geen enkel kind met ernstig ROP gemist zal worden.
Voordat een nieuwe richtlijn kan worden ingevoerd is het van belang om eerst de huidige werkwijze ten aanzien van de neonatale zorg, ROP screening en behandeling vast te stellen. Daarom werden op nationaal niveau het screeningsproces, de invloed van overplaatsingen, de incidentie van ROP, de risicofactoren alsmede de behandelcriteria en de behandeling van ROP geïnventariseerd door middel van de NEDROP studie (hoofdstukken 3-6).
Hoofdstuk 2 beschrijft een follow up studie van drie eerdere Nederlandse studies en geeft een dertigjarig overzicht van de visuele gevolgen van ROP. Daarnaast worden aan de hand van gegevens van de Nederlandse Instituten voor visueel gehandicapten, ook bijkomende handicaps geïnventariseerd bij prematuren geboren in Nederland tussen 2000 en 2009. Deze groep (2000–2009) deze groep, bestaande uit 42 kinderen, werden een geleidelijke daling van de zwangerschapsduur (GA), het geboortegewicht (BW), een toename van de duur van kunstmatige ventilatie (AV), het toedienen van zuurstof, bronchopulmonaire dysplasie (BPD) en een achterstand in de ontwikkeling en gedragsstoornissen gevonden. Vergeleken met vorige studies (1994-2000), waren er significant minder kinderen visueel gehandicapt ten gevolge van ROP en was ook de incidentie van totale blindheid gedaald van 27.5% tot 7.1% ($p<0.05$). Hoewel het aantal behandelde kinderen toenam, werd een derde niet behandeld. De incidentie van bijkomende handicaps bleef hoog op een redelijk constant niveau (73,8% vs 68,6%).

In Hoofdstuk 3 wordt de logistiek van de NEDROP studie beschreven met betrekking tot de verkregen screenings- en oogheelkundige gegevens. De deelname aan de NEDROP studie was hoog: alle screenende oogartsen, neonatologen en kinderartsen van de

neonatale intensive care afdelingen (NICU's) en de high care centra (HC's) en 1/3 van de regionale centra deden mee.

Alle kinderen, geboren met een GA<30 weken en 85-90 % van de kinderen met een GA van 30-32 weken zijn op een NICU opgenomen. Deze hoge participatie en inclusie geven daarom een goed inzicht in de logistiek van screening en in incidentie van ROP. Van de 2033 kinderen, die werden aangemeld werd 83% gescreend. In 324 kinderen (19,2%) ontwikkelde zich ROP. De incidentie van ernstige ROP was met 30 kinderen (1,8%) laag. Hiervan werden 17 kinderen (1%) behandeld. Moeilijkheden bij de retrospectieve indeling van kinderen in type 1 en type 2 ROP doen vermoeden, dat de ten tijde van de NEDROP studie geldige ETROP criteria voor behandeling niet overal waren geimplementeerd.

De mediane post menstruele leeftijd (PMA) waarop ROP voor het eerst werd vastgesteld was 34.1 weken. In 642 gevallen (38%) werd de eerste screening niet uitgevoerd binnen de vereiste 42 dagen post natale leeftijd, terwijl in 99,2% de follow up afspraak wel binnen een periode van 3 dagen van de afgesproken datum viel.

Overplaatsing naar een ander ziekenhuis verhoogde de kans om niet gescreend te worden van 12,9% naar 25% in het geval van drie overplaatsingen.

Alle door de neonatologen en kinderartsen verstrekte gegevens (GA, BW, geboortedatum, postcode en of er sprake is van een meerling) maakten een koppeling mogelijk van de NEDROP database met de al bestaande Perinatale Registratie Nederland (PRN), waar jaarlijks meer dan 95% van de kinderen geboren bij een GA <32 weken wordt aangemeld.

Van de 1561 kinderen met een GA < 32 weken en/of een BW<1500 gram, die aangemeld werden in de NEDROP studie konden 1380 kinderen (88%) gekoppeld worden aan de gegevens van de PRN.

In Hoofdstuk 4 worden op basis van deze gegevens de risicofactoren geïdentificeerd en geanalyseerd. Hierbij werd net als in de literatuur een lager risico op ROP gevonden bij meisjes en na het prenataal toedienen van glucocorticosteroiden. Ook de al eerder gerapporteerde risicofactoren als GA, BW, duur van de opname op een NICU > 28 dagen en een kunstmatige beademing > 7 dagen werden bevestigd. Nieuw was de bevinding dat ook de behandeling met stikstof oxide (iNO) een risicofactor op het ontwikkelen van ROP bleek te zijn. Deze iNO behandeling is betrekkelijk nieuw en wordt toegepast bij de ernstigst zieke neonaten.

