THE DUTCH RETINOPATHY OF PREMATURITY STUDY

NEDROP 2

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The Dutch Retinopathy of Prematurity Study

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Colophon

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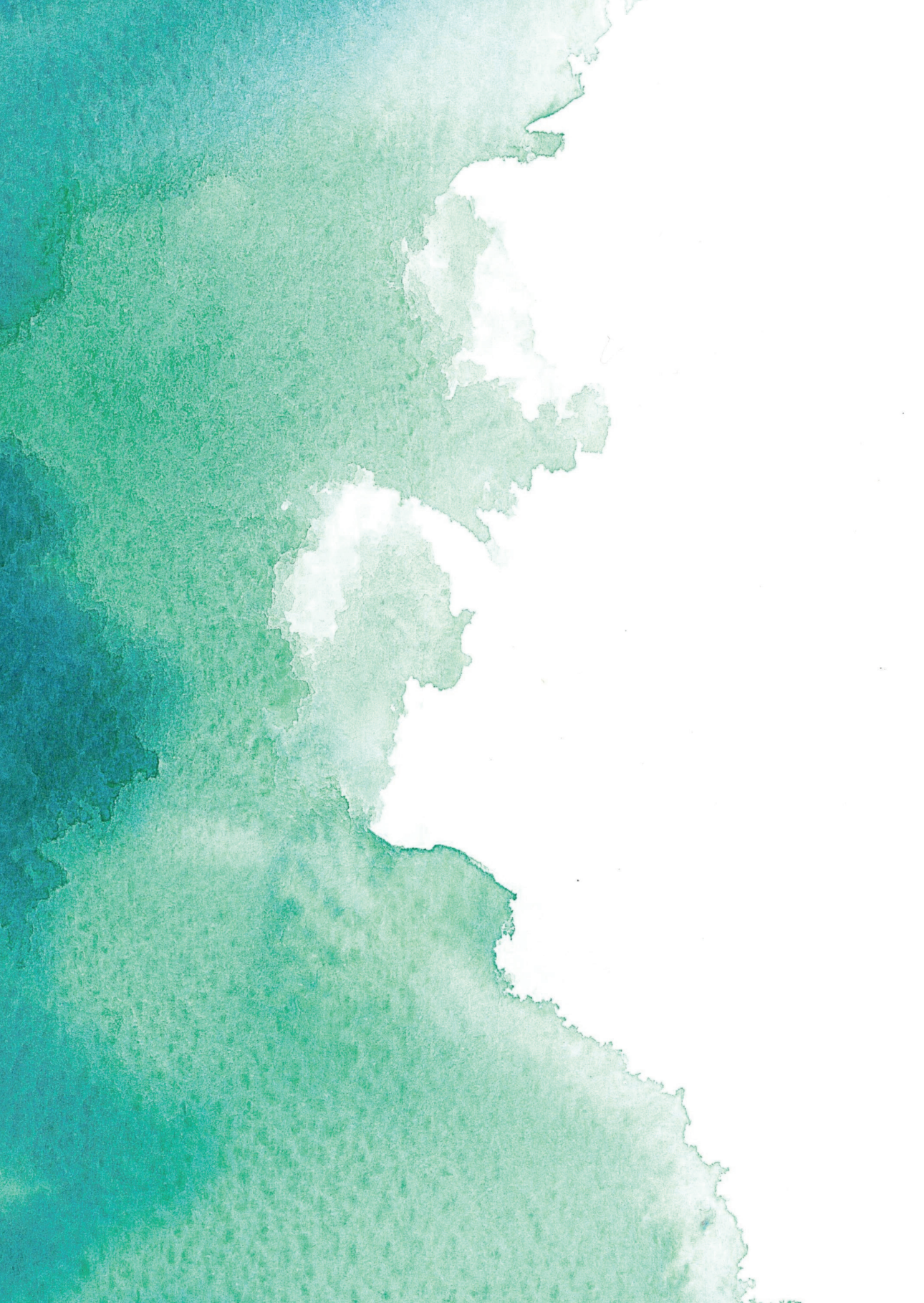
It is only with the heart that one can see rightly,
what is essential is invisible to the eye –

Antoine de Saint-Exupery in "Le Petit Prince"

Voor mijn Moeder

Abbreviations

A-ROP	aggressive retinopathy of prematurity
AP-ROP	aggressive posterior retinopathy of prematurity
BPD	broncho-pulmonary dysplasia
BW	birth weight
CRYO-ROP	cryotherapy for retinopathy of prematurity study
CVI	cerebral visual impairment
ETROP	early treatment for retinopathy of prematurity
EPO	erythropoietin
GA	gestational age
Hb	hemoglobin
HbA	adult hemoglobin
HbF	fetal hemoglobin
HIF-1	hypoxia inducible factor-1
ICROP	international classification of retinopathy of prematurity
IGF-1	insulin-like growth factor-1
MV	mechanical ventilation
NEC	necrotizing enterocolitis
NEDROP	the Netherlands retinopathy of prematurity study
NICU	neonatal intensive care unit
PDA	persistent ductus arteriosus
PMA	post menstrual age
PNA	postnatal age
PUFA	polyunsaturated fatty acid
(I)RDS	(infant) respiratory distress syndrome
ROP	retinopathy of prematurity
SaO_2	arterial oxygen saturation
VA	visual acuity
VEGF	vascular endothelial growth factor



Chapter 1

Introduction

General introduction and history

Globally retinopathy of prematurity (ROP) is the most common preventable cause of visual loss and blindness in premature infants (1). Currently, these devastating consequences of ROP are most pronounced in developing countries. Though much less common, ROP also remains a point of concern in high-income countries due to increasing survival of extremely premature and low birth weight infants. In the Netherlands, annually approximately 3 to 4 infants become visually disabled due to ROP (2).

History

ROP was first described in 1942 by Terry as *retrolental fibroplasia* (3), due to the white appearance of the pupil which was caused by retinal detachment. Hereafter, worldwide three "epidemics" of blindness due to ROP followed (4, 5). The first epidemic started in the 1940's in the US and, to a lesser extent in Western Europe, when premature babies were first treated in newly designed incubators enabling maintenance of (unmonitored and unrestricted) high oxygen concentrations for a prolonged time (6). Once the association between oxygen was made, its administration was curtailed to concentrations less than 40%. Though ROP rates nearly disappeared, mortality rate and number of babies with cerebral palsy drastically increased, eliminating the restricted oxygen policy for broad implementation (7). ROP re-emerged during the second epidemic which took place in industrialized countries in the 1980's with the ability to save even less mature babies. With significant advancements in intensive neonatal care– i.e. introduction of pulse oxygen saturation monitoring – the quality of care was improving. Nonetheless, the coverage of ROP screening and treatment was inadequate. Together with the increased number of extremely low birth weight infants (<1000 g) at risk for development of ROP, this resulted in a second wave of blindness due to ROP.

The third epidemic, has features of both first and second epidemic. It started in the 1990's and is observed until the present day in middle-income countries, i.e. South and Southeast Asia, Eastern Europe, South America, China and sub-Saharan Africa. In these countries expanding opportunities to treat more and younger premature infants are accompanied by limited recourses (i.e. shortage of equipment for continuous monitoring of supplemental oxygen) and limited knowledge and skills to examine, recognize and treat severe ROP. Furthermore, often identical screening and treatment programs are used throughout large geographical regions with variable standards of neonatal care, which therefore might not be uniformly applicable. Finally, costs of screening outside regular working hours for governmental employees and fear of litigation are emerging discouraging factors (4, 5). Altogether, these components are likely to have led to the alarming increase in ROP sequelae in these countries.

Associated morbidity

Fundamentally prematurity increases the risk of mortality and morbidity. Gestational age inversely relates to higher risk of prematurity related complications (8). Apart from ROP, preterm infants have an increased risk of many systemic conditions such as infant respiratory distress syndrome (IRDS), sepsis, necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia. These conditions in turn lead to susceptibility to systemic disorders in later life, i.e. chronic lung disease, cerebral visual impairment (CVI), nutritional disorders, neurodevelopmental delay and behavioral disabilities.

The most important ocular complications of infants with any stage of ROP in the neonatal period include: strabismus (18-33%), amblyopia (10-22%) and high refractive errors (26-31%) (9-14). Furthermore, there is a lifelong increased risk for macular dragging, retinal detachment, optic nerve atrophy, cataract, secondary glaucoma due to shallowing of the anterior chamber, microcornea, microphthalmos, corneal opacity and retinal ischemia (15-17).

As observed historically, improvements in neonatal care have led to a marked increase of premature survival. Identification of post-natal factors affecting the risk for and the course of ROP may help neonatologists and ophthalmologists to prevent the disease and to limit comorbidities with which it shares modifiable risk factors. In the Netherlands from 1972 onwards, the correlation of increased premature survival with an increase in children and adolescents developing sequelae was studied and confirmed in five consecutive inventories (2, 18-21). The last three surveys also studied concomitant disabilities, revealing a marked increase in broncho pulmonary dysplasia, developmental and behavioral abnormalities and multiple disabilities. These alarming findings underline the significance of visual function in order to sustain a degree of independent functioning within this already vulnerable population.

Poor visual outcomes due to severe ROP are largely preventable, providing that progressive stages are timely detected and treated. The occurrence of severe, sight threatening ROP, varies as it is a direct effect of the degree of prematurity and neonatal and ophthalmological care. This in turn strongly relates to regional socioeconomic standards and is known to fluctuate considerably among countries. Therefore a uniform guideline for inclusion of at risk infants cannot be widely implemented and a thorough, population based screening program is essential. In the Netherlands, data on risk factors, screening strategies, treatment outcomes and sequalae are generated through nationwide inventories (NEDROP). The first national ROP study in the Netherlands was conducted in 2009, leading to a new screening and treatment guideline in 2013, which will be discussed later into detail. Since the NEDROP study, continuous advancements and revisions of neonatal guidelines may have rendered

the 2013 ROP guideline less accurate. For this reason, it was crucial to redefine the current Dutch population at risk and provide evidence for an up to date quality guideline.

Etiology

The principal risk factor is the degree of the infants immaturity expressed as gestational age or birth weight as these two are strongly correlated. (22). Another extensively studied and important factor is oxygen, and more specifically the percentage of supplemental oxygen administered and the duration of treatment with supplemental oxygen. Particularly in the first weeks after premature birth, until 31st week of gestation, high oxygen saturation (SaO_2) ranges are detrimental for retinal vessel outgrowth and increase the risk of ROP. Moreover, target SaO_2 ranges should be carefully maintained as fluctuations in oxygen saturation are exceptionally harmful due to hypoxic-ischemic and re-perfusion injuries, which are associated with (severe) ROP (see chapter pathophysiology) (23-25).

Nevertheless, ROP has a multifactorial etiology and numerous demographic and biochemical factors, associated disorders, systemic treatments and other preterm, obstetric and/or maternal factors have been studied, among which the next are the most important:

Prematurity related: ethnicity (26), small for gestational age (27), duration NICU admission (28), respiratory distress syndrome (RDS) (28, 29), bronchopulmonary dysplasia (BPD) (30), persistent ductus arteriosus (PDA) (31), mechanical ventilation (32-36), necrotizing enterocolitis (NEC) and sepsis (37-39). Maternal: conditions associated with fetal hypoxia such as pre-eclampsia (40). Furthermore protective factors have been described such as prenatal steroids for the prevention of infant respiratory distress syndrome (IRDS) (41), treatment with surfactant (42, 43), and the immuno-protective and anti-oxidative properties of breast milk (44).

In conclusion, besides GA, BW and oxygen, the course of ROP is influenced by many components which ultimately are representative of the level of the baby's overall health. The strong relation with national neonatal and ophthalmological treatment policies causes these factors to vary or not always to be constant, and are the reason to monitor their influence on ROP outcome periodically.

Classification

In the papers presented in this thesis, ROP is classified according to second revision of the International Classification for ROP (ICROP 2) criteria (2005) (45). In this introduction we present the, recently adapted, classification according to ICROP 3 (2021) and define key changes made in the most recent revision (46):

- Addition of posterior zone II: the zone 2 disc diameters into zone II from zone I
- This is the part of zone II closest to zone I
- Definition of a notch: incursion of ROP from one zone into another, indicating a local developmental delay
- Broader definition of aggressive ROP
- Aggressive ROP (A-ROP) has replaced the previously used aggressive posterior ROP (AP-ROP), as this form of ROP does not only occur in the posterior pole
- Broader definition of plus disease: including the less severe pre-plus form
- New classification of end stage ROP (stage 5): including 3 subclassifications

Each eye is classified based on zone, plus disease, stage, and extent. ROP stages 1 and 2 without plus disease can be considered mild, because most cases resolve spontaneously and do not carry a high risk for visually disabling sequelae. Stages 3-5 and A-ROP are severe due to a higher risk of poor visual outcome. If aggressive ROP is present, this should be documented separately as more frequent examinations are warranted.

1. Location (fig. 1)
   The extent of vessel outgrowth is classified into four zones. The lower the zone number, the larger the avascular area and therefore, the higher the risk for severe ROP.
   a. Zone I
      The most posterior region, defined by a circle with radius twice the estimated distance from the optic disc center to the foveal center.
   b. Posterior zone II
      Region of 2 disc diameters peripheral to the zone I border. For practical purposes this can also be defined as the circle with a radius 3 times the distance from optic disc to macula.
   c. Zone II
      Ring-shaped region extending nasally from the outer limit of zone I to the nasal ora serrata and with a similar distance temporally, superiorly and inferiorly
   d. Zone III
      Residual crescent of peripheral retina that extends beyond zone II. To determine zone III with certainty, the nasal retina must be vascularized to the ora serrata and no ROP is present in the 2 nasal-most clock hours.

e. Notch (fig. 2B): incursion by the ROP lesion of 1-2 clock hours along the horizontal meridian into a more posterior zone than the remainder of the retinopathy. When present, this should be recorded by the most posterior zone of retinal vascularization, with the qualifier “secondary to notch”. For example, ROP in zone II in most places, but with a temporal notch extending to zone I, should be noted as: “zone I secondary to notch”, thereby distinguishing it from an eye in which most disease is present in zone I.

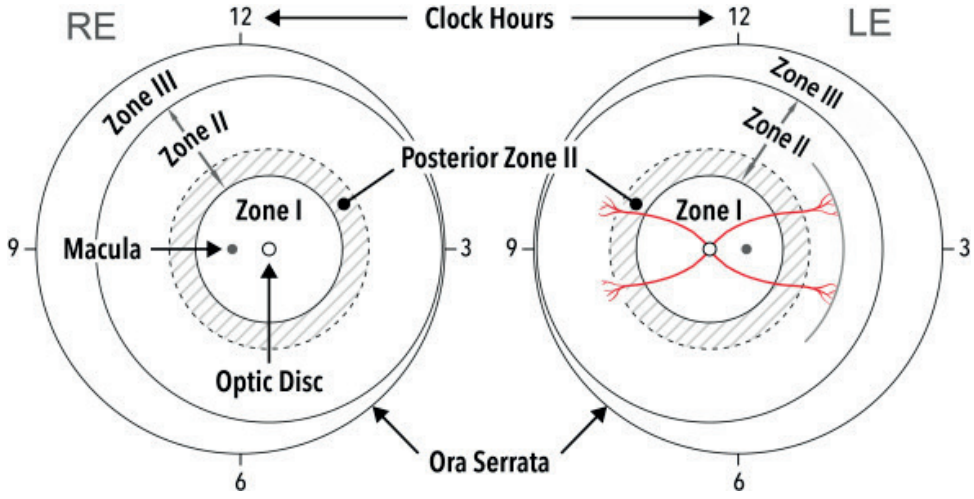


Figure 1. Location of ROP

Schema of right eye (RE) and left eye (LE) showing zone borders and clock hour sectors used to describe the location of vascularization and extent of retinopathy. Solid circles represent borders of zones I through III, and dotted circles represent borders of posterior zone II (2 disc diameters beyond zone I). A hypothetical example of examination findings is shown in LE, representing approximately 3 clock hours of stage 1 disease in zone II (note single line on drawing to document presence of stage 1 disease).

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2. Presence of plus disease (fig. 2)

   Plus disease is a sign of severe, potentially rapidly progressing ROP. It is defined as abnormal vascular dilation and tortuosity of the posterior retinal vessels present in at least 2 quadrants. Further advancement of plus disease severity is accompanied by vitreous haze and engorgement of iris vessels causing pupil rigidity. Preplus disease is also characterised by dilation and tortuosity, but insufficient for plus disease. Retinal vascular changes in ROP should be recognized as a continuous spectrum ranging from normal via preplus to plus disease.

3. Stage: to describe the appearance and severity of ROP
    a. Stage 1 (fig. 3A and 3B): characterized by a thin, flat, white demarcation line at the vascular-avascular margin/border/junction
    b. Stage 2 (fig. 3C and 3D): evolvement of the demarcation line to elevated and thickened ridge. Appearance ranges from white to pink with possible presence of small isolated tufts of neovascular tissue, called *popcorn*.
    c. Stage 3 (fig. 2E and 2F): ridge with extraretinal neovascular proliferation extending into the vitreous.
    d. Stage 4 (partial retinal detachment) (fig. 4)
        i. Stage 4a: not involving foveal region
        ii. Stage 4b: involvement of foveal region
    e. Stage 5: total retinal detachment with funnel configuration (fig. 5)
        i. 5a optic disc is visible
        ii. 5b optic disc is not visible due to retrolental fibrovascular tissue or closed-funnel detachment
        iii. 5c findings of 5b together with anterior segment abnormalities
4. Aggressive ROP (A-ROP) (fig. 6)

    Aggressive posterior ROP (AP-ROP) is a severe and rapidly progressive form of ROP in the posterior pole (zone I or posterior zone II). Typically, it occurs in the most vulnerable infants in terms of prematurity and illness, however it is increasingly seen in larger preterm infants and also located beyond the posterior retina. Therefore it is recommended to use the term aggressive ROP (A-ROP).

    Clinically two forms of A-ROP can be distinguished. In the first, all sequential stages are observed, corresponding to the typical course of ROP, but very rapidly. An alternative presentation of A-ROP is characterized by severe plus disease and rapid progression of neovascularization without being preceded by the typical stages of ROP. Furthermore, arteriovenous shunting and neovascular fronts resembling dilated vascular loops can be seen throughout the retina. These manifestations can also be seen within the ridge tissue in A-ROP presenting with the regular stages.

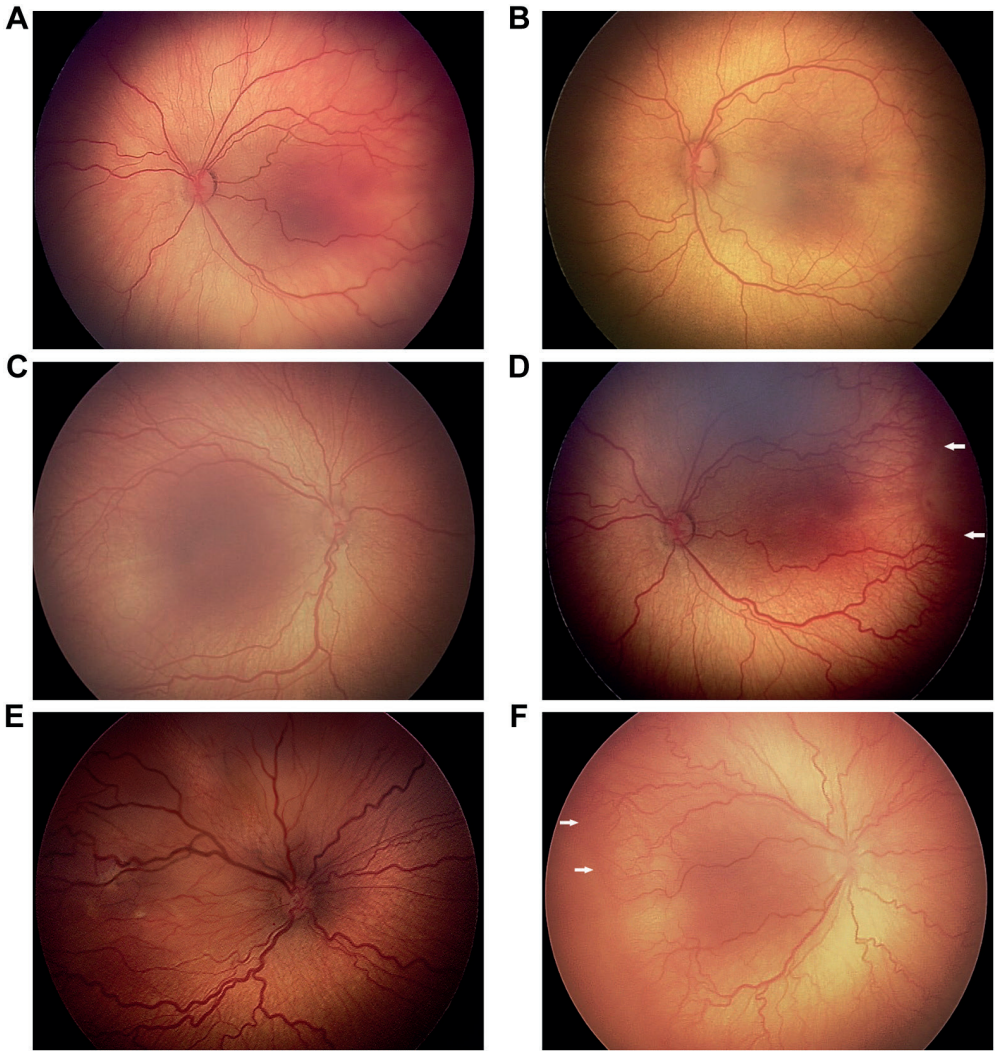

Figure 2. Plus disease and preplus disease

Note varying levels of vascular abnormality, which are assessed in the central retina within the region of zone I. **A**, Mild preplus disease, with more arterial tortuosity and venous dilation than normal. **B**, Preplus disease, with notable arterial tortuosity but minimal venous dilation. **C**, Preplus disease, with moderate arterial tortuosity and venous dilation, but considered by most committee members to be insufficient for plus disease. **D**, Plus disease with notable venous dilation and arterial tortuosity. Note that plus disease is out of proportion to visible peripheral findings, suggestive of flat neovascularization (stage 3; white arrows). **E**, Severe plus disease, with dilation and tortuosity of both arteries and veins. **F**, Severe plus disease. Note presence of ill-defined posterior flat stage 3 (arrows), which, combined with severe plus disease, is typical of aggressive retinopathy of prematurity.