Op basis van alle resultaten, die uit deze gegevens naar voren zijn gekomen werd een nieuw screeningsprotocol geschreven. Uitgangspunten hierbij waren, dat er geen enkel kind met ernstige ROP gemist mocht worden en dat het aantal screeningsmomenten beperkt moest worden. Screeningsonderzoek is stressvol voor het kind en tijdrovend voor de oogarts. In Hoofdstuk 5 wordt de uitwerking van het opstellen van een risicofactoren model beschreven en de nieuwe richtlijn bevat de volgende screeningscriteria:

GA< 30 weken en/of een BW<1250 gram en een selectie van kinderen met GA 30-32 weken en/of een BW van 1250-1500 gram met tenminste een van van de volgende risicofactoren: AV, sepsis, necrotiserende enterocolitis (NEC) en het postnataal behandelen met glucocoticosteroiden of cardiotonica.

Uit toepassing van dit nieuw ontwikkelde screeningsprotocol op onze studiegroep bleek een screeningsreductie van 29% mogelijk ten koste van het niet opsporen van 4.8% van de kinderen met een milde ROP maar met behoud van het opsporen van alle kinderen met ernstige ROP.

Tot slot werd op basis van de NEDROP gegevens een kosten-effectiviteits analyse uitgevoerd. In Hoofdstuk 6 wordt een kosten-effectiviteits analyse beschreven, die op basis van de NEDROP gegevens werd uitgevoerd. Het doel van deze studie was om de kosten van dit Nederlandse screeningsprotocol te vergelijken met andere screenings protocollen op basis van risicicofactoren of minder strenge eisen aan de opsporing van kinderen met ernstige ROP.

De kosten-effectiviteit van het huidige Nederlandse protocol verbeterde bij screening van kinderen met een GA< 30 weken en een BW< 1250 gram en kinderen met een GA van 30-32 weken en/of een BW van 1250-1500 gram met een van de al beschreven risicofactoren.

De screeningsstrategie deed het aantal te screenen kinderen met 27% afnemen. Vergeleken met het Nederlandse protocol uit 1997 verlaagde het huidige protocol de kosten met 77.500 euro per jaar. Een stringenter screeningsprotocol kan hierbovenop nog een besparing van 67.900 euro per jaar opleveren.

Als men de eis, dat er geen kinderen met ernstige ROP gemist mogen worden, laat vallen kunnen de kosten verder omlaag. Dit doet dan de kans toenemen om kinderen met ernstige ROP te missen en kan dus het aantal kinderen met een verbeterde visusscherpte doen afnemen. Omdat dit ethische vragen oproept en omdat kinderen met een betere visus een grotere kans hebben op een betaalde baan en een onafhankelijk bestaan is voor de veilige criteria gekozen bij het opstellen van het huidige Nederlandse screeningsprotocol.

In Hoofdstuk 7 wordt een speciale groep kinderen met een verhoogde kans op ernstige ROP besproken. Bij het tweeling transfusie syndroom (TTS) ontwikkelden de donor kinderen ernstige ROP in tegenstelling tot de ontvangende tweeling, die helemaal geen ROP ontwikkelde. Een groot aantal bloedtransfusies heeft mogelijk een averechts effect, doordat hiermee extra IGF-1 wordt toegevoegd. Hoewel de perifere retina van deze kinderen uitgebreid gevasculariseerd is, kunnen zij op een snelle en sterk progressieve wijze een potentieel blindheid veroorzakende ROP ontwikkelen. Deze kinderen moeten zeer nauwlettend gemonitord worden, zodat op tijd met de behandeling gestart kan worden en hierdoor blindheid kan worden voorkomen.

D

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Lieve Chris, al sinds ik je ken (ruim 17.5 jaar), heb jij een rotsvast vertrouwen in mijn kunnen. Ondanks dat de laatste jaren soms behoorlijk uitdagend waren, ben ik heel erg blij dat we ons hier doorheen hebben geslagen. Het afronden van mijn promotie zal hopelijk zorgen van wat meer rust en tijd voor ons gezin.
Mijn allerliefste meisjes, Audriane en Emaline, het allergrootste geschenk gedurende deze jaren. Ondanks alle drukte en veranderingen blijven jullie vrolijk en nieuwsgierig naar nieuwe dingen, en zingen en knutselen we heel wat af.
Mijn lieve papa en mama, Aty en Adriaan, die mij in alles steunen. Jullie zijn fantastisch en dank voor alle peptalk, helpen met literatuur, oppassen op onze lieve dochters,

huis opruimen, heen en weer rijden etc etc etc. Jullie zijn echt fantastische ouders en grootouders.
Mijn lieve schoonouders, Chris sr en Marjon, bedankt voor alle belangstelling en steun en voor het schoonmaken van het huis, eten koken en natuurlijk het oppassen op de meiden. Door jullie weet ik hoe belangrijk het is om voor gehandicapte kinderen een en ander te verbeteren.
Mijn lieve zussen en tevens paranimfen, Nina en Joline. Heel erg bedankt voor alle hulp voor mijn promotie. Het was erg gezellig om weer eens met z'n drieën op pad te zijn voor het uitzoeken van lokaties voor receptie en diner.
Mijn dierbare vrienden Niels en Serra. Zij hoorden me niet alleen aan, zij zorgden ook voor de hoognodige ontspanning. Daarnaast staan jullie altijd voor ons en de kinderen klaar. '*Sante!*'
Ook mijn overige lieve vrienden, die ik door mijn werk en gezin stukken minder heb gezien dan gewenst.
Priscilla en Conny Kroezen, doordat jullie bijna elke ochtend bereid zijn vroeg op te staan om bij ons op te passen en de kinderen op tijd op de opvang en school te brengen, draait ons gezin goed. Ontzettend bedankt voor al jullie hulp en liefdevolle verzorging van onze dames.

Last but zeker not least: Veel dank aan alle deelnemers van de NEDROP studie, zonder wiens niet aflatende grote inzet deze studie niet zo succesvol was geweest!

CV

Curriculum Vitae

CV

Arlette Jacqueline van Sorge werd op 10 november 1980 geboren te Arnhem. Na het Montessori-onderwijs volgde de middelbare schooltijd waarin zij zich onder andere intensief bezig hield met de sport synchroonzwemmen. Dit resulteerde in een tweede plek in 1997 bij de Nederlands jeugdkampioenschappen, een eerste plek in 1998 en een tweede plek in 1999 bij de Nederlands kampioenschap senioren met de groep. Tot haar 19e woonde zij in Arnhem, waarna ze na het behalen van haar Gymnasium diploma naar Amsterdam is verhuisd om Geneeskunde te gaan studeren aan de Vrije Universiteit.

Tijdens haar studie heeft ze zowel haar wetenschapsstage als haar keuze co-schap in de oogheelkunde gedaan. In 2008 heeft zij haar studie geneeskunde afgerond, en in juni van datzelfde jaar is zij aangenomen aan het LUMC voor een promotieonderzoek naar prematurenretinopatie, de NEDROP studie.

Arlette heeft haar onderzoekswerk op oogheelkundige en pediatrie congressen gepresenteerd, in Nederland, Europa en Amerika. Dit heeft tweemaal geleid tot een 'Best presentation Award' tijdens het congres van de European Paediatric Ophthalmological Society (EPOS) in Parijs (2009) en Thessaloniki (2011).

Naar aanleiding van de data van de NEDROP studie, is door het Oogfonds het New Born Eyes project opgericht. Zij plaatsten 5 Retcams in diverse Nederlandse ziekenhuizen, waarvan de eerste op 3 oktober 2012 door de toenmalige Koningin Beatrix, beschermvrouwe van het Oogfonds, aan het Medisch Centrum Alkmaar werd uitgereikt.

Haar onderzoek leidde tot een nieuwe richtlijn voor prematurenretinopathie, die sinds 2013 is geimplementeerd. Hierop volgde de ontwikkeling van een nieuwe landelijke ouder-informatie folder. In diezelfde tijd is een Richtlijn Educatie Programma (REP-Online) in de vorm van een e-learning over ROP online gegaan, waarmee accreditatiepunten te verkrijgen zijn.

Daarnaast heeft Arlette zich bezig gehouden met het ontwikkelen van een ROP-app; deze is sinds april 2014 online en te consulteren via de iPhone en iPad.

Per 1 september 2012 is Arlette in opleiding tot oogarts aan het LUMC (opleider Prof. dr. G.P.M. Luyten en plv opleider Prof. dr. N.E. Schalij-Delfos).

Arlette woont in Zwanenburg en is getrouwd met Chris Verpoorten; samen hebben zij twee dochters: Audriane (5) en Emaline (3).