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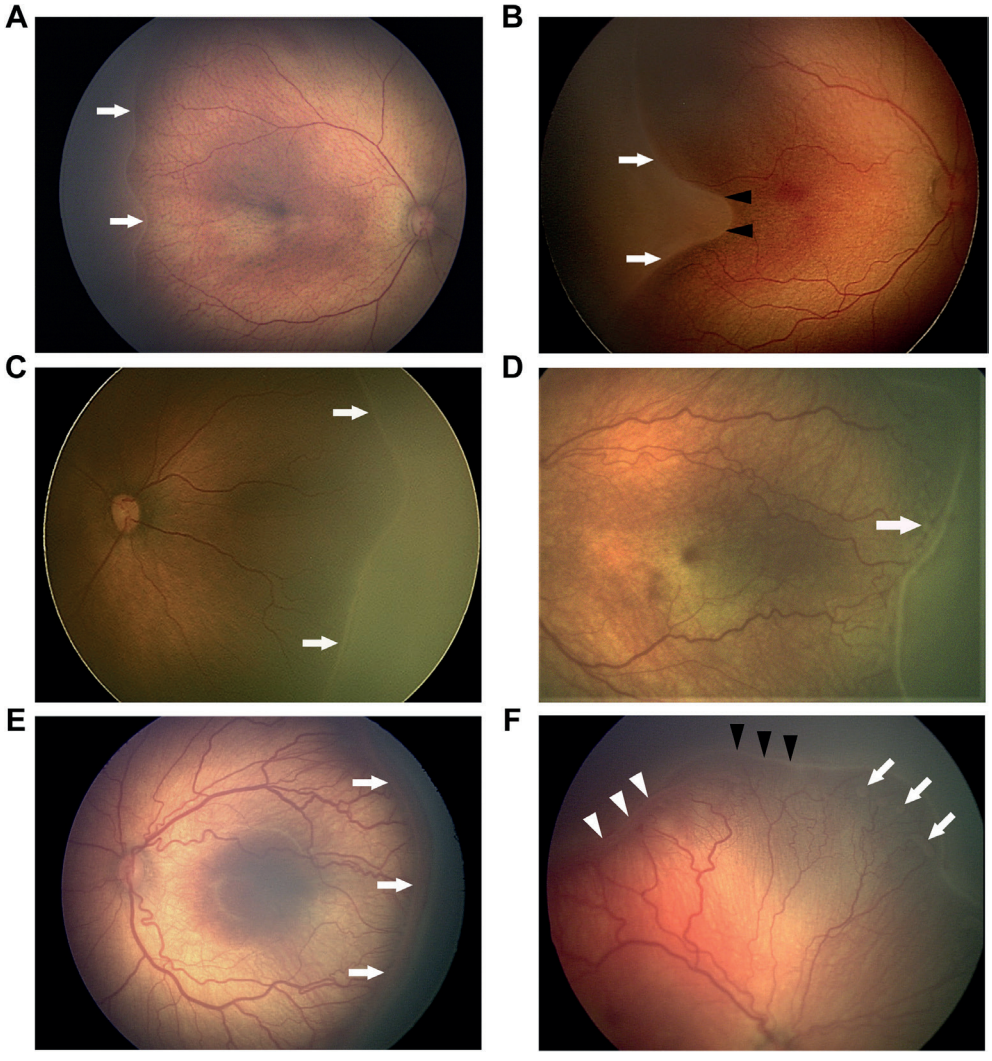

Figure 3. ROP stages 1 through 3

A, Stage 1 demarcation line at the border between vascular and avascular retina (white arrows). **B**, Stage 1 demarcation line (white arrows) and associated notch (black arrowheads) between vascular arcades that would be considered zone I secondary to notch. Note preplus disease with mild retinal vascular tortuosity and dilation. **C**, Stage 2 ridge, which is raised (white arrows) and thicker than stage 1. **D**, Stage 2 ridge. Note the so-called popcorn lesions posterior to the ridge (arrow) and preplus disease with mild vascular tortuosity and dilation. **E**, Stage 3 disease with extraretinal neovascularization (white arrows). Note plus disease with vascular tortuosity and dilation. **F**, Eye with both stage 2 (black arrowheads) and stage 3 (white arrowheads) disease and associated popcorn (white arrows). Note plus disease with vascular tortuosity and dilation. Figs 3E and 3F: Permission to reproduce previously published images from *Arch Ophthalmol* 2005;123:991-999.

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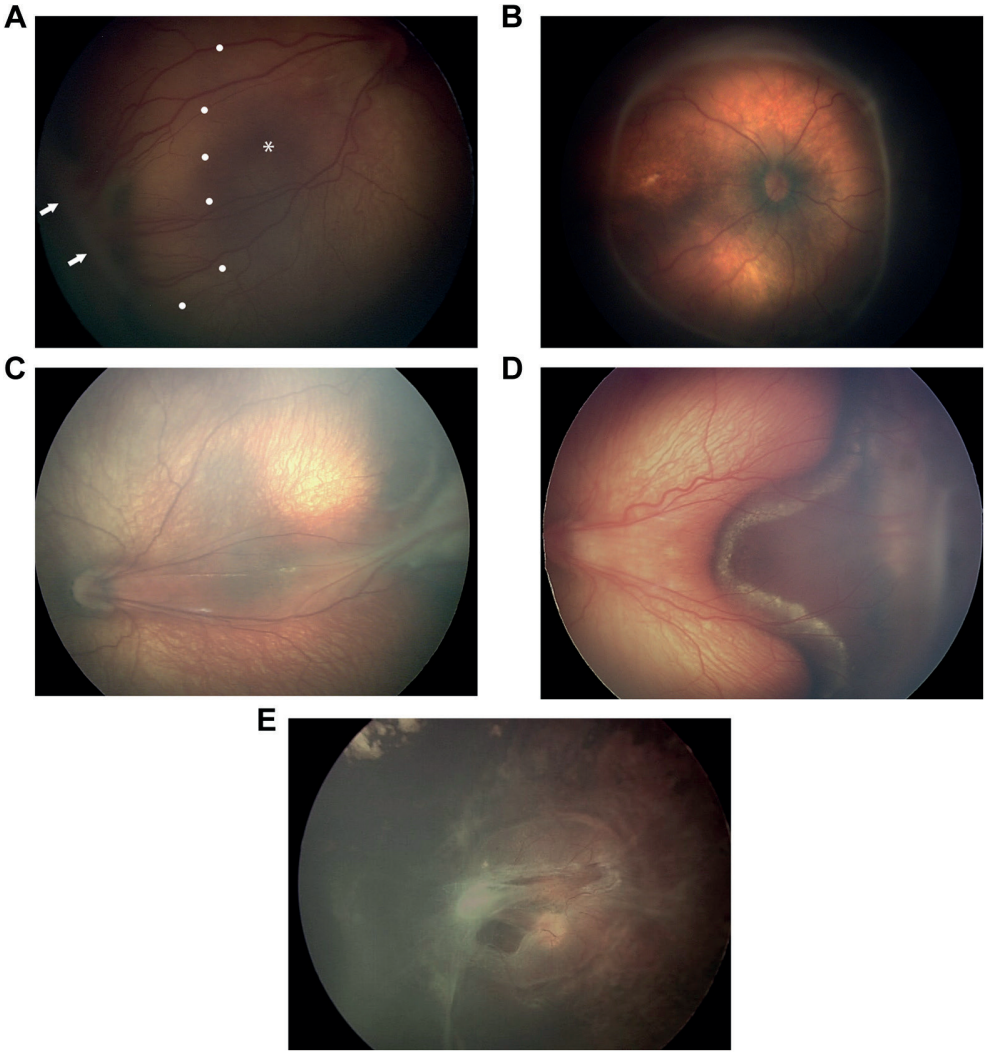

Figure 4. ROP stage 4

A, Stage 4A ROP in the temporal retina. Traction on extraretinal neovascularization leads to retinal elevation (white dots), which may be recognized during ophthalmoscopy by subtle change in brightness and loss of visible retinal pigment epithelium granularity and choriocapillaris detail. Note that the approximate foveal center (asterisk) is not elevated and the extraretinal neovascularization (white arrows) may be significantly more peripheral than the posterior extent of the detachment. **B**, Stage 4A ROP with 360° tractional retinal detachment in the area of the peripheral ridge. **C**, Stage 4B detachment involving the macula. Note straightening of the arcuate vessels and dragged of the optic disc appearance. **D**, Stage 4B detachment with associated subretinal hemorrhage and lipid exudation into the macula. **E**, Volcano-shaped stage 4B ROP. In eyes with posterior ROP, contraction of pathologic neovascularization can result in detachment of vascularized retina into a volcano-shaped configuration. Fig C: Permission to reproduce previously published images from *Arch Ophthalmol* 2005;123:991-999. Reprinted from Chiang et al.: International Classification of Retinopathy of Prematurity: Third Edition (*Ophthalmology*. 2021;128:e51–e68), with permission from Elsevier

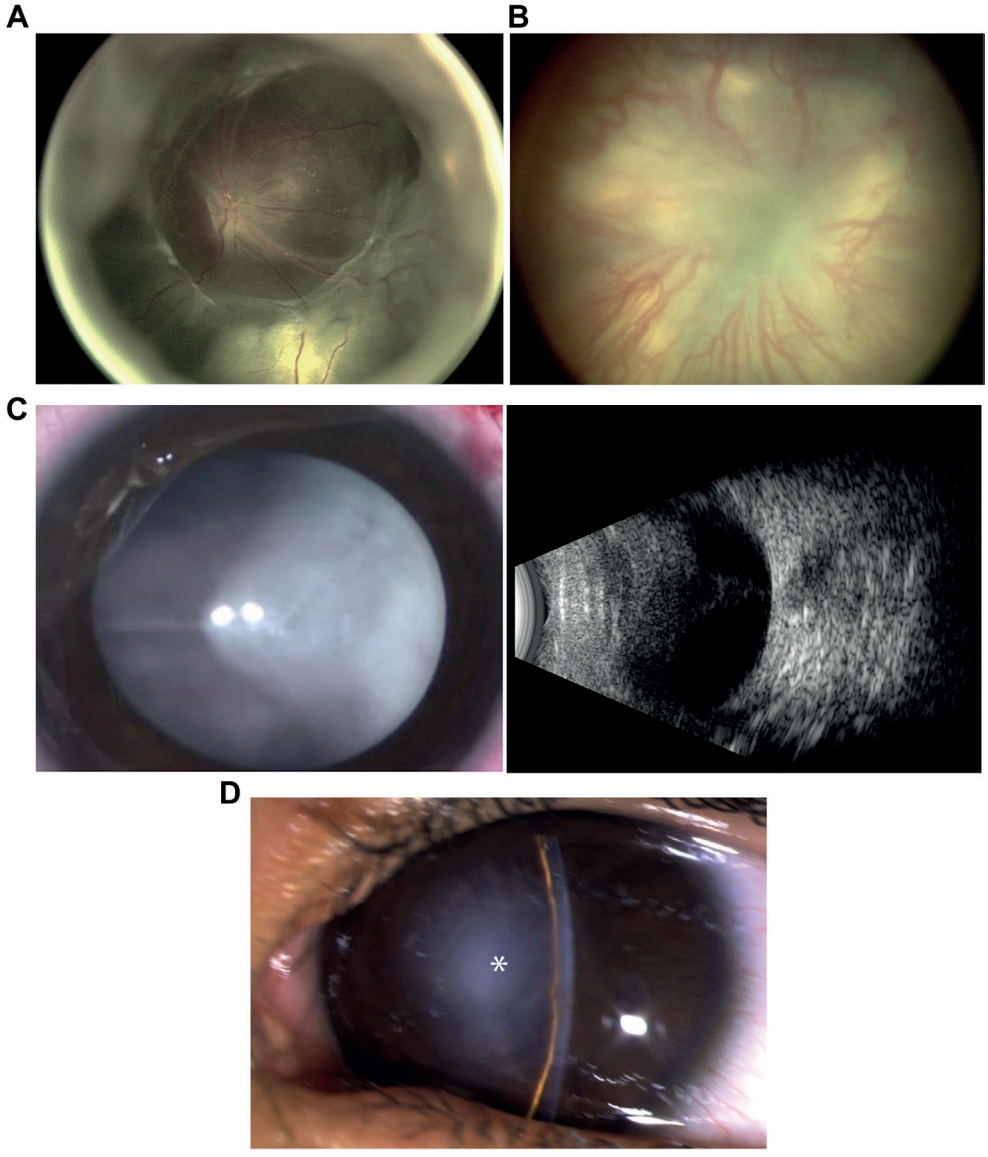

Figure 5. ROP stage 5

A, Wide-angle fundus photograph showing stage 5A ROP, characterized by a total retinal detachment with visible optic disc. Note the open-funnel configuration. **B**, Wide-angle fundus photograph showing stage 5B ROP, with no view of the optic disc because of fibrovascular tissue. **C**, External photograph of the normal anterior segment in stage 5B ROP (left side), with no view of the optic disc or retina secondary to retrolental fibrovascular tissue. B-scan ultrasonography (right side) reveals total retinal detachment with a posteriorly closed funnel configuration. **D**, External photograph showing anterior segment characteristic of stage 5C ROP with anterior lens displacement, marked anterior chamber shallowing, central iridocapsular endothelial adhesion, and central corneal opacification (asterisk) that prevent view of a closed-funnel retinal detachment. Fig 10B: Permission to reproduce previously published images from *Arch Ophthalmol* 2005;123:991-999.

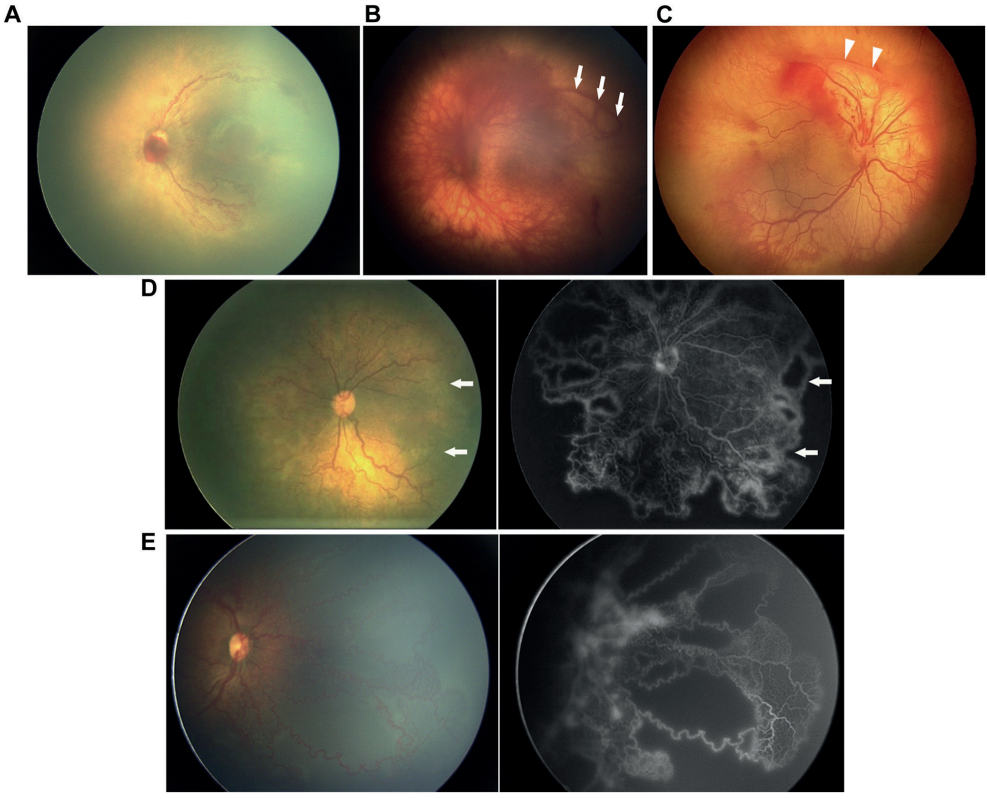

Figure 6. Aggressive retinopathy of prematurity (A-ROP)
A, Fundus photograph showing aggressive ROP (A-ROP) with severe vasoconstriction, capillary nonperfusion, nonphysiologic dilated vascular loops, and arteriovenous shunts and plus disease in zone I. **B**, Fundus photograph showing A-ROP with border between vascular and avascular retina in zone I, dilated vascular loops (white arrows), diffuse flat extraretinal neovascularization most prominent superotemporally, and severe plus disease. Note the absence of a typical stage 3 lesion. **C**, Fundus photograph showing A-ROP in zone I with severe plus disease, flat extraretinal neovascularization with fibrosis, and early contraction superiorly (white arrowheads) and intraretinal and vitreous hemorrhage superotemporally. **D**, **E**, Wide-angle fundus photographs (left sides) demonstrating A-ROP with ill-defined junction between vascular and avascular retina in zone I (white arrows) and severe plus disease, and fluorescein angiography (right sides) demonstrating significant vaso-obliteration with capillary nonperfusion. Note that no typical ROP lesions appear and vasoattenuated areas appear posterior to the ridge.

Normal retinal vascular development

Retinal vessel development begins in the 16th week of gestation, only to reach maturity around the end of full-term pregnancy: between 36 (nasal) and 40 (temporal) weeks post menstrual age (PMA) (47-49). Retinal vascularization consists of two main processes: vasculogenesis and angiogenesis. Firstly, during vasculogenesis, cells inside the optic nerve from the walls in the hyaloid artery, proliferate and migrate to the inner retina. They differentiate into endothelial cells which canalize to create capillaries. Vasculogenesis therefore can be seen as the novel formation of a primitive vascular network from precursor cells into endothelial cells. Unlike in angiogenesis, tissue hypoxia stimulating the production of vascular endothelial growth factor (VEGF) does not appear to be necessary for this process. During vasculogenesis, the four retinal vascular arcades are formed. The second major process, angiogenesis, in turn is characterized by the development of arterial and venous channels that sprout from existing blood vessels which have been completed during vasculogenesis. Angiogenesis is responsible for radial peripheral extension of arteries and veins towards the ora serrata and for increasing the vascular density of the superficial retina. The process is controlled by a balance between the release and inhibition of regulatory factors. The mechanism of release of these factors can be divided into two separate groups: oxygen regulated (VEGF and erythropoietin (EPO)) and maternally derived (i.e. insulin-like growth factor 1 (IGF-1), and omega-3 polyunsaturated fatty acids, PUFA). First, the oxygen regulated factors are under direct influence of hypoxia-inducible factor 1 (HIF-1), a nuclear transcription factor that regulates expression of VEGF and EPO (50, 51).

VEGF is necessary for normal vascular development. It is both an endothelial specific mitogen and vascular permeability factor, suggesting accountability for proliferation and vasopermeability. Maturation of the neuroretina develops independently and precedes vascular outgrowth. The progression of photoreceptors and neurons leads to an increase in thickness of the neuroretina causing physiological retinal hypoxia (with oxygen saturation (SaO_2) ranges between 50-70%), which in turn prolongs the half-life of HIF-1 leading to an accumulation in the nucleus. After HIF-1 stimulation, the expression and release of VEGF by astrocytes stimulate retinal growth towards the periphery. This angiogenesis consequently leads to a reduction of the negative-feedback effects of hypoxia and VEGF release. Similarly, the expression of VEGF by Muller cells is thought to regulate the development of the deep vascular plexus. VEGF plays a key role in the pathogenesis of ROP. The exact role of EPO remains unclear, but it is believed to be a potent ischemia induced angiogenic factor acting similarly to but independently of VEGF. Furthermore, by acting as an antioxidant EPO appears to be protective against hyperoxia-induced endothelial dysfunction and vascular loss. (52, 53).

Secondly several maternally derived factors play a key role in retinal vessel outgrowth. The most important are) IGF-1 and omega-3 and omega-6 PUFA's. IGF-1 is provided by the placenta and amniotic fluid. During fetal development, IGF-1 is a potent growth factor that also acts as a mediator of several growth hormone signalling pathways (54). PUFA are essential fatty acids that contribute to vascular integrity in endothelial membranes by forming the structural and functional component of many cell membranes and are an important precursor of factors involved in angiogenesis (55). Furthermore, they *play a protective role in vasoproliferative retinal diseases by decreasing harmful environmental factors that activate pathological processes i.e. ischemia and oxidative stress (56). PUFA's are maternally derived, and though fetal accumulation/accretion takes place throughout pregnancy, 90% of the essential deposition takes place in the third trimester (57).*

Pathology of ROP

ROP develops in two distinct phases, each calling for an individual approach (49, 58-60). Depending on the phase, both an abundance or deficiency of several factors play a key role (fig. 7). The first phase is induced by a disbalance in a variety of factors which contribute to a decreased retinal vessel growth and microvascular degeneration (obliteration) of yet formed vessels. This is then followed by a second phase of pathologic vessel growth (neovascularization), which may lead to retinal detachment.

The first, vaso-obliterative phase initiates directly after premature birth, in which the infant is shifted from physiological hypoxic intrauterine conditions to a relatively hyperoxic room air. Furthermore, in many cases, this hyperoxia is further enhanced by supplemental oxygen therapy, increasing the SpO_2 to 90-100%. Under these conditions, rapid degradation of HIF-1 follows, which leads to down-regulated expression of VEGF and EPO and therefore, to the subsequent arrest of outgrowth and obliteration of retinal capillaries.

Moreover, due to early placental disruption, prematurity is associated with low levels of maternally derived factors (IGF-1 and PUFA). These factors are pivotal for retinal angiogenesis as they *contribute to vascular integrity (55). Their absence leads to increased vascular vulnerability to* oxidative injury through harmful free radicals, which can cause damage to endothelial cells and eventually even lead to their degeneration (61). Altogether, these disrupted processes cause the arrest of normal angiogenesis, loss of some existing vessels through obliteration and therefore a poorly developed retinal vascular network.

The second, vaso-proliferative phase usually begins at 32 weeks PMA. Progression from the first to the second ROP phase is attributed to gradually developing hypoxia of the retina due to the insufficient vascularisation of the peripheral retina which cannot meet the oxygen

demand that is caused by an increasing metabolic activity of the developing neuroretina. The unperfused, hypoxic retinal tissue stimulates the production of HIF-1, VEGF and EPO in order to promote outgrowth of new blood vessels. However, in the case of ROP, this compensatory VEGF release is not gradual as in angiogenesis, but very strong and uncontrolled. Bursts of angiogenic factors during phase 2 ROP can lead to disorganised retinal vasculature with the formation of aberrant vascular buds or neovascularisations. Generally, these vessels are of poor quality and have a tendency to easily leak and bleed. In the same period IGF-1 levels increase regulating neovascularization within this stage by acting as an amplifying factor for VEGF. Neovascularisations can regress if adequate levels of oxygenation are delivered and maintained in the second phase, i.e. by providing supplemental oxygen or, when hypoxia is caused by anemia, administration of hemoglobin transfusions (see chapter treatment). In case of further progression of severe ROP however, the extended expression of angiogenic factors accumulating in the vitreous can elicit secondary vitreous cicatricial fibrosis, increasing the risk of retinal detachment and the associated blindness.

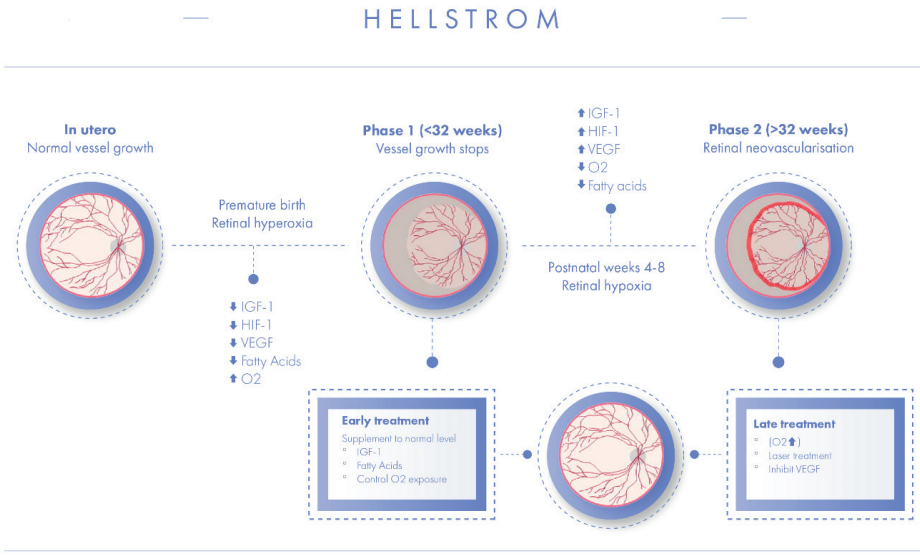

Figure 7. Major pathways of ROP
Adapted from: Hellström et al, Growth Horm IGF Res. 2016 ; 30-31: 75–80

Screening

Screening of babies at risk is pivotal as there are no externally visible signs or symptoms of ROP. The risk for unfavorable outcome increases with late treatment of severe ROP. Therefore exams should be conducted with appropriate timing and follow up to ensure timely identification of the small number of infants with progressive ROP. Due to the predictable and sequential course of ROP, the moment of screening providing reliable detection can be systematically defined. However, the incidence and risk factors for ROP depend on the general health of the population and local neonatal treatment guidelines, therefore worldwide screening recommendations vary.

The US ROP guideline advises screening in all infants with a birth weight ≤1500 g or a GA ≤30 weeks, or higher in case of risk factors. The timing of first screening is 31 weeks PMA for infants with a GA between 22-28 weeks. For those with GA >28 weeks, first screening should take place 4 weeks after birth (PNA). (62) Screening can be safely discontinued with one or more of the following criteria: vascularization is completed or has reached zone III without previous ROP in zone I or II, the age of 45 weeks PMA without ROP type 1. Infants treated with anti-VEGF should be monitored until 65 weeks PMA, with more frequent screenings between 45-55 weeks PMA because of the high risk of reactivation in this period. In the UK, all infants less than 31 weeks' GA (31 + 0-6/7) or less than 1501 gram BW are included for ROP screening. For infants born before 31+0 weeks PMA, first screening is recommended at 31 (+0-6/7) weeks PMA or 4 weeks (28-32 days) PNA, whichever is later. For infants without ROP, examinations are continued until vascularization has extended into zone III. In all other cases screening can be terminated with one of the following characteristics on 2 or more consecutive examinations: partial resolution progressing towards complete resolution, change in color of the ridge from pink to white and/or growth of vessels over the demarcation line (63). In Sweden, based on the analysis of a large group of infants during a 10-year period, only infants with a GA<30 weeks are included for screening (64). In infants born with 26 weeks or more, the first screening should take place at 6 weeks PNA onwards. The German ROP screening protocol includes preterm infants with GA <31 weeks or with BA <1500 gram if GA is not reliably known. The first exam is indicated at 6 weeks PNA (36-42 days), but not prior to 31+0 weeks PMA (65).

In the Netherlands, timing of first screening and follow-up screenings, and also the criteria for safe discontinuation of screening are based on international literature and the NEDROP studies (see below). (132, NEDROP Dutch ROP guideline, 2013: http://www.nedrop.nl/richtlijnen-en-folders.)

First screening is to be done at 5 weeks PNA (35-42 weeks PMA), but not prior to 31.0 weeks PMA

Follow-up screening

Frequency	Criterion
> 1x per week	Any ROP with plus disease in which treatment has not (yet) been decided
Weekly screening	• Avascular retina in zone I or posterior zone II • ROP 1 or 2 in zone I, without plus disease • ROP 2 or 3 in zone II, without plus disease • ROP in regression in zone I • Unreliable fundoscopic findings
Every 2 weeks	• Avascular zone II, no ROP • ROP 1 in zone II • ROP 1 or 2 in zone III • ROP in regression in zone II or III

Increase screening frequency in case of:

- Fast progression of ROP

Decrease screening frequency in case of:

- Resolution of ROP seen on multiple consecutive examinations
- No ROP detected after reaching due date (40 weeks PMA)

Termination of screening

Screening can be discontinued if one or more of the following criteria has been satisfied:

- Complete vascularization
- No presence of ROP and (temporal) vascularization extended into zone III
- Resolution of ROP at due date (PMA 40 weeks) without signs of plus disease
- No presence of type 1 ROP or worse at the age of 45 weeks PMA
- Growth of vessels through the demarcation line
- Resolution of ROP accompanied by the change in color of the ridge from pink to white

Infants treated with anti-VEGF monotherapy should be monitored until at least the age of 65 weeks PMA, with extra caution at 45-55 weeks PMA because of the high risk of ROP reactivation in this period.

Preparation for examination

One hour prior to the eye exam, a mydriatic combination of phenylephrine 2.5% and tropicamide 0.5% is instilled in each eye, using one drop of each drug. This is repeated each 15 minutes up to 2-3 times (more often with dark irises) to achieve effective mydriasis. For pain relief, oxybuprocaine 0.4% is used as topical anesthesia just prior (but minimal 30 sec) to examination when the eyelid speculum is about to be used.

Comfort care during examination

For the infant, ROP screening is an uncomfortable and distressing procedure which can have short-term effects on blood pressure, heart rate and respiratory function. Therefore screening examinations should be kept as short as possible. Furthermore, to comfort the infant during ROP screening, a combination of care techniques can be used, including: swaddling, administration of expressed breast milk and/or oral sucrose solution, pacifier and gentle human touch (66-69). Finally, parents/caregivers should be offered the opportunity to be present during the examination and to facilitate comfort care.

Parents/caregivers should be provided with written information (leaflet), well in advance of the first examination, to allow time for questions. The results of every screening examination should always be communicated to the parents. In case of no or mild ROP the information can be provided by care providers of the neonatal team. When however there is presence of severe ROP, the results and potential need for treatment, must be discussed by the attending ophthalmologist.

Logistics of (follow-up) screening and hospital transfer

The treating/attending neonatologist is responsible for consulting the ophthalmologist in case an infant requires ROP screening. After every examination, results including extent of vascularization by zone in absence of ROP or stage, zone and presence of and extent of (pre-)plus disease in case of ROP as well as the consequences for follow up should be documented.

In the NEDROP-1 it was revealed that up to 23% of transferred infants were not or not timely screened due to loss to follow-up. Therefore, to ensure more timely screening upon transfer, quality indicators have been added to the 2013 ROP guideline. When an infant is transferred to another hospital before ROP screening has started or when it is not completed, the referring neonatal team is responsible to ensure that the receiving unit knows when the first or follow-up screening examination should take place. Therefore, the specific date or calendar week of follow-up screening should be recorded (rather than follow-up *term* only, i.e. 2 weeks, as with potential postponing of the transfer, ROP screening can be delayed as well). Importance of timely screening should be discussed with parents/caregivers. For infants who are discharged home before screening is completed, follow-up outpatient appointments should be confirmed and the need of attending these appointments should be emphasized.

Treatment

The main objective of ROP treatment is to decrease the amount of free available angiogenic factors of which VEGF is the most important, eventually inhibiting further development of uncontrolled retinal neovascularization. Historically, there have been several approaches to this purpose.

In the 1970's, transscleral cryotherapy of the avascular peripheral retina emerged as the first widely accepted treatment, for severe ROP that would not regress spontaneously. The Cryotherapy for Retinopathy of Prematurity Cooperative Group trial (CRYO-ROP) demonstrated efficacy in treating so called *threshold* ROP (70, 71). Threshold ROP was defined as stage 3 ROP in at least 5 contiguous or 8 cumulative clock hours in zone I or II with presence of plus disease. In case of *pre-threshold* stages frequent (weekly) examinations were recommended. Pre-threshold ROP was defined according to disease location in case of zone I: all stages less than threshold and zone II: stage 2 ROP with plus disease, any stage 3 without plus disease or stage 3 ROP in *less* than 5 contiguous or 8 cumulative clock hours with plus disease. Benefits of treated compared to control eyes were seen in both functional and structural outcome, through reduction of retinal detachment by approximately 50% compared to untreated eyes.

Soon however, cryotherapy was replaced by diode laser, as it rendered fewer side effects (i.e. cataract, temporal dragging of macula and blood vessels), resulted in less pronounced myopia/refractive errors and was easier to apply (72-76). Moreover, in order to further reduce the number of infants with progression to end stage ROP, also the timing of treatment was questioned as some ophthalmologist advocated treatment in earlier stages to have better results (77, 78). The Early Treatment for ROP study (ETROP) confirmed the efficacy of early treatment vs. treatment at threshold ROP: an unfavorable outcome was seen in 25.1 vs. 32.8% ($p<0.001$) and visual acuity (VA) <20/200 in 24.7 vs. 29.0% ($p<0.15$) (79, 80). Following the ETROP inventory, indication for treatment was redefined. Categorizing (pre) threshold ROP was replaced by type 1 and type 2 ROP, shifting the focus of severity from disease extent in clock hours to presence of plus disease.

Until this day, the ETROP classification is widely used and encompasses treatment in the following stages:

Type 1, requiring immediate treatment:

- Zone I ROP with plus disease
- Stage 3 ROP in zone I, with or without plus disease
- Stage 2 or 3 ROP in zone II, with plus disease*

* In most countries treatment for stage 2 ROP with plus disease is only recommended when there is evident increase of the degree of plus disease, since in other cases spontaneous regression is still possible

Type 2, requiring frequent and thorough observation
- Stage 1 or 2 ROP in zone I, without plus disease
- Stage 3 ROP in zone II, without plus disease

Despite the effectiveness of laser therapy to secure preservation of the central vision, loss of peripheral visual field is acquired as the treatment is established by permanent destruction of the peripheral retina and subsequent loss of its function. Moreover, it can lead to significant structural side effects such as high myopia, macular dragging, retinal folds and cataract. Alternative possibilities, in which the integrity of the peripheral retina is preserved, are therefore continuously being investigated. Currently, the best studied alternative treatment to laser therapy is intraocular administration of anti-VEGF agents such as monoclonal antibodies (usually bevacizumab) or antibody derivatives (ranibizumab and recently aflibercept), directly intercepting the free VEGF in progressive ROP and hereby suppressing neovascularization. An additional advantage of anti-VEGF drugs is that they are administered through intraocular injection. Therefore compared to laser, this treatment modality is considerably easier to apply and does not require general anesthesia.

The first prospective, controlled, randomized trial to investigate the effectivity of anti-VEGF drugs vs. laser therapy was the Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) study (81). Eyes with ROP stage 3 with plus disease in zone I or II enrolled in the study. The primary outcome was recurrence of ROP requiring treatment within 54 weeks PMA. Laser showed a 22.0% recurrence vs. 4.0% in the anti-VEGF treated group (p=0.002), however this superiority was only significant in infants with zone I ROP (p=0.003) and not in zone II (p=0.27) (82). Since these promising results of the BEAT-ROP, many studies were conducted to further investigate effectivity, timing, dosage and also the safety of using anti-VEGF drugs in severe ROP, providing useful but often contradictory data (83-87).

In 2019, the results of the second prospective randomized controlled trial on anti VEGF-drugs vs laser therapy for ROP were published. The *Ranibizumab vs. laser therapy for the treatment of very low birthweight infants with ROP* (RAINBOW) study (88) enrolled 225 infants with ROP type 1 (except for ROP 2+ in zone II), who were randomized and treated with either 0.1 or 0.2 mg of ranibizumab or laser therapy with a follow-up period of 24 weeks. The study revealed superiority of the highest dosage of ranibizumab compared to laser with regard to absence of structural abnormalities 2% vs 9%, odds ratio (OR) 5.68 (95% CI 0.60-54.0; p=0.10), high myopia 5% vs 20% OR 0.19, 95% CI 0.05-0.69; p=0.012) and vision-related quality of life scores. A recent 2-year extension study confirmed the ocular

outcomes of the original RAINBOW trial and showed no notable difference in the effects on neurodevelopmental outcome, growth, blood pressure or respiratory symptoms compared to laser therapy. Furthermore, no late complications affecting vision were found. (89).

Another large US retrospective secondary analysis, including data of 1167 eyes in 640 infants, showed that treatment of type 1 ROP before 36 (0/7) weeks PMA with anti-VEGF causes less retinal detachments than laser (0% vs 7.9%, $p< 0.001$) within 8 weeks after treatment (90). After this age the study showed that both treatments have very low short-term retinal detachments. The authors attribute these benefits of anti-VEGF at a young age to ROP being located more posteriorly – and therefore being more aggressive due to a larger avascular area with a higher VEGF production – in which direct interception of VEGF by intravitreal drugs provides a faster mechanism of action.

A Cochrane Review from 2018, including six trials with a total of 383 infants, evaluating the efficacy of anti-VEGF drugs either as monotherapy or in combination with cryo/laser therapy in infants with Type 1 ROP (91), showed that anti-VEGF as monotherapy reduces the risk of refractive errors in later childhood but does not reduce the risk of retinal detachment or recurrence of ROP. Furthermore, while anti-VEGF might reduce the risk of recurrence of ROP in infants with zone I ROP, it can potentially result in higher risk of recurrence requiring retreatment in those with zone II ROP. The long-term systemic adverse effects and local potential beneficial effects (i.e. less pronounced refractive errors) remained unknown. Insufficient data prevents strong recommendations favouring routine use of intravitreal anti-VEGF agents - either as monotherapy or in conjunction with laser therapy - in preterm infants with type 1 ROP.

For four major reasons, anti-VEGF has not yet replaced laser therapy uniformly in the Netherlands as well as in other countries, especially in the treatment of ROP in zone II. Firstly, treatment with anti-VEGF should be considered with great caution as there are still many uncertainties about appropriate dosage, timing and type of drug (92-95). Secondly, VEGF is a critical cytokine in the fetal organ development. Apart from inhibiting pathologic retinal angiogenesis to treat neovascular outgrowth into the vitreous, anti-VEGF may also interfere with normal retinal development. Studies have shown findings (i.e. hyperfluorescent lesions on fluorescein angiography, the presence of shunt vessels or abnormal branching and even absence of foveal avascular zone) supporting the hypothesis that anti-VEGF drugs can eventually render underdevelopment of the retinal and choroidal vasculature (96-98). Moreover, treatment with intravitreal injection of anti-VEGF has been associated with systemic VEGF suppression which can cause organ underdevelopment and neurodevelopmental delay in this already highly susceptible population (99-106). Thirdly, treatment with anti-VEGF therapy warrants long and more frequent follow-up (up to 6-8 months) due to the higher risk of late recurrence than with

laser therapy (<3 months) (107-110) and therefore more frequent need for additional treatment (83, 111). For parents/caregivers, especially when referred from a long distance to the treatment center, it may be difficult to maintain routine follow up and therefore, a greater risk of the potential subsequent devastating consequences. Finally, as long as the Dutch neonatal policy advises against active life-supporting treatment of premature babies before 24.0 weeks of gestation, the number of infants with zone I ROP is low, which is why the expertise for treatment of these stages is limited, but slightly increasing. Therefore in sum, in the Netherlands, the treatment of first choice remains laser photocoagulation for Type 1 ROP in Zone II. In the upcoming guideline (2023) treatment with anti-VEGF is advised as first choice treatment for type -1 ROP in zone I, especially in the case of A-ROP, ROP needing treatment before 35 weeks PMA and/or in patients who are particularly vulnerable to the risks of transport to a treatment center or anesthesia.

Treatment with oxygen

Contrarily to phase I, in which oxygen is considered a risk factor for ROP, in the second phase, (> 32 weeks GA), oxygen has been postulated as protective. The rationale behind this theory is that phase 2 of ROP arises with the further development of the neuroretina, which becomes metabolically active and requires more oxygen. This demand however is not met by the underdeveloped retinal vasculature. The subsequent retinal hypoxia in turn leads to uncontrolled release of growth factors resulting in the outgrowth of excessive blood vessels. Providing higher systemic oxygen targets could result in more oxygen availability to the hypoxic retina, preventing the ROP cascade to further advance uncontrollably.

An important study investigating the role of oxygen in this second phase to prevent progression of ROP was the STOP-ROP trial (2000) (112). Infants with pre-threshold ROP were treated with higher (96-99% SaO_2) vs lower (85-94% SaO_2) oxygen saturation targets. The outcome was progression to threshold ROP. A favorable trend for supplemental oxygen was observed, however this did not reach statistical significance (RR 0.84, 95% CI 0.70, 1.02). Furthermore, the intervention group showed more pulmonary complications, longer hospital stay and prolonged need for supplemental oxygen and diuretics.

Despite these apprehensions, possibly also resulting from a suboptimal set up of the STOP-ROP study (i.e. extensive inclusion time, intervention carried out too late, interval between two screenings too long and enrollment goal to provide sufficient power of the evidence not reached), the attitude towards supplemental oxygen in the Netherlands is more positive. Over the years, a considerable number of infants with ROP with pre-plus disease has been successfully treated with higher oxygen targets. This can be considered especially beneficial for infants with oxidative injury caused by frequent fluctuations in oxygen saturations or with an increased risk for anesthesia and transport. Based on this experience, the upcoming new Dutch guideline (2023) advises infants with pre-plus disease to be treated with

saturation targets >95%, with a maximum duration of 2 weeks. During this period and also after discontinuation, these infants should be screened frequently (at least once a week, depending on the severity of ROP).

Anemia & red blood cell transfusion

Low hemoglobin levels are often observed in premature infants due to a combination of underdevelopment of the hematopoietic system, severe pulmonary instability and therefore iatrogenic blood loss due to frequent blood sampling (113). Anemia affects the oxygen carrying capacity which can lead to a decrease in tissue oxygenation even with seemingly satisfactory SaO_2 levels. The risk for severe anemia increases with decreasing GA. It therefore is not surprising that a large number of extremely low birth weight infants require red blood cell (RBC) transfusion during their hospital stay (114).

At birth, neonatal hemoglobin (Hb) predominantly consists of foetal hemoglobin (HbF), which gradually declines until disappearance, approximately at the age of 1-2 years. HbF has greater affinity for oxygen compared to adult hemoglobin (HbA), facilitating oxygen binding in utero (fig. 8). Furthermore, HbF transports less oxygen to tissue than HbA, subsequently generating the required physiological hypoxic conditions that promote tissue vascularization by the upregulation and release of VEGF and other angiogenic mediators. For the management of premature anemia, infants are not treated with HbF but with blood transfusions that contain HbA. This causes the oxygen dissociation curve to shift to the right, consequently increasing tissue oxygen availability.

The association of progression of ROP with RBC transfusions has been identified in the 1950's (115). Since then, many studies were conducted to clarify the exact mechanism of possible causality (116-122). The literature however has often shown to be contradictory due to small sample size, the lack of consideration of confounders and a shortage of studies studying the effect of transfusions separately, during the first phase of ROP on one hand and the second phase on the other. Furthermore, the transfusions in these studies are not primarily given to optimize ROP outcome, but in order to treat systemic instability during the first weeks after birth, far before first signs of ROP appear (121, 123, 124).