A

Addendum

SAMENVATTING RICHTLIJN PREMATURENRETINOPATHIE

(Goedgekeurd tijdens de Algemene Ledenvergadering van het Nederlands Oogheelkundig Gezelschap (NOG) in maart 2013.)

In onderstaande samenvatting staat een opsomming van de uitgangsvragen en aanbevelingen die in de richtlijn zijn beschreven betreffende prematurenretinopathie.

Uitgangsvraag 1

Wat zijn de **inclusie criteria** voor het screenen op ROP?

- Welke kinderen ontwikkelen ROP en hoeveel kinderen ontwikkelen een ernstige ROP?
- Wat zijn de perinatale risicofactoren voor het ontwikkelen van ROP?

De werkgroep adviseert ROP-screening van de volgende kinderen:

- Alle kinderen met een zwangerschapsduur < 30 weken en/of geboorte gewicht < 1250 gram.
- Alle kinderen met een zwangerschapsduur tussen de 30-32 weken en/of een geboorte gewicht tussen 1250-1500 gram welke één of meer van de volgende risicofactoren hebben:
  - Behandeling met kunstmatige ventilatie
  - Sepsis
  - Necrotiserende enterocolitis (NEC)
  - Behandeling met cardiotonica vanwege hypotensie
  - Postnatale behandeling met corticosteroïden
- Als differentiatie met de beschreven risicofactoren niet betrouwbaar uit te voeren is, wordt screening geadviseerd van:
  - Alle kinderen met een zwangerschapsduur < 32 weken en/of een geboorte gewicht < 1500 gram.

De werkgroep adviseert terugkoppeling van de bevindingen van screening door de oogarts aan kinderarts en verpleging om de bevindingen mee te kunnen wegen bij het beleid en optimaal monitoren van de zuurstofsaturatie te waarborgen.

Uitgangsvraag 2

Welk **screeningsschema** moet gehanteerd worden?

- Vanaf welke Post Menstrual Age (PMA) of Post Natal Age (PNA) moet gestart worden met screenen?
- Welke screeningsfrequentie wordt geadviseerd?

1e screening:

5 weken (35 - <42 dagen) na de geboorte maar niet voor 31 weken PMA:
Zwangerschapsduur 24 weken: 7 weken na geboorte
Zwangerschapsduur 25 weken: 6 weken na geboorte
Zwangerschapsduur ≥ 26 weken: 5 weken na geboorte

Vervolg controle:

Criteria	Frequentie
ROP met plus disease wanneer besloten wordt nog niet te behandelen (zie H 4)	Meer dan 1x per week
Avasculair in zone I ROP 1 of 2 in zone I, geen plus ROP 2 of 3 in zone II, geen plus ROP in regressie, zone I Fundus onvoldoende te beoordelen	Wekelijks
Avasculair zone II, geen ROP ROP 1 zone II ROP 1 of 2 zone III ROP in regressie, zone II en zone III	1x per 2 weken

Screeningsfrequentie ophogen: snel progressieve ROP

Screeningsfrequentie afbouwen:
- Bij meerdere vervolg onderzoeken afname ernst ROP
- Uitgerekende datum zonder ROP (PMA 40 weken)

Einde screening indien één van de volgende criteria bereikt is:
- Volledige vascularisatie
- Geen ROP, vaten zone III bereikt (= temporaal avasculair, nasaal vascularisatie voltooid)
- Duidelijke regressie ROP als uitgerekende datum bereikt is (PMA 40 weken), waarbij er geen sprake mag zijn van plus disease.
- Duidelijke groei van vaten over de demarcatielijn richting ora serrata
- Duidelijke regressie van ROP met verandering van de kleur van de wal van roze naar wit

Noot:
- Cave re-activatie ROP bij verslechtering patiënt na afbouwen screeningsfrequentie of als screening gestaakt is bij niet volledige vascularisatie.

Wanneer afgeweken wordt van de richtlijn dient men dit met reden te vermelden in het dossier van het kind. De hoofdbehandelaar bespreekt de mogelijke afwegingen met de ouders. Zo nodig dient onderzoek alsnog zo snel mogelijk gepland te worden.

Uitgangsvraag 3

Wat zijn de overwegingen bij **overplaatsing en verwijzing**?