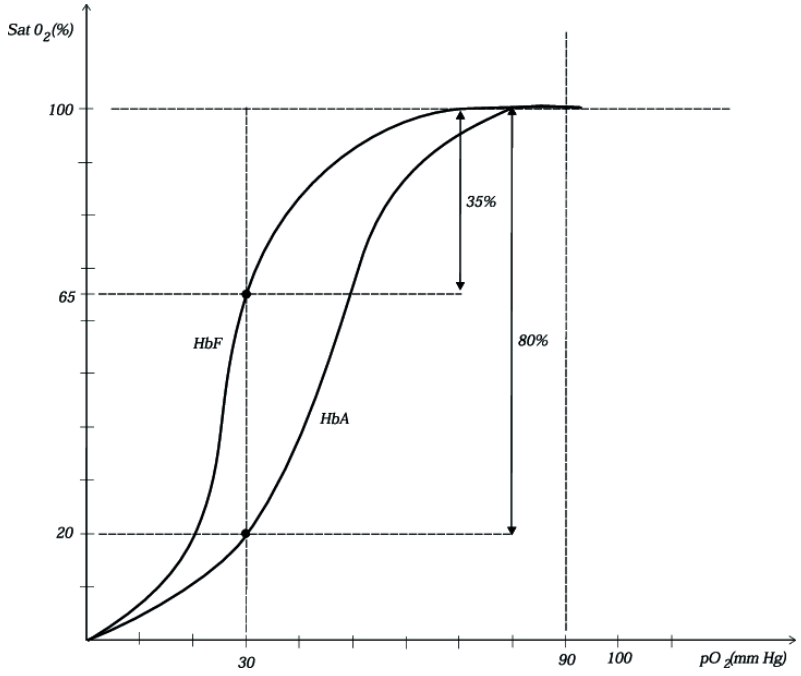

Figure 8. Oxygen dissociation curves for HbF and HbA
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As mentioned before, ROP is a two phased disorder each characterized by contrasting mechanisms which should also be managed independently. RBC transfusions can be both harmful and beneficial, depending on the timing in which they are given. Despite the lack of studies on the effect on progression to severe ROP, based on ROP theory and empirical experience, administration of RBC transfusions should be conducted with caution during phase I (before 32.0 weeks PMA) because they can increase the already existing hyperoxia. On the other hand, in phase 2 (32.0 weeks PMA onward), anemia should be closely monitored, in order to prevent progression of ROP caused by the subsequent (neuro)retinal hypoxia (125-127). For this reason, in infants with pre-plus disease, the upcoming new Dutch neonatal guideline (2023) advises to treat anemia with red blood cell transfusions in infants with pre-plus disease, when the Hb is <7.0 mmol/L (instead of 5.5 mmol/L) aiming to avoid treatment warranting ROP.

Recent topics of interest

The course of ROP also relates to the overall systemic health of a child and therefore also directly to the standard of neonatal care. Since neonatal practice is outlined by national neonatal protocols, ROP screening and treatment guidelines cannot be implemented uniformly and should be adapted to regional demographics and local neonatal care.

In 2009, the first national ROP inventory was carried out in the Netherlands (NEDROP 1). Principally, the aim of the NEDROP 1 was to provide insight on incidence, screening and treatment of ROP of all Dutch babies born in 2009 that were eligible for the ROP screening program (128, 129). The study demonstrated critical aspects of screening: in more than one third of babies screening was not performed within the required period and the risk for loss to follow-up increased up to 23% with hospital transfer (129). Finally it was revealed that due to incomplete data, 24% of treated infants could not be classified according to the Early Treatment for ROP criteria (ETROP)(130), that already applied since their publication in 2004. Subsequently in 2013 a new guideline was adopted stressing the ETROP criteria and encompassing quality indicators that were broadly emphasized in the Dutch National Monitoring System for Quality in Health Care.

The second major objective was to yield evidence for a new screening and treatment guideline in which the number of screened infants could be reduced while warranting 100% detection of severe ROP (131). The 2013 guideline therefore also adopted stricter, risk based inclusion criteria for screening, presumably lowering the number of infants that require ROP examinations by nearly one third (132).

However, since NEDROP 1 and the implementation of the new guideline, several crucial changes were carried out in Dutch neonatal care protocols. Firstly in 2010, the age limit of resuscitation and premature life-support was lowered from 25.0 to 24.0 weeks of gestation. Gestational age inversely relates to the risk of prematurity related complications (8) and the survival of babies of borderline viability directly generates an increase in number of infants susceptible to ROP and other neurodevelopmental disabilities.
Secondly, most Dutch neonatal intensive care units (NICU's) adopted higher oxygen saturation targets (SaO_2) during the first weeks after birth, as a large meta-analysis demonstrated that these targets ensure better survival and less necrotizing enterocolitis than lower SaO_2 limits (133). The same study revealed that babies treated with higher SaO_2 have a higher risk of developing ROP. Consequently it was anticipated that a higher number of infants would develop (severe) ROP since 2009.

Due to strict Dutch privacy laws, no continuous ROP registry exists in the Netherlands, limiting the access to ongoing up to date data. The Dutch Perinatal Registry (Perined)

is available, which is used by neonatologists and pediatricians to monitor perinatal outcomes. A segment on ROP outcome is included, but often renders incomplete data because the ROP data are unknown or because screening has not yet been completed or sometimes, not initiated due to early hospital transfer. Therefore, not only current ROP demographics, but also the effects and safety of the new guideline remain unknown. Together with the earlier described essential changes in neonatal policy, a second nationwide investigation became imperative. Especially considering the expected increase in number of extremely premature babies, monitoring of ROP figures remains important and may be helpful in safely reducing the burden of unnecessary screening.

Aim of this thesis

This thesis outlines the results of the second, prospective, national ROP inventory (NEDROP 2). The aim of this study was to provide current data on ROP in the Netherlands, to evaluate the effect of the implementation of quality indicators and monitor the influence of nationwide protocol changes that were implemented after NEDROP 1 in 2009.

With continuous advances in maternal and neonatal care, the survival of high-risk extremely premature infants increases, together with the number of infants needing ROP screening examinations and the risk of severe ROP. Concerns were raised by Dutch pediatric ophthalmologists, who since several years observed more treatment demanding ROP in their clinical practice. Therefore, in addition this dissertation aims to gain more insight in the ever changing ROP demographics, in order to provide well-founded data for an up-to date national screening and treatment guideline hereby improving ROP management in our country.

In **chapter 2**, a nationwide inventory on all infants treated for ROP between 2010-2017 is discussed. Main results include: neonatal parameters, treatment number, characteristics and outcome and the influences of crucial neonatal policy changes. Further, in the most recent guideline (2013) more restricted screening inclusion criteria were implemented reducing the number of infants who need screening by nearly one third. Together with the increasing number of infants at risk, it became imperative to assess if any infants with visual impairment (VI) due to ROP had been missed for screening. A retrospective inventory was performed at the Dutch institutes for children with VI and blindness due to ROP born between 2009-2018, of which the results are presented in **chapter 3**.

In **chapter 4** we prospectively investigated the Dutch ROP population at risk in the year 2017, and hereby assessed the population size at risk after screening reduction (2013), the current incidence of ROP and severe ROP, adherence of ophthalmologists to the Early Treatment

of ROP criteria, timing accuracy of (follow-up) screening examinations and the treatment ratio and outcome. Moreover, effects were evaluated of the newly implemented quality indicators, aiming to reduce attendance failure of follow-up appointments, in particular for those transferred or discharged from the hospital before screening has started.

Chapter 5 describes the evaluation of associated risk factors in the same population. As the Dutch ROP guideline is partly based on risk-based inclusion criteria, this study was crucial in order to determine safety of the current, or a potential need for adjustment of the future guideline.

Chapter 6 presents an extensive analysis of potential new screening inclusion criteria for the new guideline. The goal of this study was to further reduce the number of infants to be screened, simultaneously providing a high enough predictive value to detect all infants with treatment demanding ROP.

Finally, in **chapter 7** we discuss the main findings of this thesis, and provide insight in our ideas for future research on ROP in the Netherlands

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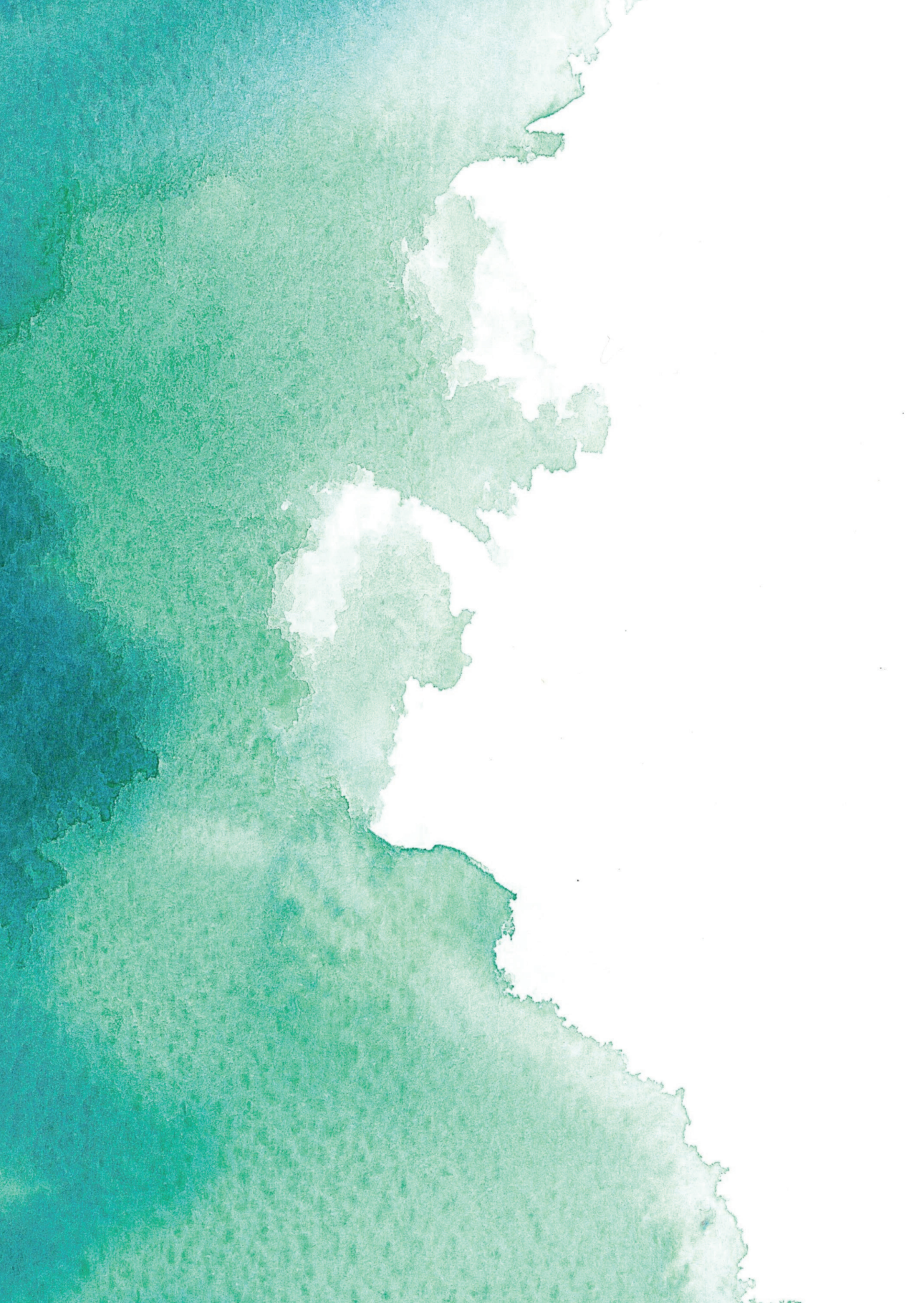

Chapter 2

Increase in treatment of retinopathy of prematurity in the Netherlands from 2010 to 2017

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Abstract

Purpose

Compare patients treated for Retinopathy of Prematurity (ROP) in two consecutive periods.

Methods

Retrospective inventory of anonymized neonatal and ophthalmological data of all patients treated forROPfrom 2010 to 2017 in the Netherlands, subdivided in period (P)1: 1-1-2010 to 31-3-2013 and P2: 1-4-2013 to 31-12-2016. Treatment characteristics, adherence to early treatment forROP(ETROP) criteria, outcome of treatment and changes in neonatal parameters and policy of care were compared.

Results

Overall 196 infants were included, 57 infants (113 eyes) in P1 and 139 (275 eyes) in P2, indicating a 2.1-fold increase in ROP treatment.No differences were found in mean gestational age (GA) (25.9 _ 1.7 versus 26.0 _ 1.7 weeks, p = 0.711), mean birth weight (791 _ 311 versus 764 _ 204 grams, p = 0.967) and other neonatal risk factors for ROP. In P2, the number of premature infants born <25 weeks increased by factor 1.23 and higher oxygen saturation levels were aimed at in most centres. At treatment decision, 59.6% (P1) versus 83.5% (P2) (p = 0.263) infantswere classified as Type 1 ROP(ETROP classification). Infantswere treated with laser photocoagulation (98 versus 96%) and intravitreal bevacizumab (2 versus 4%). Retreatment was necessary in 10 versus 21 (p = 0.160). Retinal detachment developed in 6 versus 13 infants (p = 0.791) of which 2 versus 6 bilateral (p = 0.599).

Conclusion

Inperiod2,thenumberofinfantstreatedaccordingtotheETROPcriteria (Type 1) increased, the number of ROP treatments, retinal detachments and retreatments doubled and the absolute number of retinal detachments increased.Neonatal data did not provide a decisive explanation, although changes in neonatal policy were reported.

Introduction

Retinopathy of prematurity (ROP) is a sight threatening disorder caused by abnormal retinal vessel development in premature infants (1). As more is known about the pathological mechanisms, optimising the infant's condition is warranted in order to prevent the turning point to severe and potentially blinding ROP. However, neonatal risk factors cannot always be completely controlled and therefore, timely ophthalmic screening and treatment remain essential. In the Netherlands, changes possibly influencing the development of severe ROP were debated as paediatric ophthalmologists had the impression that since several years the number of infants developing severe ROP had increased. Certain factors might have contributed to this development. First, following a nationwide ROP inventory called the NEDROP study (2009), a new Dutch ROP guideline was implemented in April 2013, in which the screening inclusion criteria were altered (2, 3). This revision would reduce the number of eligible infants by almost one third, without missing treatment warranting ROP (4). Secondly, in the same guideline, the early treatment for ROP (ETROP) criteria were emphasized (5), as the NEDROP study showed that they were not yet widely implemented in the Netherlands: in almost a fourth of infants treated for ROP, no classification could be made into type 1 or 2 ROP . Overall, adherence to the ETROP protocol implicates treatment in earlier stages, which could consequently result in an increase in the number of infants requiring ROP treatment. Moreover, changes in neonatal care might have increased the risk for severe ROP since the NEDROP study. In 2010 the age limit of admitting and actively treating premature infants in Dutch neonatal intensive care units (NICU's) was lowered from 25.0 to 24.0 weeks of gestation. Furthermore, following the Neonatal Oxygenation Prospective Meta-analysis (NeOProM, 2014) (6), higher oxygen saturation (SaO_2) levels during the first weeks of life were implemented in most Dutch NICU's. This adjustment warrants better survival but also increases the risk for severe ROP (7).

The aim of this study was to investigate changes in the prevalence and characteristics of infants requiring ROP treatment in the Netherlands since the implementation of the new Dutch ROP guideline in 2013. Furthermore, treatment characteristics and anatomical outcome of ROP treatment were investigated.

Materials and methods

The present study was initiated and coordinated by the Leiden University Medical Center. Data of infants treated for ROP were retrospectively obtained from patient files from all Dutch NICU's. All data were delivered depersonalized and coded using randomly assigned numbers, therefore informed consent was not required according to the General Data Protection Regulation (GDPR) (8) and the local medical ethical committee. Upon inclusion,

patients were categorised into period 1 (old guideline): treated from January 1st 2010 until March 31st 2013 (duration of inclusion of 39 months) and period 2 (new guideline): from April 1st 2013 until December 31st 2016 (45 months). The primary outcome is the number of treated infants per group. Subsequently, the number of treatments was compared to the premature birth-rate in the same period. National birth numbers were obtained from the Dutch neonatal registry platform, *Perined* (9). Data of the participating hospitals were compared for birth rate, number of ROP treatments, retreatments and outcome, with preservation of individual privacy.

Infants treated in period 1 (from January 1st 2010 until March 31st 2013) were treated according to the old guideline, which advised screening infants with a GA <32.0 weeks and/or BW <1500 gram. From April 1st 2013 (period 2), the Dutch ROP screening guideline recommends screening neonates with GA <30.0 weeks and/or BW <1250 and a selection of infants with GA 30.0-32.0 weeks and/or BW 1250-1500 gram with presence of one or more of the following risk factors: mechanical ventilation (MV), sepsis, necrotizing enterocolitis (NEC), administration of postnatal glucocorticoids or hypotension treated with inotropic agents. For ROP treatment, classification according to the ETROP is used, which advises treatment of so called type 1 ROP (5). However, in the Netherlands ROP stage 2+ in zone II is only treated when plus disease is progressive. The participating hospitals were asked to indicate if the SaO_2 policy was adjusted during the study period and if so, what targets are used. Neonatal data were obtained on gender, GA, BW and the presence of relevant risk or protective factors for ROP being: multiple birth, sepsis (defined as clinically ill with positive blood cultures), intraventricular haemorrhage (IVH, according to the classification of Levene (10)) or periventricular leukomalacia (PVL, according to the classification of De Vries (11)), presence of a treated patent ductus arteriosus (PDA), infant respiratory distress syndrome (IRDS), bronchopulmonary disease (BPD, defined as oxygen dependency at 36.0 weeks post menstrual age (PMA)), NEC with perforation, hyperglycaemia (>8.0 mmol/L), twin-to-twin transfusion syndrome (TTTS), hypotension treated with inotropic agents, duration of NICU-admission >28 days, MV >7 days, oxygen administration >28 days, treatment with packed red blood cells, treatment with inhaled nitric oxide (iNO) and pre-and postnatally administered glucocorticoids. Data to evaluate details of treatment consisted of PMA, postnatal age (PNA) at time of treatment decision and treatment, and maximum zone and stage of ROP. ROP was classified according to the Revised International Classification of Retinopathy of Prematurity (2005) and categorized into type 1 or 2 ROP according to ETROP criteria (12). Furthermore, characteristics of treatment and possible retreatments were evaluated. Eventually anatomical outcome, i.e. retinal detachment (RD) was recorded.

Statistical analyses

Statistical analyses were performed using SPSS Statistics software version 23.0 IBM Corp., Armonk, N.Y., USA. For quantitative variables, we used number (n), mean (standard deviation (SD)) and medians (ranges). For categorical variables, proportion (%) was reported. P-values for continuous variables were calculated by using Mann-Whitney U test. In case of categorical and/or binary variables, the Pearson's Chi-Square test or Fischer's Exact test was used. To correct for the difference in inclusion periods (period 1: 39 months vs. period 2: 45 months), a correctional factor was used (45/39 = factor 1.15).

Results

During the seven-year study period, data of 196 treated infants from 10 hospitals were obtained. Period 1 counted 57 infants (113 eyes), period 2: 139 infants (275 eyes) (table 1). The prevalence of ROP treatment in the group of infants born in the Netherlands with GA <32.0 weeks was 1.1% (57/5276) in period 1 and 2.3% (139/6019) in period 2 (fig. 1), representing a 2.1-fold increase since the implementation of the new guideline.
Comparing national birth rates between the two inclusion periods, the number of newborns with GA 25.0 - <28.0 and 28.0 - <32.0 weeks remained relatively stable. However, the group of infants with GA <25.0 weeks increased by nearly one fourth (fig. 1 and table 1). The range of live births, defined as all live births excluding neonatal death (<28 days after birth), among the 10 participating hospitals is shown in figure 2. In the overall study group, mean GA and BW were 25.9 ±1.7 weeks and 771 ±240 grams respectively. Mean GA was similar between the two treatment groups (period 1: 25.9 ±1.7 weeks, period 2: 26.0 ±1.7 weeks (p=0.711)) as well as mean BW (period 1: 791 ±311 and period 2: 764 ±204 grams (p=0.967)). No statistically significant differences were found in the prevalence of neonatal risk factors (table 2). All NICU's implemented the NeOProM SaO_2 criteria since their publication, however one hospital adapted a slightly lower and broader range (85-93%). At treatment decision, 150 infants (period 1: 34, period 2: 116) were categorised as type 1 ROP, four (period 1: 1, period 2: 3) as type 2 ROP and 42 (period 1: 22, period 2: 20) did not meet the ETROP criteria or could not be classified due to missing data (table 3). Mean overall age at treatment decision was 36.7 ±2.5 weeks and comparable between the two groups (table 4). ROP stage 3 or higher was found in 49.1% of infants in period 1 vs. 57.6% in period 2 (p=0.144). Between the participating hospitals, median proportion of infants with ROP stage ≥3 at treatment decision was 57% with an interquartile range of 35% (range 20-90%).

Treatment was performed by ten ophthalmologists in seven hospitals. Overall, laser photocoagulation of the retina was the predominant modality of primary treatment (97.0%),

six infants received intravitreal Bevacizumab (IVB) (4 bilateral, 2 unilateral) of which five in period 2. Apart from one infant in period 1 and three infants in period 2, all patients were lasered bilaterally. Mean follow-up age was 31.5 ±24.3 months in period 1 and 13.3 ±12.6 in period 2. Overall, following primary treatment, ROP recurred within 21 ±13 days and was retreated in 31 patients (15.8%) (period 1: 10 (17.5%), period 2: 21 (15.1%) *p*=0.160). Retreatment characteristics are described in table 4.

Progression into retinal detachment (RD, ROP stage 4 or 5) occurred in 19 (9.7%) patients of which 8 bilateral (2 vs. 6, *p*=0.599). Mean PMA at first treatment was higher in the RD group but did not reach statistical significance (*p*=0.743). Considering other risk factors and treatment characteristics, these groups were comparable. Of the laser treated infants 18/190 (9.5%) vs. one of six (16.7%) primarily IVB treated infants developed retinal detachment (*p*=0.462). Treatment characteristics and the occurrence of risk factors did not differ statistically significant comparing infants developing RD to those that did not. The highest treatment and retreatment rates were found in centres where the youngest infants were born. The percentage of recurrence varied between 10.0% and 37.5% and RD between 1.8 and 15.6% (ranges shown in fig. 3).