- Wat zijn de overwegingen bij overplaatsing op niet-oogheelkundige gronden naar een ander ziekenhuis
- Wat zijn de overwegingen bij overplaatsing, op oogheelkundige gronden, naar een ziekenhuis met meer faciliteiten en/of expertise (academisch of regionaal)

Beslisboom: overplaatsing op niet oogheelkundige gronden naar ander centrum:

1) Bij geboorte: kalenderweek waarin screening plaats moet vinden wordt vastgelegd
2) Screening vindt plaats volgens protocol
3) Overplaatsing aan de orde en screening nog niet afgerond?
   - Inschatten risico op ROP
   - Kinderarts / neonatoloog overlegt, zo nodig, met kinderarts / neonatoloog in ontvangende ziekenhuis om te bepalen of:
   - Voldoende expertise en continuïteit aanwezig?

Ja: Overplaatsen
Nee: Niet overplaatsen naar dit centrum

Overplaatsing naar een centrum met meer faciliteiten en/of expertise?*

1) Als beoordeling en/of behandeling in het betreffende centrum niet mogelijk is
2) Als sprake is van onduidelijkheid over stagering en/of beloop

Als behandeling noodzakelijk is en in het huidige centrum onvoldoende faciliteiten en/of expertise voor behandeling aanwezig zijn

Geadviseerd wordt om regionale afspraken te maken over het overplaatsingsbeleid van prematuren met een verhoogd risico op ROP.

Toelichting:

* Centrum met faciliteiten en/of expertise voor screening:

- Expertise en logistiek voor ROP screening is aanwezig en neonatologische zorg passend bij de ernst van de situatie kan geboden worden.
- De continuïteit van de screening (NB absenties van oogarts, waarneming) is gewaarborgd.

Uitgangsvraag 4

Bij welke criteria moet ROP **behandeld** worden?

Behandeling van ROP dient te gebeuren volgens de ETROP criteria:
Type 1 ROP:

- ROP zone I met plus disease
- ROP 3 zone I met / of zonder plus disease
- ROP 3 zone II met plus disease
- ROP 2 zone II met progressie van of ernstige plus disease

Type 2 ROP: Dient nauwlettend in de gaten gehouden te worden.

- ROP 1 of 2, zone I zonder plus disease
- ROP 3 zone II zonder plus disease

Laagdrempelig overleg met een centrum met ROP expertise wordt geadviseerd.

Bij ernstige ROP en behandeling van ROP verdient het aanbevelingen de situatie vast te leggen met fundusfoto's.

Transpupillaire laser is de behandeling van eerste keus.

Behandeling van ROP dient uitgevoerd te worden door een oogarts met ervaring op dit gebied.

Uitgangsvraag 5

Welke **logistieke** aspecten tav ROP screening zijn van belang om het proces efficiënt te laten verlopen?

- Randvoorwaarden afdeling / ziekenhuis voor screening:
  - Verpleegkundig personeel
  - Materieel
  - Screenende oogartsen
- Hoe wordt de eerste screeningsafspraak geregeld?
- Hoe wordt gezorgd voor optimale mydriasis?

- Wie is verantwoordelijk voor het regelen van follow-up van screening bij overplaatsing van een kind?
- Hoe wordt de overdracht van informatie geregeld naar collegae?

De screening dient zo snel mogelijk uitgevoerd te worden, gedurende het onderzoek moet de algemene conditie van het kind in de gaten gehouden worden.

De oogarts wordt geassisteerd door een ervaren zorgverlener zodat tijdens de screening het kind goed gepositioneerd wordt en het onderzoek naar behoren kan worden uitgevoerd.

Voor optimaal comfort van het kind adviseert de werkgroep dat tenminste 30 seconden voor het plaatsen van de ooglidspreider een lokaal anaestheticum wordt toegediend.

De screening dient zo comfortabel als mogelijk te verlopen, dit kan door middel van juiste positionering, sucrose, speen en / of inbakeren van het kind.

Er dienen lokale afspraken gemaakt te zijn over hoe de logistiek in het ziekenhuis geregeld is betreffende het maken van de eerste- en de vervolg screening en het opvangen van acute situaties.

Met het toedienen van mydriatica dient 1 uur voor screening begonnen te worden. Beiderzijds 1 druppel tropicamide 0.5% en 1 druppel fenylefrine 2.5%, dit wordt na 15 minuten herhaald en dient in totaal 2 of 3 keer te gebeuren. Als de pupil niet wijd wordt dient de oogarts geïnformeerd te worden.

De hoofdbehandelaar is verantwoordelijk voor de juiste informatievoorziening voor follow-up bij overplaatsing van een kind.