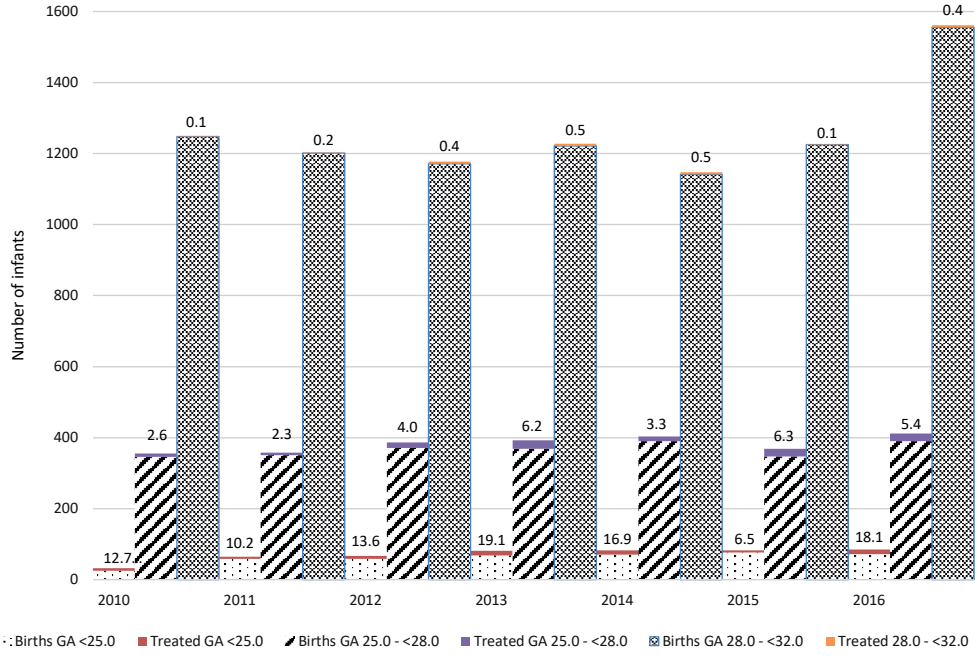

Figure 1. Annual live births according to gestational age in weeks at birth (pattern filled) and number of treatments (solid filled). Labels represent the percentage of treated infants in the corresponding age category.

Table 1. Number of live births in the Netherlands according to gestational age for period 1 and period 2, and the increment corrected for the difference in inclusion time (1.15).

GA (weeks)	Period 1 *n*=57	Period 2 *n*=139	Increment
28.0 - <32.0	3927	4368	**0.97**
25.0 - <28.0	1159	1383	**1.03**
<25.0	190	268	**1.23**

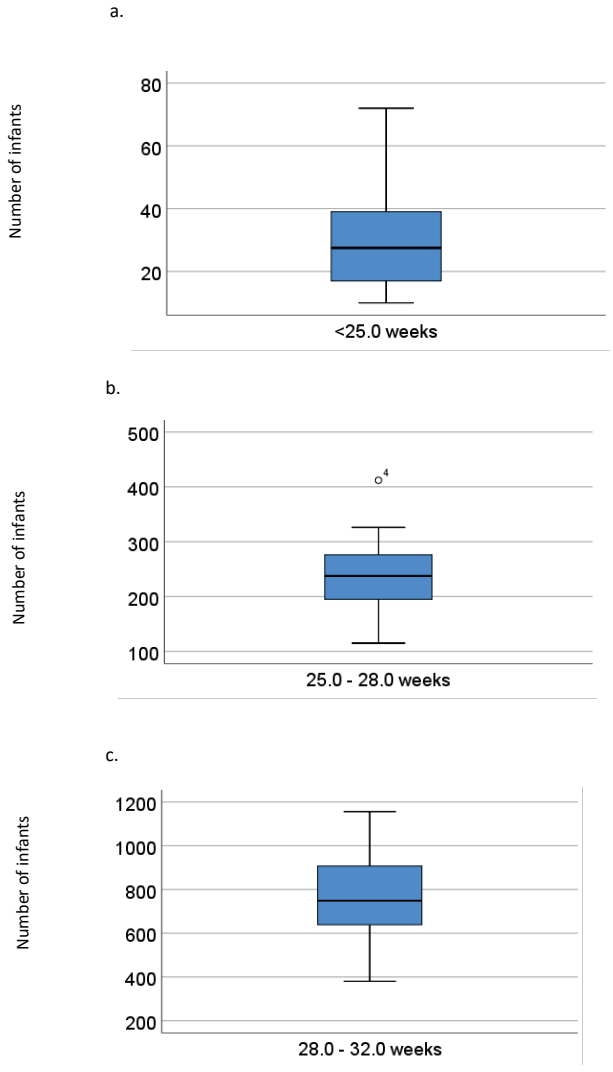

Figure 2 a, b and c Boxplots representing median (ranges) of live births in the 10 participating hospitals from 2010-2017 with a) GA <25.0 weeks: 28 (10-72), b) GA 25 - <28.0 weeks: 238 (115-412) and c) GA 28.0 - <32.0 weeks: 749 (380-1156).

Table 2. Risk factors of the overall group of infants treated for ROP between 2010-2017, period 1 and infants that developed retinal detachment (latter group from both periods) .

	Period 1 *n*=57	**Period 2** *n*=139	**Infants with RD** *n*=19	***p*-value** period 1 vs. 2
Obstetric characteristics and interventions (*n*,%)				
Prenatal glucocorticoids	35 (72.9%)	90 (69.2%)	11 (64.7%)	0.650*
Multiple birth	18 (33.3%)	58 (43.6%)	11 (61.1%)	0.195*
Infant characteristics (mean (SD))				
GA in weeks	25.9 (±1.7)	26.0 (±1.7)	26.4 (±1.9)	0.711†
Mean (SD) BW in grams	791 (±311)	764 (±204)	827 (±233)	0.967†
Female gender *n* (%)	28 (49.1%)	67 (48.2%)	11 (57.9%)	0.844*
Neonatal morbidity (*n*,%)				
Sepsis	35 (64.8%)	89 (66.4%)	13 (72.2%)	0.834*
IVH/PVL	29 (50.9%)	57 (41,0%)	6 (33.3%)	0.659*
Patent ductus arteriosus	44 (83.0%)	108 (81.2%)	16 (88.9%)	0.772*
IRDS	51 (89.5%)	129 (96.3%)	16 (88.9%)	0.575*
BPD	44 (77.2%)	105 (79.5%)	13 (72.2%)	0.764*
NEC	4 (7.0%)	15 (11.3%)	4 (22.2%)	0.427*
Hyperglycaemia (>8 mmol/l)	21 (36.8%)	52 (39.7%)	7 (38.9%)	0.993*
TTTS	2 (3.8%)	9 (7.1%)	1 (5.6%)	0.627*
Neonatal Interventions (*n*,%)				
NICU admission >28 days	47 (100%)	120 (96.0%)	16 (100%)	0.325†
MV > 7 days	40 (87.0%)	109 (84.5%)	13 (76.5%)	0.687*
Oxygen administration >28 days	35 (76.1%)	109 (85.8%)	12 (70.6%)	0.217*
Packed cells	51 (98.1%)	122 (93.9%)	16 (88.9%)	0.398‡
Hypotension treated with inotropic agents	21 (36.8%)	37 (26.6%)	7 (38.9%)	0.124*
iNO	7 (13.4%)	20 (15.5%)	2 (11.8%)	0.945*
Postnatal glucocorticoids	33 (66.6%)	72 (55.0%)	6 (37.5%)	0.221*

BPD, bronchopulmonary disease; BW, birth weight GA, gestational age; iNO, inhaled nitric oxygen; IRDS, infant respiratory distress syndrome; IVH, intraventricular haemorrhage; MV, mechanical ventilation; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; RD, retinal detachment; TTTS, twin-to-twin transfusion syndrome

* = Pearson's Chi-Square Test

† = Mann-Whitney U test

‡ = Fischer's Exact Test

Table 3. ROP- type and stage at treatment decision per treatment period.

			Period 1 *n*=57	**Period 2** *n*=139
ETROP type I			**34 (59.6)**	**116 (83.5)**
Zone	**Stage**	**Plus**		
I	3	+	-	4 (2.9)
II	3	+	18 (31.6)	68 (48.9)
I	2	+	1 (1.8)	2 (1.4)
II	2	+	15 (26.3)	42 (30.2)
ETROP type II			**1 (1.8)**	**3 (2.1)**
II	3	-	1 (1.8)	3 (2.1)
No ETROP			**22 (38.6)**	**20 (14.4)**
II	2	-	-	2 (1.4)
II	1	+	1 (1.8)	-
III	3	+	2 (3.5)	2 (1.4)
III	3	-	-	1 (0.7)
III	2	+	5 (8.8)	5 (3.6)
III	1	+	-	1 (0.7)
Ns	3	+	6 (10.5)	2 (1.4)
Ns	3	-	1 (1.8)	-
Ns	2	+	1 (1.8)	-
Na	4a	+	-	1 (0.7)
Na	4b	+	-	1 (0.7)
Ns	Ns	Ns	6 (10.5)	5 (3.6)

ETROP, early treatment for ROP-criteria; na, not applicable; ns, not specified.

Table 4. Treatment characteristics in infants treated for ROP in Periods 1 and 2 and in those who developed retinal detachments from both periods.

	Period 1 *n*=57	**Period 2** *n*=139	**Infants with RD** *n*=19	***p* value** period 1 vs. 2
Age at treatment (mean (SD))				
PMA at first detection of ROP	34.2 ± 2.2	34.2 ± 2.3	34.5 ± 2.1	0.941*
PMA at treatment decision	36.6 ± 2.3	36.7 ± 2.5	36.3 ± 2.1	0.680*
PMA at first treatment	37.8 ± 2.3	37.3 ± 3.3	39.1 ± 7.2	0.791*
PNA at first treatment	12.0 ± 3.8	11.5 ± 3.2	12.9 ± 6.6	0.790*
Primary treatment (*n*,%)				
Laser	56 (98%)	134 (96%)	18 (95%)	
Bevacizumab	1 (2%)	5 (4%)	1 (5%)	
First recurrence (*n*,%)	10 (17.5)	22 (15.8)	17 (89.5)	0.390†
Unilateral additional laser	3	2	1	
Bilateral additional laser	3	8	4	
Unilateral TPPV	1	5	4	
Bilateral TPPV	2	2	5	
Unilateral IVI Bevacizumab	0	2	2	
Bilateral IVI Bevacizumab	1	3	1	
Second Recurrence (*n*,%)	3 (5.2)	9 (6.5)	11 (57.9)	0.598†
Unilateral additional laser		1	1	
Bilateral additional laser		1	1	
Unilateral TPPV	2	4	6	
Bilateral TPPV	1	3	3	
Infants with retinal detachment (*n*,%)	6 (10.5)	13 (9.4)	-	0.791†
Bilateral	2	6	8	0.599†

IVI, intravitreal injection; PMA, post menstrual age; PNA, postnatal age; RD, retinal detachment; TPPV, trans pars plana vitrectomy

* = Mann-Whitney U test

† = Chi square test

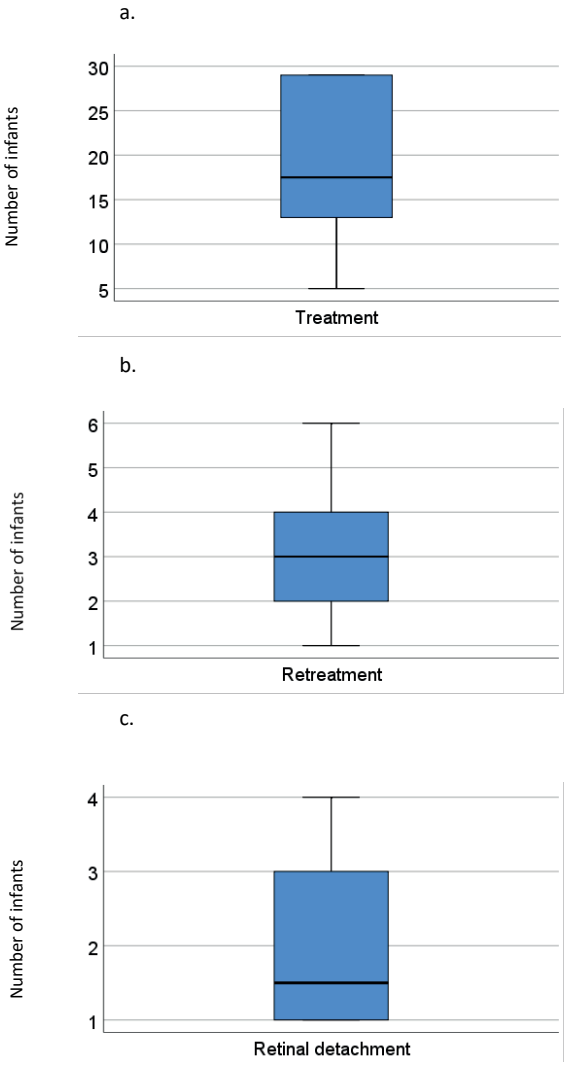

Figure 3 a, b and c. Boxplots representing median (range) of a) treatments: 19 (5-29), b) retreatments: 3 (1-6) and c) retinal detachment: 1.5 (1-4) in the 10 participating hospitals from 2010-2017.

Discussion

This study investigated the number and characteristics of infants treated for ROP and the results of ROP treatment in the Netherlands from 2010-2017. Since the implementation of the new Dutch ROP guideline in 2013, the number of treatments and infants developing retinal detachment due to ROP have more than doubled. The increase in our study corresponds to the increase reported in the United Kingdom, Sweden, Denmark and Australia (13-17). Several aspects could be considered to explain this development.

First, the number of infants who, based on gestational age (GA) at birth, are at particular risk for (severe) ROP has notably increased since 2013. While the overall number of newborns with GA <32.0 weeks, the age most screening guidelines use as cut off point for screening, remained stable, the subgroup with GA <25.0 weeks increased by nearly one-fourth. This can be explained by a significant change in neonatal policy. Compared to other countries, Dutch neonatologists maintained a relatively restrictive policy on active neonatal intensive care treatment of extremely premature born infants, because of the particularly poor survival and increased morbidity in even younger infants (18-21). In 2010 however, this threshold was lowered from GA 25.0 to 24.0 weeks, as a similar incidence of severe disabilities was demonstrated, compared to those with GA 25.0 weeks (22). The observed increase in number in this group (fig. 1 and table 1) suggests that the policy change only gradually showed effect since 2013 (41% increase from 190 in period 1 to 268 in period 2) which is of particular interest for our study. Nonetheless, the absolute amount is relatively small and consequently did not reach statistical significance. Moreover, a recent inventory on the two-year follow-up of infants born at 24.0 weeks showed no significant difference in the occurrence of severe ROP (stage ≥3) compared to infants born at 25.0 weeks of GA (23). Thus, it seems more likely that the increase in extremely premature infants in period 2 could only partially explain the increase in ROP treatment.

Another factor potentially contributing to the increase in treatment of ROP, was the introduction of higher oxygen saturation levels in most Dutch NICUs following the NeOProM meta-analysis (6). It is hypothesized that the adoption of higher SaO_2 in the first phase of ROP increases the risk for the development of treatment demanding ROP. This can be explained by the two-phased pathogenesis (1, 7, 24). During the first, so called vaso-obliterative phase, a relatively *hyperoxic* extrauterine environment suppresses the release of angiogenic factors, i.e. vascular endothelial growth factor (VEGF), which are crucial for normal vessel development. Moreover, oxidative stress leads to obliteration of yet formed vessels (25, 26). This process is enhanced by even higher O_2 levels. Subsequently the second, vaso-proliferative phase initiates, usually around the post menstrual age (PMA) of 32.0 weeks. In this phase, poorly developed and obliterated blood vessels are unable to meet the increasing metabolic activity (and oxygen demand) of the thriving neuroretina. In turn, local areas of

ischemia stimulate compensatory vessel growth by releasing large amounts of angiogenic factors. In case of severe ROP however, poor quality neovascularisations develop with a tendency to leak and bleed with a high risk of retinal detachment through fibrous traction (27, 28). Therefore, it is hypothesized that the adoption of even higher SaO_2 targets in the first phase increases the risk for the development of treatment demanding ROP. Potentially, this could have resulted in more frequent progression into type I treatment requiring ROP in period 2, however more detailed data is required to confirm this hypothesis.

Third, a new Dutch ROP guideline was implemented in 2013. The primary goal of the 2013 guideline was to reduce the number to be screened, while no severe ROP would be missed. This measure however only regards infants with no or *mild* ROP, thus, a direct influence on the present population is not expected. More important for our inventory, the 2013 guideline emphasized the ETROP criteria. This is the first study since 2009 to investigate the extent of the nationwide ETROP implementation. We found an improved documentation, suggesting better awareness of plus disease: the percentage of infants that could not be categorised into type 1 or type 2 decreased from 38.6% (22/57) in period 1 to 14.4% (20/139) in period 2. However, not only did the percentage of infants with high ROP stages (3 or more) at treatment decision not decrease as expected when *earlier* treatment is performed, it slightly increased from 49.1% to 57.6%. Moreover, the age at treatment decision was nearly identical (table 4), while the age at treatment was (not significantly) higher in the group that developed retinal detachment, suggesting that some infants in the RD group were treated relatively late. Internationally there is debate about treating ROP stage 2+ in zone II. Within the ETROP cohort 75.6% of infants had stage ≥3 at treatment decision (5). Also in studies from other countries in which the ETROP criteria are used, the percentage of infants with stage ≥3 ROP is high: 93.2% in Germany, where ROP stage 2+ in zone II is not listed as treatment indication and 97.5% in Sweden, where only ROP stages 3-5 are considered *severe* (29, 30). In addition, these inventories showed higher retreatment numbers; 31.1 and 19% respectively vs. 16.3% in the present study. Finally, even after excluding those infants from our cohort that were treated for stage 2+ ROP in zone II, the increase in treatment remains analogous (table 3). Our inventory implies that though awareness of the ETROP criteria improved in the Netherlands, attention to timely treatment should still be stressed. Furthermore, differences were observed between the participating hospitals in birth rates, treatment, retreatment numbers and outcomes (fig. 2 and 3). As expected, higher treatment and retreatment rates were found in centres in which more extremely premature infants were born. Other possible explanations for the variation could lie in different neonatal policies, the availability of an experienced surgical team or easy accessibility to a treatment centre.

Finally, six infants were primarily treated with intravitreal Bevacizumab (IVB), an agent antagonizing VEGF. Mintz-Hittner et al. (31) demonstrated that compared to laser, IVB is

solely favourable in zone I ROP. Therefore, the current Dutch guideline (2013) advises the use of anti-VEGF, only as treatment for ROP in zone I and as a last resort. In the present study, the number of infants with ROP in zone I is low (table 3), which can be explained by the age restriction of 24.0 weeks for active neonatal treatment. For unknown reasons, all infants treated with anti-VEGF agents were diagnosed with ROP in zone II. Moreover, incidence of progression to retinal detachment was slightly higher to that of the laser treated group, which might indicate that these infants had a bad prognosis and anti VEGF was given as last resort treatment. There are some limitations to our study. First, due to the retrospective setup, a limited set of data was available. For example, details about oxygen saturation levels and iNO-treatment were unknown, which could have provided more opportunities for in-depth analyses. Furthermore, as no prospective registry of infants with ROP exists in the Netherlands, the incidence of severe ROP in the overall ROP population remains unknown. In the future, a national prospective study could give rise to more well-founded conclusions in these matters.

To conclude, since the implementation of the new ROP guideline twice as many infants were treated for ROP presumably due to a larger population at risk, an unfavourable oxygen regime and better awareness of screening logistics and treatment. The corresponding increase of infants developing end stage ROP suggests room for even more attention to the treatment criteria.

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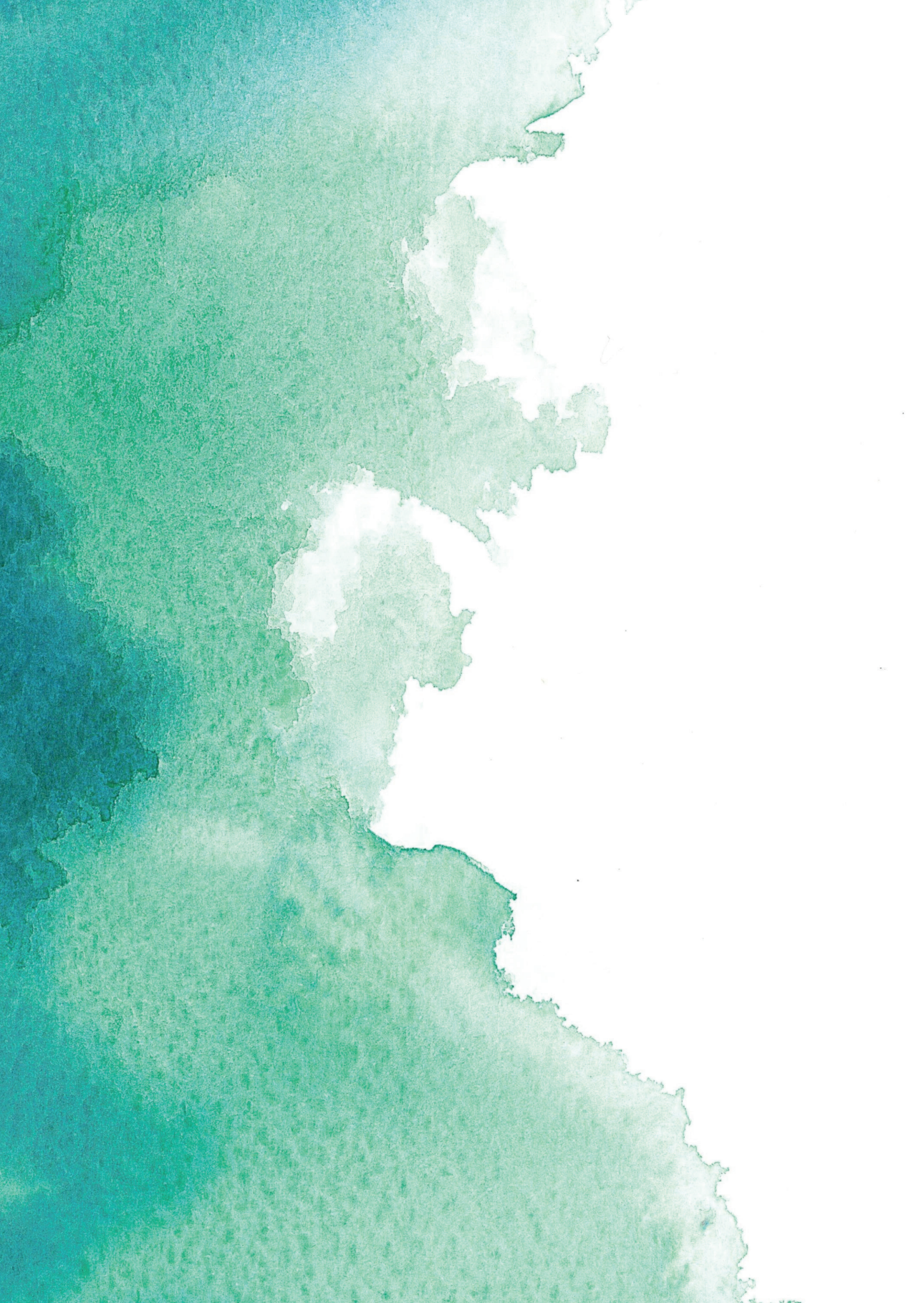

Chapter 3

Increased incidence of severe retinopathy of prematurity following a new national guideline

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Editor,

The NEDROP-study, a national inventory on Retinopathy of Prematurity (ROP) in the Netherlands (2009), showed that early treatment criteria for ROP (ETROP) were not yet widely implemented[1, 2]. ROP was found in 19.2% of which 5.2% required treatment and 1.8% developed an end-stage ROP (stage 4 or 5). Subsequently, a new ROP- guideline was introduced in 2013 emphasizing the use of ETROP-criteria[3]. To investigate the influence of the new guideline on incidence of severe ROP and outcome of ROP-treatment, a retrospective investigation was conducted using anonymized data of infants treated in three Dutch teaching hospitals between 2010 and 2016. In total, 57 subjects were identified and divided into group A (A): 16 infants (32 eyes) treated from January 1st 2010-April 1st 2013 and group B (B): 41 infants (79 eyes), from April 1st 2013-July 1st 2016. After correction for the duration of inclusion, a 2.7-fold increase in ROP-treatments was found. The groups were comparable regarding median (inter quartile range) gestational age (A: 25.2 (1.4), B:26.2 (2.1) weeks, *p*=0.204), median birth weight (A: 715 (184) and B: 730 (205) grams, *p*=0.972), neonatal interventions and comorbidities associated with ROP (table 1). Time and stage of ROP at first detection and treatment decision did not differ significantly between the groups, with the exception of median post menstrual age (PMA) at treatment decision being higher in B than in A (*p*=0.025, table 1). In A, ROP recurred and required retreatment with laser in two eyes in two infants, vs. 8 eyes in five infants in B (*p*=0.429). Apart from one patient (B) developing stage 5 ROP unilaterally, all infants had a favourable anatomical outcome at median follow-up age of 42 (33) (A) and 18 (12) (B) months. Conceivably explaining the difference in PMA at treatment decision was the adoption of higher oxygen saturation target levels during the first phase of ROP following a meta-analysis on optimal oxygenation of extremely preterm infants, applied in 2 of the 3 hospitals from 2014 onwards (NeOProM)[4]. Considering the two-phased ROP-pathogenesis, the first (vaso-obliterative) phase is caused by a deficit in factors such as vascular endothelial growth factor (VEGF), crucial for vessel development. VEGF-release is directly regulated by oxygen. Thus, a (relatively) hyperoxic extra-uterine environment due to higher oxygen saturation levels can lead to its decrease during the first weeks of life. Low VEGF-levels suppress the impulse for vascular outgrowth and moreover, cause obliteration of yet formed vessels. As the metabolic activity of the maturing neuroretina increases, oxygen deficit due to vascular incompetence leads to areas of hypoxia increasing VEGF-release. This in turn promotes the second, vaso-proliferative phase, defined by emerging neovascularisations on the verge of the vascularised and avascularised retina, forming the most important risk factor for permanent visual impairment due to retinal detachment. We hypothesize that higher oxygen targets in phase 1 in group B resulted in delayed onset of phase 2 due to a lag in VEGF-release. Another reason for the increase in ROP-treatments could be the adoption of ETROP-criteria, advising treatment in earlier ROP-stages. In A, ROP-stage>3 was found in 73.3%% vs. 64.9% in B (*p*=0.555), carefully suggesting a small trend towards better adherence to the new treatment criteria. Nevertheless, our cohort

represents a subgroup of treated infants. For a more conclusive statement on the influence of our new guideline, extension to a national cohort is necessary. To conclude, more infants were treated for ROP since the adoption of the new guideline. Better adherence to the ETROP-criteria can partly explain this increase and changes in oxygen regimen presumably postponed the age at treatment decision.

Table 1. Risk factors and treatment characteristics in the groups treated according to the old (A) vs. new (B) Dutch retinopathy of prematurity-guideline.

	A (*n*=16 infants, 32 eyes*)*	**B (*n*= 41 infants, 79 eyes)**	**p-value**
Neonatal Characteristics			
GA*	25.2 (1.4)	26.2 (2.1)	0.204**
BW*	715 (184)	730 (205)	0.972**
Obstetric characteristics and interventions			
Prenatal glucocorticoids	64.3%	75.7%	0.473†
Multiple birth	25.0%	46.0%	0.116†
Neonatal morbidity			
Sepsis	68.8%	74.4%	0.753†
IVH/PVL	43.8%	24.4%	0.062†
IRDS	93.7%	92.3%	1.000†
BPD	68.6%	69.2%	0.259†
NEC with perforation	12.5%	21.8%	0.815†
Hyperglycaemia (> 8 mmol/l)	56.3%	30.8%	0.081†
Neonatal Interventions			
Packed cells	93.8%	91.7%	0.795*
iNO	18.8%	21.1%	0.819*
Postnatal glucocorticoids	100%	58.8%	0.058***
AV > 7 days	87.5%	84.6%	0.783*
Treatment characteristics			
PMA at first ROP detection*	33.7 (1.64)	33.7 (3.71)	0.832**
PMA at treatment decision*	34.8 (1.29)	36.1 (3.71)	0.025**
PMA at treatment*	34.9 (1.93)	36.8 (3.93)	0.070**

AV, artificial ventilation; BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; iNO, inhaled nitric oxide, IRDS, infant respiratory distress syndrome; IQR, inter quartile range; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PMA, postmenstrual age; PVL, periventricular leukomalacia.

* Result shown as median (IQR)

** Mann-Whitney U test

*** Fisher's Exact test

† Pearson's Chi-Square Test

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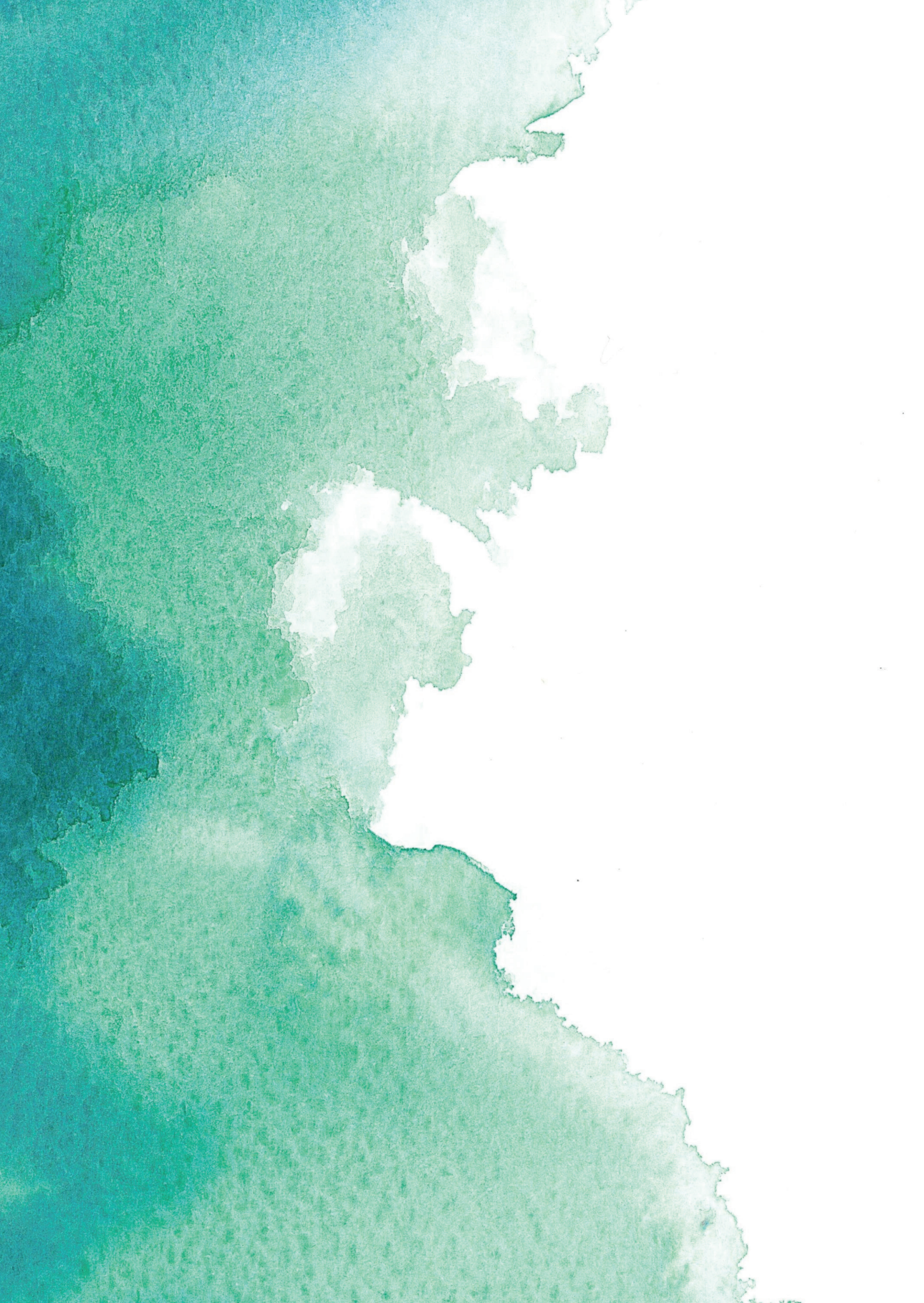

Chapter 4

Nationwide inventory on retinopathy of prematurity screening in the Netherlands

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Synopsys

In 2017, the number of Dutch infants with severe retinopathy of prematurity doubled since 2009. Successful implementation of the new national guideline, including risk-based screening criteria, led to a nearly one-third reduction in screened infants.

Abstract

Purpose

Provide up-to-date insight in incidence of retinopathy of prematurity (ROP), logistics of screening and treatment in the Netherlands and influence of the new national ROP guideline in which more stringent screening criteria were implemented and the Early Treatment for ROP criteria (ETROP) were emphasized.

Methods

Multicenter prospective nationwide study including all preterm infants, born in the Netherlands in 2017, and considered eligible for ROP screening. Anonymized data from ophthalmologists and pediatricians were merged. Outcome data were compared to the first national ROP inventory (NEDROP-1, 2009).

Results

In 2017, 1492 infants were live born with gestational age (GA)<32 weeks (2009: 1662); 1287 infants were eligible for screening (2009: 2033). Ophthalmologists screened 1085 infants, vs 1688 in 2009, corrected with factor 1.114 for the difference in number of live births, a 28.4% (479/1688) decrease in screened infants was seen. Among surviving infants with GA<32 week, ROP was found in 305/1492 babies, 20.4% (2009: 324/1662, 19.5%) of which 49/1492 stage≥3, 3.3% (2009: 30/1662, 1.8%). In all infants report on presence or absence of plus disease was provided, according to the ETROP criteria. Treatment was performed in 39 infants. Of infants with ROP stage ≥3, 3/49 (6.1%) progressed to retinal detachment (2009: 6/30, 20.0%).

Conclusion

The overall ROP incidence expressed as a percentage, remained stable but the number of infants that developed severe ROP nearly doubled. A near one third reduction in screened infants shows satisfactory implementation of the new screening criteria. A notable decrease in retinal detachment delineates improved treatment outcome.

Introduction

Retinopathy of prematurity (ROP) is a mostly self-limiting yet, potentially blinding disease in premature infants. While knowledge and experience on the pathological mechanisms progress, management success rates improve. However, advances in neonatal care lead to increasing survival of extremely premature infants, subsequently causing the group particularly at risk for ROP to grow[1-3]. Moreover, neonatal risk factors cannot always be fully controlled, therefore, timely screening and treatment remain the foundation for preventing irreversible vision loss due to progressive ROP.

The first Dutch nationwide ROP inventory, the NEDROP study (NEDROP-1, including infants completely screened for ROP and born between January 1st and December 31st 2009)[4], resulted in the implementation of a new ROP screening and treatment guideline in 2013[5, 6].

In 2009 ROP was found in 324/1688 (19.2%) screened infants (17.4% mild, 1.8% severe). Furthermore, critical aspects on the logistics and reporting of screening were revealed: 1) in 624/1688 (37.0%), first screening was not performed within the required period, 2) risk of loss to follow-up increased with hospital transfer and 3), nearly one-fourth of treated infants (23.5%) could not be classified according to the Early Treatment for ROP criteria, (ETROP[7]), due to incomplete data reporting on plus disease.

Upon these findings several measures were taken. Firstly, quality indicators were added to the Dutch National Monitoring System for Quality in Health Care, in which documentation of the required time period of (follow-up) screening and defined ophthalmological findings in the transferal letter were made obligatory. Secondly, a parental information folder was developed, which is to be handed before first screening, in order to stress the importance of ROP screening. Third, a section about treatment was added to the guideline, in which the ETROP treatment criteria were emphasized and widely promoted through conferences, courses, etc. Further, following detailed risk-analyses, more stringent and risk factor based screening inclusion criteria were introduced in 2013[6], allowing a predicted 29.0% reduction of screened infants without missing severe ROP. Finally, to help achieve good implementation, a screening and follow-up NEDROP-app was developed for pediatricians and ophthalmologists.

Yet, since 2009, the risk for (severe) ROP increased, due to the lowering of GA limit for active treatment from 25.0 to 24.0 weeks in Dutch neonatal intensive care units (NICU's) (2010)[8, 9], and implementation of higher oxygen saturation target limits (NeOProM, 2014[10]). As all these policy changes are likely to influence incidence, risk factors and logistics of screening and treatment since the first NEDROP, a second nationwide ROP inventory was performed: the NEDROP 2.

Methods

This multicenter, prospective, population-based study was initiated and approved by the Leiden University Medical Center. In the Netherlands, neonatal data are recorded in a national perinatal register called Perined. Data are only recorded after parental approval.

All babies born between January 1st and December 31st of the year 2017 who were eligible for ROP screening were reported by neonatologists and pediatricians. They prospectively reported a coded dataset consisting of date of birth, four digits of the ZIP code, GA, BW and the index number in case of multiple birth (1/2, 2/2, 1/3, etc.). Through a separate notification form, ophthalmologists provided the same code of the infants they screened, together with the following ophthalmological findings: date of first examination, suggested and executed dates of follow-up examinations, ROP classification, reason for discontinuation of screening, hospital transfer and, if applicable, date and modality of treatment. Eventually, neonatal and ophthalmological data were merged.

According to the 2013 guideline[11], screening applies to infants with GA<30.0 weeks and/or birth weight (BW)<1250 gram and GA 30.0-32.0 weeks and/or BW 1250-1500 gram with presence of one or more of the established risk factors: mechanical ventilation, sepsis, necrotizing enterocolitis (NEC), postnatal glucocorticoids and hypotension treated with inotropic agents. If the presence of risk factors is uncertain, screening is recommended according to the old guideline, advising examination of all infants with GA<32.0 weeks and/or BW<1500 grams[6].

First screening examination should be scheduled in the 5th postnatal week (35-42 days), but not before 31.0 weeks of postmenstrual age (PMA). Screening examinations were considered timely if performed within three days of scheduled date.

ROP was categorized into type 1 and type 2 ROP. For the purpose of comparison to NEDROP 1, ROP was also classified into mild (stages 1 and 2) or severe (stage 3 or higher, including Aggressive Posterior ROP (APROP)) according to the ICROP classification (revisited 2005)[12].

For incidences, national live born premature infants were used as denominator, for which the same cut-off GA was used as in 2009 (<32.0 weeks). Birth rates were obtained from Perined and the Dutch Central Bureau of Statistics[13, 14].

Statistical analysis

Numerical values are reported as median (25-75% interquartile range (IQR) or range). Statistical analysis was performed with SAS Enterprise Guide 7.1 (SAS Institute, Cary, North Caroline USA) and R (version 3.6.1). Frequencies of events were compared using

Pearson's Chi-square test or Fisher's exact test when a cell count was smaller than five. For the comparison of multiple groups pairwise comparisons were calculated. Population parameters were treated as known and a binomial test was used to compare a frequency with a birth rate. Logistic regression was used, when correction for covariates was required.

Results

Population

In 2017, 1492 babies with GA<32.0 weeks were live born (2009: 1662). Participation of all Dutch hospitals (80) involved in ROP screening was realized, including 10 NICU's, 16 high-care centers (HC) and 54 regional centers (RC).

Between January 1st and December 31st of 2017, neonatologists and pediatricians identified 1287 infants eligible for screening (table 1). Infants were born at a NICU (1171; 91.0%), a HC (61; 4.7%), RC (51; 4.0%) and in a foreign (3) or unknown (1) hospital (together 0.3%). Population characteristics are shown in table 2a.

In total, 1085 babies were fully screened vs. 1688 in 2009. Corrected with factor 1.114 for the difference in number of live births between 2017 and 2009, (which gives a hypothetical number of 1209 screened infants), this was a 28.4% (479/1688) reduction of screened infants (table 1).

Two hundred two infants were not (fully) screened. Of them, 120 died before screening was completed. Fifty-seven infants were wrongly included as did not fit the screening inclusion criteria. The remaining 25 (1.9% of the infants eligible for screening) were not screened or lost to follow-up because of: transfer abroad (1), no show at follow-up appointment (4) or unknown reason (20).

Table 1. Data from first (2009) and second (2017) NEDROP studies

	2009	2017
Live born babies	1662	1492
GA 28.0 - 32.0	1303	1092
GA 25.0 - <28.0	313	331
GA <25.0	46	69
Eligible for screening*	2033	1287
Fully screened	1688 (83.0%)	1085 (84.3%)
Timely first screening	1064 (63%)	849 (78.2)
GA**	30.1 (28.6-31.4)	29 (27.3-30.4)
BW**	1320 (1050-1560)	1150 (935-1350)
Infants transferred	822	906
Lost to follow up after transfer	189/822 (23.0)	22/902 (2.4%)°
Number of screenings total	3891	3750
Number of screenings no ROP	2402	1981
Number of screenings with ROP	1489	1769
ROP total	324	305
Incidence among live births	19.5%	20.4%
Type 1 ROP †	21	38
Type 2 ROP†	10	15
Stage 3 or higher	30	49
Treatment	17	39
Retinal detachment	6	3

BW, birth weight in grams; GA, gestational age in weeks; IQR, interquartile range; ROP, retinopathy of prematurity.

*According to Dutch pediatricians

** Median (interquartile range) of screened infants

° This group includes only infants who survived and met the new screening criteria

† Incomplete data on plus disease for 2009

Table 2. NEDROP 2 population characteristics a. the NEDROP 2 study population, b. screening and c. ROP detection shown as median (IQR).

	Screened for ROP	No ROP	Overall ROP	Mild ROP	Severe ROP
a. Population	1085	780	305	256	49
GA*	29.0 (27.3-30.4)	29.6 (28.3-30.9)	27.1 (26.0-28.7)	27.6 (26.3-28.9)	25.7 (24.9-26.6)
BW*	1150 (935-1350)	1213 (1029-1414)	938 (760-1150)	975 (800-1178)	750 (319-865)
Multiple pregnancy, *n* (%)	278 (25.6)	192 (24.6)	86 (28.1)	78 (30.5)	8 (16.3)
b. Screening					
Examinations per patient	3 (2-4)	2 (1-3)	5 (3-7)	4 (3-6)	9 (8-11)
1st exam PMA	34.4 (32.9-36.0)	35.0 (33.6-36.4)	32.6 (31.7-34.1)	33.0 (31.9-34.3)	31.9 (31.2-33.1)
1st exam PNA	5.4 (5.0-6.0)	5.3 (5.0-5.9)	5.6 (5.0-6.1)	5.4 (5.0-6.0)	6.1 (5.6-6.9)
Timely, *n* (%)	849 (78.2)	599 (76.8)	250 (82.0)	211 (82.4)	39 (79.6)
Too late, *n* (%)	236 (21.8)	181 (23.2)	55 (18.0)	45 (17.6)	10 (20.4)
c. ROP					
1st detection PMA	NA	NA	34.1 (33.0-35.7)	34.3 (33.0-35.9)	33.6 (32.1-34.6)
1st detection PNA	NA	NA	6.7 (5.4-8.3)	6.6 (5.3-8.0)	7.3 (6.5-9.1)

BW, birth weight; GA, gestational age; IQR, interquartile range; NA, not applicable; PMA, post menstrual age; PNA, postnatal age; ROP, retinopathy of prematurity. Mild ROP: stages 1-2, severe ROP: stages ≥3.
* t-test no ROP vs. overall ROP p <0.001

Screening

A total of 1085 infants was screened in 3750 screening examinations. Infants who developed ROP were screened 1769 times, those with no ROP, 1981 times (table 1). The number of examinations increased with the severity of ROP (table 2b and table 3).