Na screening dienen de volgende gegevens op het consultvel te staan:
- bij onvolledige vascularisatie zone aangeven
- bij ROP de graad en zone, aanwezigheid van (pre)-plus disease
- vervolg van screening
- mogelijke behandeling

In de overplaatsingsbrief van de kinderarts dient specifieke informatie over ROP vastgelegd te zijn: bevindingen bij onderzoek en afspraken over vervolgscreening of vermelding dat screening nog niet heeft plaats gevonden. Geadviseerd wordt om de kalenderweek te vermelden waarin (vervolg) screening moet plaatsvinden.

Uitgangsvraag 6

Hoe worden **ouders** geïnformeerd?

- Over screening en schema
- Bevindingen van screening
- Over ROP

Er wordt een begrijpelijke, informatieve ROP folder aan de ouders uitgereikt voordat de eerste screening zal plaatsvinden.

Informeer de ouders over dag(deel) waarop de screening plaats vindt.

Zorgverleners bepalen in samenspraak met de ouders of deze bij de screening aanwezig zullen zijn.

Na de screening worden de ouders van de bevindingen op de hoogte gesteld. Bij (dreigende) ernstige afwijkingen gebeurt dit in principe door de oogarts.

In het dossier wordt een notitie gemaakt over de inhoud van het gesprek met de ouders.

A

Samenstelling werkgroep

- Drs. J.L.A.M. Hillegersberg, neonatoloog St. Antonius Ziekenhuis, Nieuwegein.
- Dr. F.T. Kerkhoff, oogarts, Maxima Medisch Centrum, Veldhoven.
- Drs. I.L.A. van Liempt, oogarts, Amphia Ziekenhuis, Breda.
- Dr. L.J. van Rijn, oogarts, Vrije Universiteit Amtsterdam en Onze Lieve Vrouwe Gasthuis, Amsterdam.
- Prof. dr. N.E. Schalij-Delfos, oogarts, Leids Universitair Medisch Centrum. Leiden (voorzitter).
- Prof. dr. H.J. Simonsz, oogarts, Erasmus MC-Sophia, Rotterdam.
- Drs. A.J. van Sorge, arts-onderzoeker, Leids Universitair Medisch Centrum, Leiden.
- Drs. G.J. van Steenbrugge, directeur Vereniging Ouders van Couveusekinderen, Leidschendam.
- Dr. J.U.M Termote, neonatoloog, Universitair Medisch Centrum Utrecht / lokatie Wilhelmina KinderZiekenhuis, Utrecht.

ROP INFORMATION FOLDER

ROP screening

U krijgt deze folder omdat uw kind gescreend moet worden op een oogaandoening: prematurenretinopathie. Hierin kunt u nog eens nalezen waarom dit onderzoek noodzakelijk is bij uw kind.

Wat is Prematurenretinopathie?

Het netvlies (retina) is een onderdeel van het oog dat essentieel is voor het zien. De bloedvaten die dit netvlies van voeding voorzien zijn pas in de laatste weken van de zwangerschap volgroeid. Bij een te vroeg geboren kind zullen deze bloedvaten in de eerste levensmaanden dus nog moeten uitgroeien. Door veel oorzaken kan de normale groei van deze bloedvaten verstoord worden. Er is dan sprake van prematurenretinopathie, ook wel ROP genoemd.

Waarom worden te vroeg geboren kinderen oogheelkundig onderzocht?

Bij een klein aantal kinderen met ROP ontstaat een ernstige vorm die behandeld moet worden. Met deze behandeling wordt geprobeerd om blind- of slechtziendheid te voorkomen. Om die behandeling tijdig te kunnen uitvoeren is het belangrijk dat ROP in een vroeg stadium herkend wordt. Dit gebeurt door middel van een oogonderzoek.

Welke kinderen worden gescreend?

Kinderen die bij hun geboorte minder dan 1250 gram wegen en/of geboren zijn na een zwangerschapsduur die korter is dan 30 weken

en

Kinderen die bij hun geboorte tussen de 1250 gram en 1500 gram wegen en/of geboren zijn na een zwangerschapsduur tussen de 30 en 32 weken, die één van de volgende behandelingen / aandoeningen hebben gehad: beademing, sepsis, necrotiserende enterocolitis (NEC), behandeling met bepaalde medicijnen (cardiotonica) vanwege lage bloeddruk of behandeling met corticosteroïden na de geboorte.

A

Als er bij uw kind ROP is ontstaan zijn er twee mogelijkheden:

1. De ROP verdwijnt spontaan en de bloedvaten groeien alsnog op een normale wijze door. Gelukkig gebeurt dit bij het merendeel van de kinderen.
2. De ROP gaat steeds een stadium verder.

Na de screening wordt u door een zorgverlener van de bevindingen op de hoogte gebracht. Bij (dreigende) ernstige afwijkingen gebeurt dit door een oogarts.

Behandeling

Bij een klein aantal kinderen zal er vervolgens behandeling nodig zijn. Doorgaans is dit een laserbehandeling die kan worden uitgevoerd in een aantal gespecialiseerde centra. Het kan dus zijn dat uw kindje tijdelijk moet worden overgeplaatst naar een ander ziekenhuis. Met deze behandeling wordt het deel van het netvlies dat zuurstoftekort heeft uitgeschakeld, waardoor de productie van de stofjes, die de uitgroei van bloedvaten stimuleren, af neemt. Soms lukt dit onvoldoende wat kan betekenen dat nogmaals behandeling nodig is. In een enkel geval kan het voorkomen, dat ondanks alle inspanningen een kindje toch blind- of slechtziend wordt.

Uw kind

Wanneer er voor uw kind een afspraak ten behoeve van screening op ROP is ingepland, wordt u hierover geïnformeerd. U hoort op welke dag of dagdeel de screening plaats vindt.
Een onderzoek bij uw kindje kan vervelend zijn om te zien, maar het kan voor uw kind prettig zijn als u er wel bij bent. Overleg daarom met de zorgverleners van de afdeling of u bij het onderzoek aanwezig zult zijn.

Als uw kind overgeplaatst wordt, zullen de gegevens inclusief de termijn voor het eventuele vervolgonderzoek doorgegeven worden aan het volgende ziekenhuis. Mocht uw kind naar huis gaan en nog gescreend moeten worden dan krijgt u daarvoor een afspraak mee. Mocht deze afspraak echt niet door kunnen gaan dan moet op korte termijn een nieuwe gemaakt worden.
Wij willen u graag het belang van ROP-screening uitleggen. Het kan zijn dat dit met deze folder niet helemaal gelukt is en u toch nog met vragen bent blijven zitten. Raadpleeg in dat geval gerust uw arts voor verdere informatie.

Uw artsen

U heeft contact gehad met:

Neonatoloog / kinderarts: .....

Oogarts: .....

Nuttige websites

couveuseouders.nl
oogartsen.nl
nedrop.nl

Deze folder is tot stand gekomen in samenwerking met:

NOG Nederlands Oogheelkundig Gezelschap
NVK
VOC Vereniging van Ouders van Couveusekinderen

Zones
De mate van uitgroei van de bloedvaten wordt ingedeeld in 3 zones. In zone 1 zijn de bloedvaten het minst uitgegroeid en in zone 3 vrijwel volledig.

Stadia
ROP kent 5 stadia waarvan stadium 1 en 2 het meeste voorkomen. Dit zijn de mildste vormen.
Bij stadium 3 ontstaan er woekeringen van de bloedvaten en neemt de kans op bloedingen uit deze slechte bloedvaten toe.
Door bloedvaten die het oog in groeien en bloedingen in het oog, kan het netvlies van zijn plaats getrokken worden. In stadium 4 heeft het netvlies gedeeltelijk en in stadium 5 helemaal los gelaten. Dit laatste wordt ook wel het eindstadium van ROP genoemd.

Plus disease
Er wordt ook naar de dikte en kronkeling van de bloedvaten gekeken. Als de vaten erg dik en kronkelig zijn wordt dit 'plus disease' genoemd. Het aanwezig zijn van plus disease is geen goed teken, en meestal een reden om te behandelen.

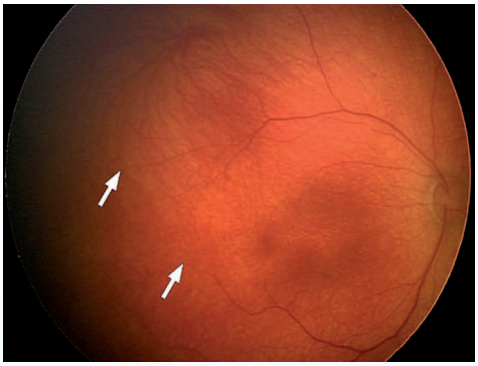


Foto van niet volledig uitgegroeide bloedvaten.
De pijltjes wijzen naar de plaats waar de uitgroei van bloedvaten gestopt is.