Data about initial screening and first detection of ROP are shown in table 2b and 2c. At first screening, 924 infants had no ROP, ROP stage 1 was reported in 125, stage 2 in 34 and stage 3 in two infants. In 236 (21.8%) first screening was performed after the recommended date. At first screening, 40 infants that were screened too late already developed mild (stage 1: 28, stage 2: 12) and two stage 3 ROP. Follow-up examinations were carried out timely in 97.1%. In the remaining group, follow-up was performed outside this interval (range 4-67 days), without consequences for the outcome.

Table 3. Characteristics of infants with ROP specified per stage.

	n	GA	BW	Screenings	Plus disease (*n*)	Treated (*n*)	Type 1 (*n*)
No ROP	780	29.6 (24.0-34.9)	1210 (500-2900)	2 (1-10)	n.a.	n.a.	n.a.
ROP 1	159	28.1 (24.4-32.1)	1020 (450-2350)	4 (1-10)	1	0	0
ROP 2	97	26.7 (24.0-31.4)	898 (520-1530)	6 (1-17)	9	8	8
ROP 3	44	25.7 (24.0-30.9)	750 (410-1415)	10 (2-19)	26	26	25
ROP 4	2	26.0 (25.6-26.4)	621 (578-665)	14 (9-19)	2	2	2
ROP 5	1	26.1	520	27	1	1	1
APROP	2	25.9 (25.1-26.6)	893 (785-1000)	7 (5-8)	2	2	**2**

Gestational age (GA, weeks), birth weight (BW, grams) and number of screenings shown as median with minimum-maximum range in brackets. APROP, aggressive posterior ROP.

ROP

Of the 1085 screened infants, 305 (28.1%) developed ROP. Among 1492 live births with GA<32.0 weeks the overall ROP incidence was 20.4%, assuming no ROP occurred in the unscreened population (table 1). Median GA and BW were lower in babies developing ROP compared to those that did not (both p<0.001, table 2). The severity of ROP stages increased with decreasing GA (p<0.001, figure 1).

Information on presence or absence of plus disease was provided in 304/305 (99.7%) of the overall ROP population (present in 41, absent in 263 and not noted in one infant with stage 1 ROP), and in 100% of treated infants. Thirty-eight infants could be categorized into type 1 and 15 into type 2 ROP. For unknown reasons, six babies with type 1 ROP were not treated (ROP 3+ in zone II (3) and ROP2+ in zone II (3)). Eventually, in all six, ROP regressed spontaneously. Maximum ROP stage 1 was found in 159, stage 2 in 97 and stage ≥3 in 49 cases (table 3). At time of first detection, ROP was located in zone I in 22, posterior zone II in 4, zone II in 189 and zone III in 90 cases. Treatment was performed in 39 infants. At treatment decision, 33 had type 1 ROP, three type 2 ROP and three could not be categorized because they did not fit the ETROP criteria: two with ROP in zone III and one with stage 2 without plus. Eventually, despite treatment,3 babies with ROP stage 3+ at treatment decision progressed into retinal detachment (table 1, table 3). Two babies with GA 30.0 weeks - one infant with BW 1415 gram, NEC, sepsis and need for inotropic agents for hypotension and one with BW 1360 gram, prolonged mechanical ventilation and inhaled nitric oxide - developed stage 3 ROP, illustrating the need for risk based inclusion criteria to detect outliers in our population.

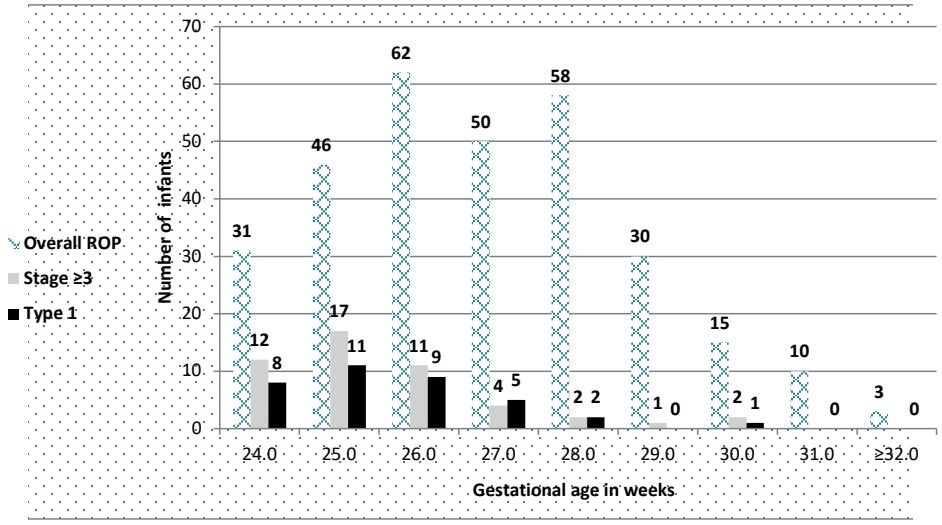

Figure 1. Number of infants with overall, stage ≥3 and type 1 retinopathy of prematurity (ROP) and their distribution of gestational age in weeks. The severity of ROP significantly increased with decreasing GA (p<0.001).

Transfer

Overall, 381/1287 (29.6%) babies were not transferred from the hospital of birth. Other infants were transferred up to six times. In the non-transferred group, the proportion of not screened infants was 126/381, 33.1%, however, the majority of them died before first screening (116/126, 92.1%). After excluding the deceased infants and those that were referred according to the old criteria (7), only 3/265 (1.1%) were not screened. In the transferred group 76 infants were not screened of which 4 died and 50 were wrongly referred. After exclusion of these, the number of not screened infants was 22/902, 2.4% p<0.2. Logistic regression showed no relation between the number of transfers and number of babies lost to follow-up (OR 1.2, p=0.195).

Discussion

The NEDROP 2 study is a prospective, population-based inventory, based on data of all infants born in 2017 and referred for ROP screening in the Netherlands. It is the second national inventory to study the natural course of ROP and adherence to the adapted screening and treatment guideline following the NEDROP 1 (2009)[4]. The then calculated reduction of 29%[6] for infants needing ROP screening was found to be 28.4% in our 2017 study population. However, the number of screening examinations did not decrease as much as the number of screened children (from 3891 in 2009 to 3750 in 2017 , a reduction of only 3.6%). We attribute this to an increase in infants with lower GA (+18 with GA<28.0

weeks and +23 with GA<25.0 weeks), who require relatively more screening examinations. Thus, the implementation of new inclusion criteria for screening in 2013 relieved the burden of screening of the overall population, did not substantially reduce the overall workload for ophthalmologists but enabled them to focus on babies with the highest risk.

The overall ROP incidence within the screened population increased from 19.2% in 2009 to 28.1% in 2017. However, among all live born babies with GA<32.0 weeks, this was 19.5% in 2009 and 20.4% in 2017, and thus, relatively stable assuming there was no ROP in the unscreened population (table 1). The increase within the screened population can be therefore attributed to the implementation of risk factor criteria focusing on high risk babies for ROP.

The occurrence of ROP is largely dependent on GA, BW, survival and the presence of ROP associated risk factors during the neonatal period[15]. Therefore, comparing incidences to other countries is challenging as neonatal policies, survival and screening criteria may differ. Survival for infants born at 24 weeks (as % of live borns) was 34.4% in the Netherlands in the period 2011-2017[16]. Other similar national population-based cohorts report however survival rates varying from 31% to 67% in 24-week infants[17]. This may be reflected in ROP incidence. Even among cohorts with similar mean population GA and BW, varying ROP incidences can be observed: i.e. Sweden (2012: overall 24.0% of which 8.7% severe[18]; 2015: 24.1% overall 8.5% severe[19]), Switzerland (6472 infants between 2006-2015: overall 9.2%, severe 1.8%[20]) and a large cohort from 29 Canadian and US hospitals (7483 infants between 2006-2011: 43.1% overall, 6.1% severe[21]).

We observed an increase in severe ROP (stage ≥3) among live born neonates with GA<32.0 weeks, from (30/1662) 1.8% in 2009 to (49/1492) 3.3% in 2017 (table 1). Additionally, the absolute number of ROP treatments has more than doubled from 17 (2009) to 39 (2017). This is supported by previous findings, i.e. twice as many infants requiring ROP treatment in the Netherlands between 2010-2016, found in an earlier retrospective inventory[22,23], and findings from countries such as Denmark[24], the UK[2, 25] and Sweden[3]. We hypothesize that several essential changes in Dutch neonatal care contributed to this increase.

Firstly, in 2010 the age limit for active neonatal treatment was lowered from 25.0 to 24.0 weeks of gestation[8, 9]. As anticipated, this has indeed led to a higher number of infants who, based on GA, are at particular risk for severe ROP. While the overall number of preterm infants with GA<32.0 weeks decreased from 1662 (2009) to 1492 (2017), the subgroup born GA<25.0 weeks increased by 50% (table 1). Although survival of extremely premature infants in the Netherlands is still in the lower range compared to other high income countries, with continuously improving survival of these neonates, awareness of concomitant conditions such as (severe) ROP remains crucial[16].

Secondly, surprisingly the NEDROP 1 revealed that the ETROP criteria[7], which apply since their publication in 2004, were not yet fully implemented in the Netherlands[4]. The former guideline dating from 1997 did not include a directive on ROP treatment, therefore possibly, utilization into practice stayed behind. Subsequently, the criteria were emphasized in the 2013 guideline, which might lead to treatment decision in earlier (less advanced) stages and therefore, might increase the number of infants requiring treatment. The present study shows a notable improvement of report on plus_disease in both overall population and treated group (from 83.0 to 99.7% and 76.5 to 100% respectively), delineating the need for periodic monitoring of screening and treatment outcomes in order to improve national guidelines and their implementation. Although the proportion of infants with end stage ROP decreased, ROP stages at treatment decision were comparable in both studies and thus truly earlier treatment was not observed. So more awareness for signs of disease progression remains important.

Thirdly, following the NeOProM meta-analysis, higher oxygen saturation targets are now globally advised[10, 26], because of better survival and lower risk of NEC. Simultaneously however, an increased risk for severe ROP is expected. Since in the Netherlands *higher* SaO2 target limits were accepted in most NICU's, we hypothesize that when applied during the first weeks of life, the oxygen regime could have contributed to the increase in severe ROP.

ROP is predominantly self-limiting. However, undiagnosed and untreated progressive stages can lead to devastating and life-long consequences. Our inventory demonstrates the benefits of measures taken to promote timely screening, as this number notably decreased from 624/1688, 37.0% in 2009[4] to 236/1085, 21.8% (p<0.001). Still, over one fifth is not screened within the required period. Moreover, two infants already had stage 3 ROP at first screening, performed at six and ten weeks PMA. Therefore, as ROP has a narrow window of opportunity for treatment, the importance of well-timed screening must be stressed continuously.

The well-known obstacle in ROP screening of loss to follow-up due to hospital transfer[27, 28] was addressed in the 2013 ROP guideline and our results illustrate the positive effect of the increased awareness of both physicians and parents: within the transferred group, the number of not screened infants decreased from 189/822, 23.0% (2009)[4] to 22/9022.4%% (2017). Still, the absolute number of loss to follow-up is twice as high in transferred infants compared to the non-transferred group. Considering a higher number of transferred infants compared to NEDROP 1, marked by the fact that in 2017 only 29.6% of all infants were fully screened in hospital of birth (vs. 59.6% in 2009), we underline this issue of concern in future hospital transfers.

The main strength of this study is its design which gives insight in annual incidence, screening and treatment of ROP in the Netherlands. Data were provided by both ophthalmologists and pediatricians, therefore apart from nationwide insight in ROP, screening referral and guideline adherence could also be monitored. The identical study design allowed comparison with NEDROP 1 and thus, to evaluate the influence of policy changes in ROP care. Still, due to the new screening inclusion criteria many infants with a low ROP risk were no longer included in the present study, thus, the two study populations were not entirely comparable. To correct for this difference, the number of surviving infants was used as denominator instead of the screened population. Finally, all data were collected anonymously. For this reason, in infants who were not screened, it was impossible to determine if they eventually developed ROP.

To conclude, the overall ROP incidence in the Netherlands was comparable to 2009, but the number of infants with treatment requiring ROP nearly doubled. A 28.4% reduction in infants screened for ROP was accomplished since the implementation of new, risk-based screening inclusion criteria, shifting the focus of ROP screening to babies with the highest risk. The number of infants lost to follow-up due to hospital transfer has decreased, but the risk for not being screened remains. Although the general opinion might be that the screening program functions properly, this study shows that periodic evaluation is valuable and should be mandatory.

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Competing interests

None

Contributorship statement

Research design was done by K.T., N.S. and J.T.. Acquisition and analysis of data was performed by K.T. and A.S.. The authors S.B. and K.T. were responsible for statistical analysis. The article was written by K.T., N.S and J.T. and was critically revised and approved for publication by A.S..

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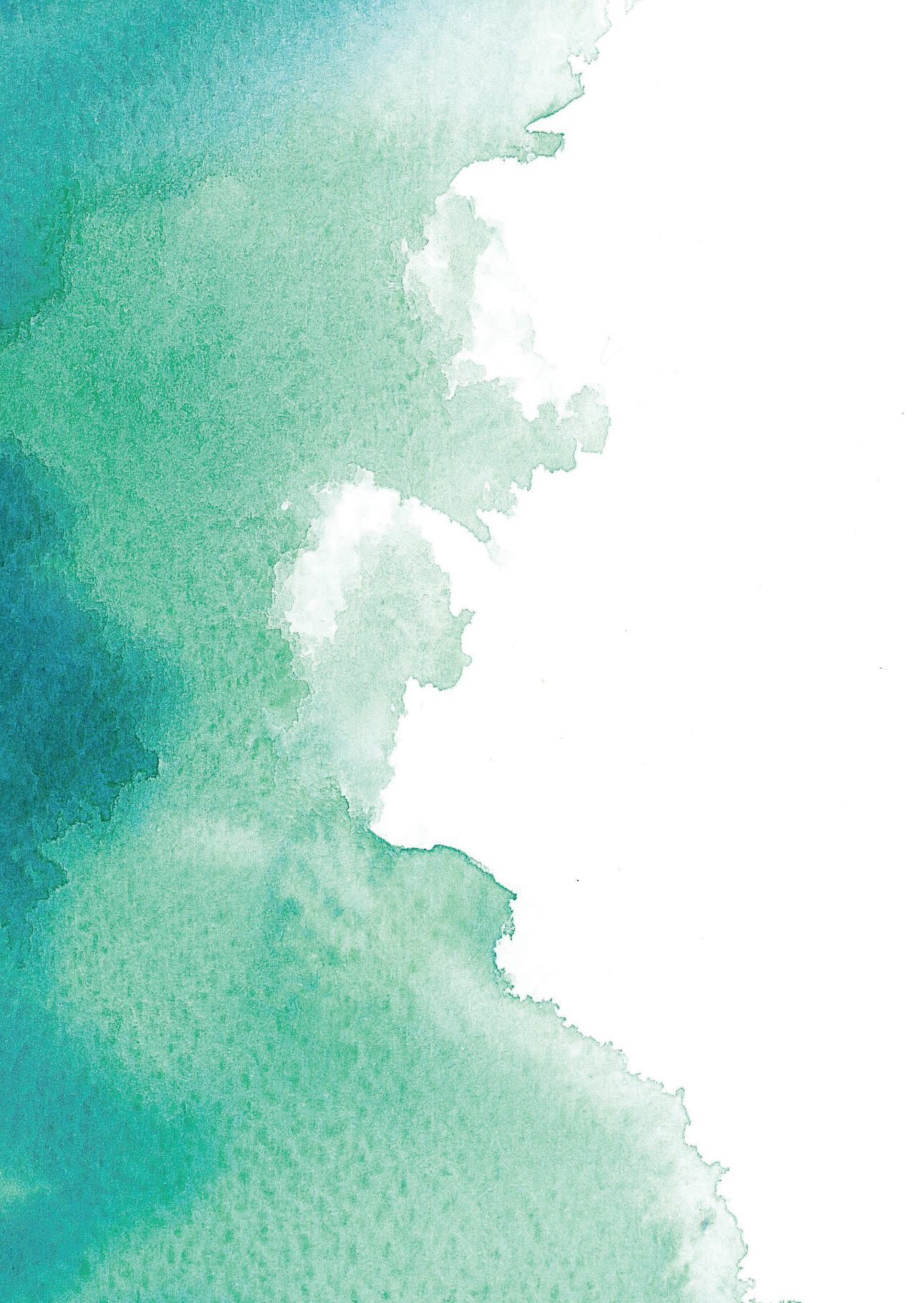

Chapter 5

Risk factors for retinopathy of prematurity in the Netherlands: a comparison of two cohorts

Evaluation of risk factors on ROP in The Netherlands

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Abstract

Introduction

Retinopathy of Prematurity (ROP) remains an important cause for preventable blindness. Aside from gestational age (GA) and birth weight (BW), risk factor assessment can be important for determination of infants at risk of (severe) ROP.

Methods

Prospective, multivariable risk-analysis study (NEDROP-2) including all infants born in 2017 in the Netherlands considered eligible for ROP screening by pediatricians. Ophthalmologists provided data of screened infants, which were combined with risk factors from the national perinatal database (Perined). Clinical data and potential risk factors were compared to the first national ROP inventory (NEDROP-1, 2009). During the second period, more strict risk factor based screening inclusion criteria applied.

Results

Of 1287 eligible infants 933 (72.5%) were screened for ROP and matched with the Perined data. Any ROP was found in 264 infants (28.3% of screened population, 2009: 21.9%), severe ROP (sROP) (stage ≥3) in 41 (4.4%, 2009: 2.1%). The risk for any ROP is decreased with higher GA (odds ratio (OR) 0.59, 95% coincidence interval (CI) 0.54-0.66) and increased for small for GA (SGA) (1.73, 1.11-2.62), mechanical ventilation >7 days (2.13, 1.35-3.37) and postnatal corticosteroids (2.57, 1.44-4.66). For sROP, significant factors were GA (OR 0.37, CI 0.27-0.50), SGA (5.65, 2.17-14.92), postnatal corticosteroids (3.81 1.72-8.40) and perforated necrotizing enterocolitis (7.55, 2.29-24.48).

Conclusion

In the Netherlands sROP was diagnosed more frequently since 2009. No new risk factors for ROP were determined in the present study apart from those already included in the current screening guideline.

Introduction

Worldwide, retinopathy of prematurity (ROP) continues to be an important cause of childhood blindness (1, 2). Although usually self-limiting, ROP requires treatment in approximately eight percent of the overall screened population to prevent irreversible visual impairment (3). Major risk factors of ROP are gestational age (GA) and birth weight (BW) (1). Still, ROP is a multifactorial disorder influenced by other aspects, e.g. maternal factors, medical interventions, insufficient treatment and comorbidities (4). Since these factors are strongly correlated to neonatal care, ROP screening should be adapted to local incidences and risk factors.

In 2009, the first nationwide inventory in the Netherlands to study ROP risk factors (NEDROP) was performed (5). Several well-known factors were confirmed: GA, BW, length of stay (LOS) in the neonatal intensive care unit (NICU) and mechanical ventilation longer than 7 days (MV>7 days). Treatment with inhaled nitric oxide (iNO) was newly identified.

Subsequently, together with extensive cost-effectiveness analyses, a new ROP screening guideline was implemented in 2013 (table 1) (6). GA and BW were lowered and risk factors were included (i.e.: MV, sepsis, (perforated) necrotizing enterocolitis (NEC), postnatal corticosteroids and hypotension treated with cardiotonic agents). This adjustment would allow a reduction in screened infants by 29% without missing sROP needing treatment.

Since then, several developments in Dutch neonatal care might have influenced the incidence and risk factors for ROP. First, the GA limit for active neonatal care was lowered from 25.0 to 24.0 weeks in 2010. Furthermore, following an interim meta-analysis of the NeOProM group of studies, oxygen saturation targets of NICU-admitted neonates were raised in 2014 (7). Together with residual confounders, these changes increased the risk for ROP, which was confirmed in an inventory on ROP-treatment in the Netherlands, revealing a notable increase of ROP treatment (8), from n=57 between 2010-2013 to n=139 between 2013-2016.

As it has nearly been a decade since the first NEDROP study, the purpose of this consecutive, NEDROP-2 inventory was to determine the present risk factors associated with ROP.

Table 1. Inclusion criteria for ROP screening according to the previous and current Dutch guideline.

Guideline	Previous (1997)	Current (2013)
GA/BW	<32.0 weeks and/or <1500 grams	<30.0 weeks and/or <1250 grams
Additional inclusion	-	30.0-32.0 weeks and/or 1250-1500 grams and presence of ≥1 risk factor

Methods

Study design

The NEDROP-2, a multicenter, prospective inventory, studied infants born in 2017 and eligible for ROP screening according to the current guideline (2013), using risk-based criteria (figure 1).

Patients and data

First, pediatricians reported infants eligible for ROP screening, on admission, by a set of coded data: date of birth (DOB), four digits of the zip code, GA, BW and when applicable, the index of multiple birth (1/2, 2/2, 1/3, etc.). Second, ophthalmologists reported screened infants using the same code.

Definitions of neonatal risk factors were identical to 2009 and were obtained from the national perinatal registry, Perined. Extremely low birth weight (ELBW) was defined as BW<1000 gram. Small for GA (SGA) as BW<-2 s.d. (9). Oxygen exposure was defined as number of days fully exposed to supplemental oxygen. Bronchopulmonary dysplasia (BPD) was defined as need of supplemental oxygen at 36 weeks post menstrual age (PMA). NEC was included when perforated. Sepsis was defined as clinical signs of sepsis and a positive blood culture, early and late sepsis were included. Severe intraventricular hemorrhage (IVH) was classified according to the definition of Papile (stage≥3) (10) and cystic periventricular leukomalacia (PVL) to the definition of De Vries (grade 2-3) (11). Patent ductus arteriosus was included when treated with indomethacin, ibuprofen, paracetamol or surgery. Hyperglycemia was defined as a blood sugar≥8.0 mmol/L. Longer stay at a NICU (>28 days) and prolonged MV (>7 days) were regarded as indicators of severe illness. Ophthalmologists documented zone and maximum ROP stage, plus disease and ROP-treatment. ROP was classified according to the International Classification of ROP and categorized according to the Early Treatment for ROP criteria (12, 13). In the Netherlands, ROP 2+ in zone II is only treated with presence of severe or progressive plus disease. For comparison with the NEDROP-1, ROP stage 1-2 was defined as mild, stage 3-5 as sROP. Aggressive Posterior-ROP (APROP) and ROP in zone I with

plus disease were also considered sROP. In the present cohort only one infant was found with APROP and no infants with ROP zone I with plus disease. Based on the individual code, neonatal and ophthalmological data were merged.

Statistical analysis

Due to differences in inclusion criteria, comparison of incidence of sROP between NEDROP-1 and NEDROP-2 was calculated by using live births as denominator. Clinical data of infants with any degree of ROP or sROP were compared using t-tests or Chi2-tests where appropriate. A p-value<0.05 was considered significant. Multivariable analysis was performed for 'any ROP' and 'severe ROP', by backward analysis to reduce the final model as much as possible, using the software package 'R' (https://www.r-project.org). Odds ratios and 95% confidence intervals were presented. With more than 900 infants studied and an estimated incidence of mild ROP of 20% and sROP of 3-5%, the power of the study was more than 0.90 to examine at least 5 variables for 'any ROP' and 'severe ROP'.

Results

Participation of all Dutch hospitals (80) involved in ROP screening was realized. Pediatricians reported 1287 infants eligible for screening according to the 2013 guideline. DOB and zip code generated the highest merging rate for the NEDROP-2 database with the perinatal registry, resulting in a combined dataset of 1106/1287 babies (85.9%) (figure 1). Not all data could be merged because of registry errors or no record in Perined. Of the 1106 coupled neonates 933 (84.4%) were actually screened for ROP. Infants were not screened due to death before first screening (103/173), transfer abroad (1/173), no show up (3/173), old criteria used (49/173) and unknown reasons (17/173). The remaining 21/173 infants (1.9%) were falsly not screened. Median (IQR) overall GA and BW of the screened infants were 28.9, 27.3-30.3 weeks (NEDROP-1: 29.8, 28.1-31.1) and 1150, 935-1350 grams (NEDROP-1: 1260, 1020-1500) respectively. Other clinical characteristics are presented in table 2.

ROP was found in 264 infants (28.3%) of whom 223 (23.9%) had mild, 41 (4.4%) sROP, 36 (3.9%) type 1 and 11 (1.2%) type 2 ROP. ROP was inversely associated with increasing GA and BW (table 2). Only 5/41 infants with sROP had a GA>28.0 weeks, in none GA was >30.0 weeks. All five were severely ill, SGA and/or required extensive neonatal interventions (i.e., sepsis, prolonged MV).

After adjusting for GA and SGA, risk factors achieving statistical significance for any ROP were MV>7 days and postnatal corticosteroids (table 3a) and for sROP perforated NEC and postnatal corticosteroids (table 3b). Although MV>7 days was also significantly associated with severe

ROP (OR 3.00 (1.35-7.03, p=0.008) , administration of postnatal corticosteroids had higher odds for the development of severe ROP. In our final models no interactions were found.

In figure 2, an estimated risk of (severe) ROP is shown based on our model. It becomes clear that apart from GA, risk factors play an important role for the development of sROP in infants born <30.0 weeks. The difference in probability to develop any ROP between high and low risk infants remains almost the same for every week of gestation. In contrast, for sROP this difference decreases with increasing GA. Finally, for infants with a GA<26.0 weeks with a high risk profile, the risk to develop any ROP is almost equal to sROP.

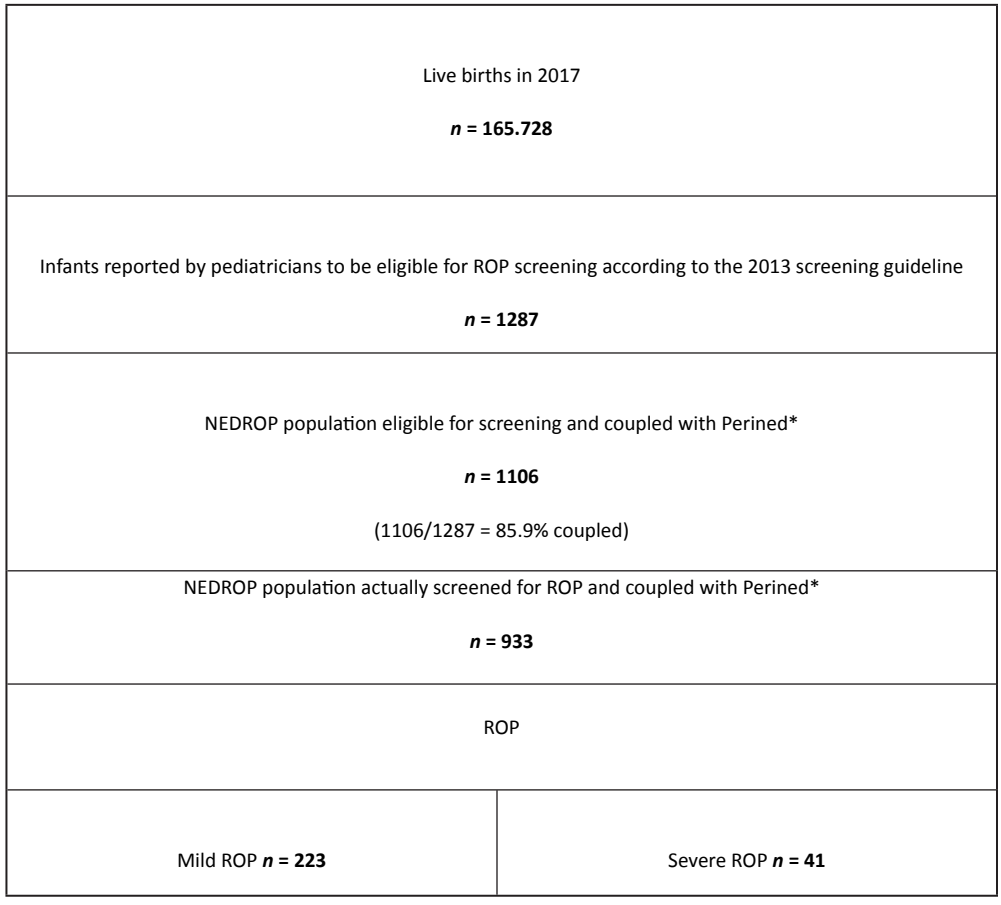

Figure 1. Population flow chart.
ROP retinopathy of prematurity, *Perined: national perinatal registry

Table 2. Descriptive statistics

Characteristic	Total (*n*, %)	No ROP (*n*, %)	ROP stage 1 or 2 (*n*, %)	ROP stage 3 and above (*n*, %)	*p*-value
	933 (100)	**669 (71.7)**	**223 (23.9)**	**41 (4.4)**	
Apgar 5 (IQR)	8 (2)	8 (2)	8 (2)	7 (2)	0.019
GA median (IQR) min-max	28.9 (3.0) 24.0-32.9	29.4 (2.6) 24.0-34.9	27.6 (2.5) 24.0 – 32.0	25.7 (0.6) 24.1 – 30.0	<0.001
BW median (IQR) min-max	1150 (415) 410 – 2510	1210 (375) 500-2510	975 (380) 450 – 2350	700 (231) 410 – 1415	<0.001
Female gender	401 (43.0)	273 (40.8)	103 (46.2)	25 (61.0)	0.022
ELBW <1000 gram	293 (31.4)	143 (21.4)	114 (51.1)	36 (87.8)	<0.001
SGA P<-2 s.d.	221 (23.7)	163 (24.4)	46 (20.6)	12 (29.3)	0.362
Multiple birth	236 (25.3)	162 (24.2)	68 (30.5)	6 (14.6)	<0.001
LOS NICU (days)					
0	24 (2.6)	21 (3.1)	3 (1.3)	0	<0.001
>28	545 (58.4)	464 (69.4)	77 (34.5)	4 (9.8)	
>28	364 (39.0)	184 (27.5)	143 (64.1)	37 (90.2)	
Mechanical ventilation (days)					
0	497 (53.3)	407 (60.8)	86 (38.6)	4 (9.8)	<0.001
>7	254 (27.2)	195 (29.1)	53 (23.8)	6 (14.6)	
>7	170 (18.2)	62 (9.3)	78 (35.0))	30 (73.2)	
missing	12 (1.3)	5 (0.7)	6 (2.7)	1 (2.4)	
Supplemental O_2 (days)					
0	224 (24.0)	189 (28.3)	32 (14.3)	3 (7.3)	<0.001
>28	399 (42.8)	310 (46.3)	83 (37.2)	6 (14.6)	
>28	240 (25.7)	111 (16.6)	97 (43.5)	32 (78.0)	
missing	70 (7.5)	59 (8.8)	11 (4.9)	0	
Sepsis	353 (37.8)	239 (35.7)	85 (38.1)	29 (70.7)	<0.001
IVH stage ≥3	48 (5.1)	28 (4.2)	15 (6.7)	5 (12.2)	0.037
Cystic PVL	10 (1.1)	4 (0.6)	4 (1.8)	2 (4.9)	0.017
IRDS	479 (51.3)	316 (47.2)	135 (60.5)	28 (68.3)	<0.001
BPD	98 (10.5)	43 (6.4)	38 (17.0)	17 (41.5)	<0.001
Treated PDA	173 (18.5)	89 (13.3)	66 (29.6)	18 (43.9)	<0.001
NEC with perforation	24 (2.6)	11 (1.6)	5 (2.2)	8 (19.5)	<0.001
Hyperglycaemia (>8.0 mmol/l)	140 (15.0)	79 (11.8)	44 (19.7)	17 (41.5)	<0.001
Hypotension treated with inotropes	145 (15.5)	80 (12.0)	46 (20.6)	19 (46.3)	<0.001
iNO	54 (5.8)	21 (3.1)	23 (10.3)	10 (24.4)	<0.001
Packed cells	415 (44.5)	257 (38.4)	122 (54.7)	36 (87.8)	<0.001
Postnatal corticosteroids	100 (10.7)	31 (4.6)	46 (20.6)	23 (56.1)	<0.001

All characteristics are described as absolute number (n) and percentage of total (%), except for Apgar, BW and GA, for which median (IQR) and/or minimum to maximum values were used.
Apgar 5, Apgar score 5 minutes after birth; BPD, bronchopulmonary dysplasia (supplemental oxygen at 36 weeks PMA); BW, birth weight in grams; ELBW, extremely low birth weight; GA, gestational age in weeks; iNO, inhaled nitric oxide; IRDS; infant respiratory distress syndrome; IQR (interquartile range) IVH, intraventricular hemorrhage; LOS NICU, length of stay at neonatal intensive care unit; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PMA, post menstrual age; PVL, periventricular leukomalacia; SGA, small for gestational age. *P*-value: No ROP vs. ROP stage 1 or 2, ROP stage 3 and above including APROP.

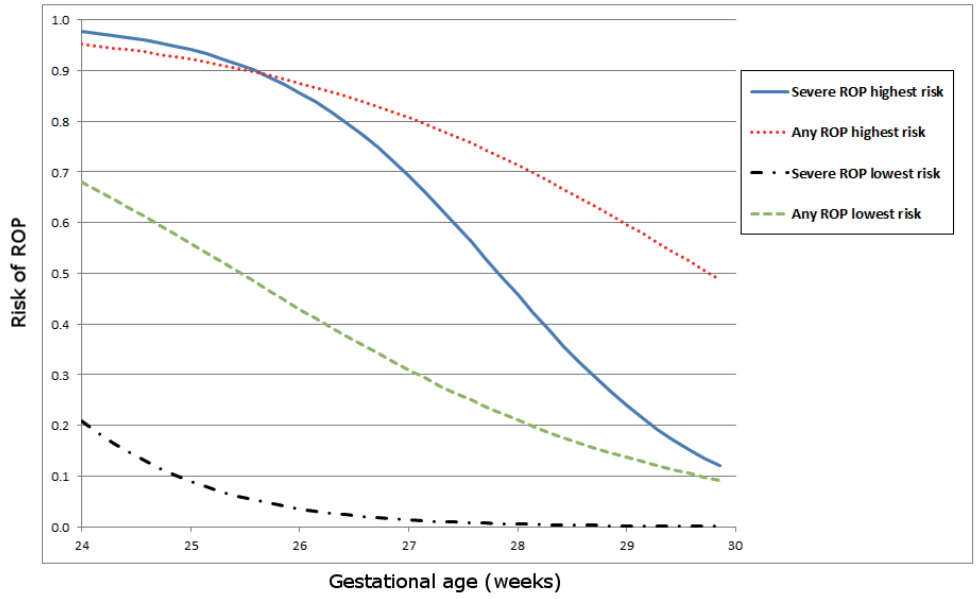

Figure 2. Risk of (severe) ROP versus GA in weeks. Highest risk for any ROP defined as: exposure to all risk factors in Table 3 and lowest risk for any ROP: not exposed to any risk factors in Table 3. Highest risk for severe ROP: exposed to all risk factors in Table 4 and lowest risk for severe ROP: not exposed to risk factors in Table 4. ROP, retinopathy of prematurity; GA, gestational age.

Table 3a. OR for any ROP, multivariable analysis, after adjusting for GA and SGA.

Risk factor	OR	95% CI	*p*-value
Higher GA (weeks)	0.59	0.54 – 0.66	<0.001
SGA	1.73	1.11 – 2.62	0.014
MV>7 days	2.13	1.35 – 3.37	0.001
Postnatal corticosteroids	2.57	1.44 – 4.66	0.002

Table 3b. OR for severe ROP, multivariable analysis, after adjusting for GA and SGA.

Risk factor	OR	95% CI	*p*-value
Higher GA (weeks)	0.37	0.27 – 0.50	<0.001
SGA	5.65	2.17 – 14.92	<0.001
Perforated NEC	7.55	2.29 – 24.48	<0.001
Postnatal corticosteroids	3.81	1.74 – 8.40	<0.001

Discussion

In this second nationwide inventory on ROP and its risk factors (NEDROP-2), a ROP incidence of 28.3% was found. The incidence of sROP was 4.4%. Risk factors found for overall ROP were GA, SGA, prolonged MV and treatment with postnatal corticosteroids. For sROP, risk factors were GA, SGA, NEC, and postnatal corticosteroids. Prolonged MV was also associated with sROP, but postnatal corticosteroids had higher odds and in our cohort all infants who received corticosteroids had prolonged ventilation.

Overall ROP incidence in the NEDROP-1 was 21.9%. Comparing the absolute ROP incidence of the current study to that of the NEDROP-1 study is difficult, as inclusion criteria for ROP screening were narrowed since 2013, which meant that infants with GA 30.0-32.0 weeks and/or with BW 1250-1500 gram without risk factors were no longer included, resulting in a lower denominator. Pediatricians reported 1287 eligible infants in NEDROP-2, compared to 1900 in NEDROP-1, a reduction of 32%, which concords with the estimated 29% reduction after narrowing our screening inclusion criteria. Another explanation for fewer reported infants may be the lower number of live births in 2017. The percentage of infants of the reported population that could be coupled and screened was almost the same for both studies: 933/1287 72.5% (NEDROP-2) and 1380/1900 72.6% (NEDROP-1). The higher incidence of ROP found in NEDROP-2 might be explained by more immature infants, fewer low-risk infants through narrowing of the inclusion criteria and a lower birth number.

Compared to the NEDROP-1, the incidence of sROP was higher (4.4% vs 2.1%, p<0.05), but also this difference should be interpreted with caution since the number of eligible infants differed and more immature infants were included. However, the incidence of sROP among all live births with GA<32.0 weeks registered in Perined was 41/1452 (2.8%) in 2017, 29/1602 (1.9%) in 2009, p=0.06. A limitation to our study includes that eight infants with sROP could not be coupled to the Perined database and were therefore excluded. If they would have enrolled, the increase between 2009 and 2017 would have reached statistical significance, as in 2009 only 1 patient with sROP could not be coupled (p=0.009). The results of another Dutch study, showing a doubling of treatments from 2013-2017 compared to 2010-2013, support this result (8). Similar increases in sROP have been reported in Sweden, Denmark and the UK (14-16).

Risk factors for ROP in NEDROP-2 were GA, SGA (<-2 s.d.), prolonged MV and treatment with postnatal corticosteroids. GA and prolonged MV were also found as risk factor in NEDROP-1. In this latter study the 95%-CI for postnatal corticosteroids bordered on 1, with a p-value of 0.08. An explanation for postnatal corticosteroids reaching statistical significance in NEDROP-2 could be that since the change in our national treatment policy in 2010 more infants with GA>24.0 weeks, frequently needing postnatal corticosteroids, survive. Compared to NEDROP-1, iNO and prolonged stay on the NICU were no longer present as risk factor and female gender was no longer protective. An explanation may be that both iNO and LOS are strongly associated with MV, as in the Netherlands iNO is almost only administered through MV and long-standing MV is only used in level III NICUs. In addition, LOS during the last decade may have been shortened by the expansion of level II+ neonatal stepdown-units. Further, in NEDROP-2 there were more female infants with ROP (31.9%) compared to male (25.6%). Also this may be the result of increased survival in extremely preterm female infants (17). Since analysis of risk factors for sROP was not possible in NEDROP-1 because of the small number of infants with sROP, a comparison of risk factors is not possible. Finally, in the present dataset, information about prenatal corticosteroids was not available and could not be analyzed.

Our present risk factors are consistent with other recent studies in high income countries. GA and BW are still the strongest known risk factors for (treatment requiring) ROP (18). Both factors are related to the extent of immaturity of neural and vascular retinal development at birth. The lower GA and BW, the more profound the loss of growth factors normally provided by the intrauterine environment, the longer the exposure to adverse postnatal events and as a consequence of these, the higher the retinal vulnerability to insult (1). Razak and Faden demonstrated that also smaller size for gestation was associated with increased odds of any ROP, sROP and treated ROP (19). The retina of SGA babies has already intrauterine been exposed to neuroendocrine and metabolic adaptations which may increase the development of ROP. SGA infants are often treated with supplemental oxygen, a risk factor for ROP, because of increased risk of respiratory distress syndrome, BPD and NEC. They also have

lower insulin-like growth factor-1 levels, causing an arrest in retinal vessel growth, resulting in phase 1 of ROP and they have an increased prevalence of Frizzled-4 gene variation, a gene associated with increased risk of ROP (19).

Prolonged MV is among the most frequently identified risk factors for ROP(20). In a Danish study blood transfusion and MV were the only new risk factors to predict treatment-demanding ROP in addition to GA, SGA, multiple birth and male sex (21). Prolonged MV is often associated with high percentages of supplemental oxygen and fluctuations in oxygen saturation levels.

The most recent Cochrane-study reported an increase in sROP after late systemic postnatal treatment with corticosteroids (>7 days), but no increase in blindness (23). In our cohort we found an increased risk for postnatal corticosteroids for any ROP as well as sROP. An explanation for this may be that in the Netherlands most infants receive late corticosteroid treatment, as early treatment is associated with gastrointestinal bleeding, perforation and cerebral palsy.

NEC was an additional risk factor for ROP in the predicting model of Gonski (24). The exact relationship between NEC and ROP is unclear. Animal studies showed that systemic inflammation affects retinal angiogenesis (18).

From our estimated risk model (figure 2) , it is clear that for Dutch infants with a GA<26.0 weeks with a high risk profile the risk to develop ROP or sROP is almost equal. This means that if such an infant develops ROP, the chance is extremely high it will also develop severe, treatment requiring ROP. This may be explained by the fact that many of these infants have a complicated clinical course. Our risk model may be important for future intervention studies and can also be a help to explain the risk of ROP to parents. Limitations of our study are loss of patients after merging, risk of bias as a result of not being able to completely match the databases and restricted presence of risk factors present in the Perined database, especially the known influence of oxygen fluctuations on the development of ROP we were not able to measure.

Since 2013, the Dutch screening guideline for ROP has been adjusted, based on the results of NEDROP-1. The most important aim of screening is that infants with sROP, needing treatment, are timely detected. The present study, which indicates GA, SGA (P<-2 s.d.), NEC and postnatal corticosteroids as risk factors for sROP, with the available data did not indicate new factors apart from those already included in our present guideline. Severe ROP in NEDROP-2 was only found in infants with GA<30.0 weeks, as to 5 infants with GA 30.0-32.0 weeks in NEDROP-1. Whether our guideline can be adjusted in the future needs more

evaluation. To answer this, a study on cost-effectiveness of screening in the Netherlands is currently being conducted.

In conclusion, severe ROP was diagnosed more frequently since the last inventory on ROP. Risk factors for severe ROP were GA, SGA, NEC, and postnatal corticosteroids. All these factors are included in our screening guideline, emphasizing the benefits of our risk based guide line.

Acknowledgements

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Statement of Ethics

This study was initiated and coordinated by the Leiden University Medical Center. Approval was obtained by the local medical ethical committee. In the Netherlands, neonatal data are recorded in a national perinatal register called Perined. For this registry parents have to give their approval. As ROP is part of Perined, informed consent for the present study was waivered.

Conflicts of Interest Statement

The authors have no conflits of interest to declare.

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Author Contributions

Research desgin was done by K.T., N.S. and J.T. All authors provided data for analysis. Acquisition and analysis of data was performed by K.T. and S.K. The authors F.G. and K.T. were responsible for statistical analysis. The article was written by K.T., J.T. F.G and N.S. and was critically revised and approved for publication by P.A., P.D., F.D., J.H., S.K., R.K., E.W., J.L., C.M., F.S., K.S., M.T. and R.W.

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