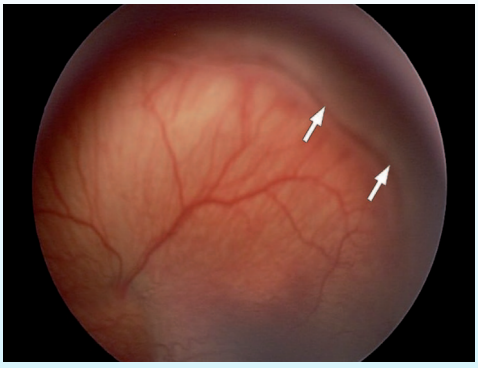


Foto van ROP.
De pijltjes wijzen naar de overgang van het gebied met en zonder bloedvaten.
Op de overgang is een verdikte wal te zien met vaatwoekeringen .
Ook zijn de vaten op deze foto dikker, dit is een teken van 'plus disease'.
Er is hier sprake van een ROP stadium 3+

A

Sommige ziekenhuizen onderzoeken alle kinderen met een geboortegewicht onder de 1500 gram en/of een zwangerschapsduur korter dan 32 weken.

Uw arts kan u hier meer over vertellen.

Wanneer wordt gescreend?

Het eerste onderzoek vindt in de 5e week na de geboorte plaats, maar niet voor de 31e week van de oorspronkelijke zwangerschapsduur.

Afhankelijk van de resultaten van het onderzoek en de leeftijd van uw kindje kan het nodig zijn dat het onderzoek na een aantal weken herhaald wordt.

Hoe verloopt het onderzoek?

Het opsporen van ROP gebeurt in de meeste gevallen door middel van een 'oogspiegel onderzoek'. In sommige ziekenhuizen maakt men gebruik van een speciale fotocamera, de Retcam.

Uw kindje krijgt eerst meerdere oogdruppels toegediend door de verpleging. Deze oogdruppels zorgen ervoor dat de pupillen wijd worden. Dit is noodzakelijk om het netvlies goed te kunnen beoordelen.

Nadat de druppels goed zijn ingewerkt kijkt de oogarts. De verpleegkundige assisteert tijdens het onderzoek en zorgt voor een comfortabele en goede positie van de baby. Soms vindt het onderzoek niet plaats op de afdeling waar uw kindje opgenomen is maar bijvoorbeeld op de polikliniek oogheelkunde.

Om het oog goed open te houden tijdens het onderzoek, wordt een spreidertje tussen de oogleden geplaatst. Dit vinden ouders vaak vervelend om te zien. Om te voorkomen dat uw kindje last heeft van het spreidertje geeft de oogarts vooraf verdovende oogdruppels.

De oogarts onderzoekt vervolgens het oog op tekenen van ROP. Hiervoor schijnt hij met een lampje in het oog, en kijkt door een loep naar het netvlies. Het onderzoek zal ongeveer een kwartier in beslag nemen. Tijdens het onderzoek huilen kindjes soms omdat zij het felle licht niet prettig vinden.

Ontstaan en indeling van ROP

Wanneer de bloedvaten die het netvlies van voeding voorzien niet voldoende uitgegroeid zijn, kan zuurstoftekort ontstaan in dat deel van het netvlies waar nog geen bloedvaten gegroeid zijn. Het netvlies probeert dit zuurstoftekort te corrigeren en gaat stofjes (angiogene factoren) afgeven die de uitgroei van bloedvaten stimuleren. Wanneer te veel van deze stofjes worden afgegeven kunnen woekeringen van de bloedvaten ontstaan. Omdat deze bloedvaten van slechte kwaliteit zijn kunnen ze gaan lekken en daardoor kan in het ergste geval het netvlies loslaten.

ROP wordt ingedeeld in zones en stadia.

EXAMINATION FORM

ROP onderzoeksformulier

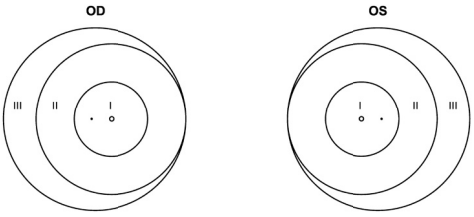
Gegevens patiënt / patiëntensticker

Naam:
BSN:
Geboortedatum:

Zwangerschapsduur:
Geboortegewicht:
Beademing ja / nee
Postnatale steroïden ja / nee
Sepsis ja / nee
NEC ja / nee
Cardiotonica ja / nee

Kalenderweek 1ste screening:

Datum	Avasculair		Zone I-III		AP-ROP		ROP graad 1-5		Plus disease		Behandeling		Datum vervolgonderzoek
	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	



Datum	Avasculair		Zone I-III		AP-ROP		ROP graad 1-5		Plus disease		Behandeling		Datum vervolgonderzoek
	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS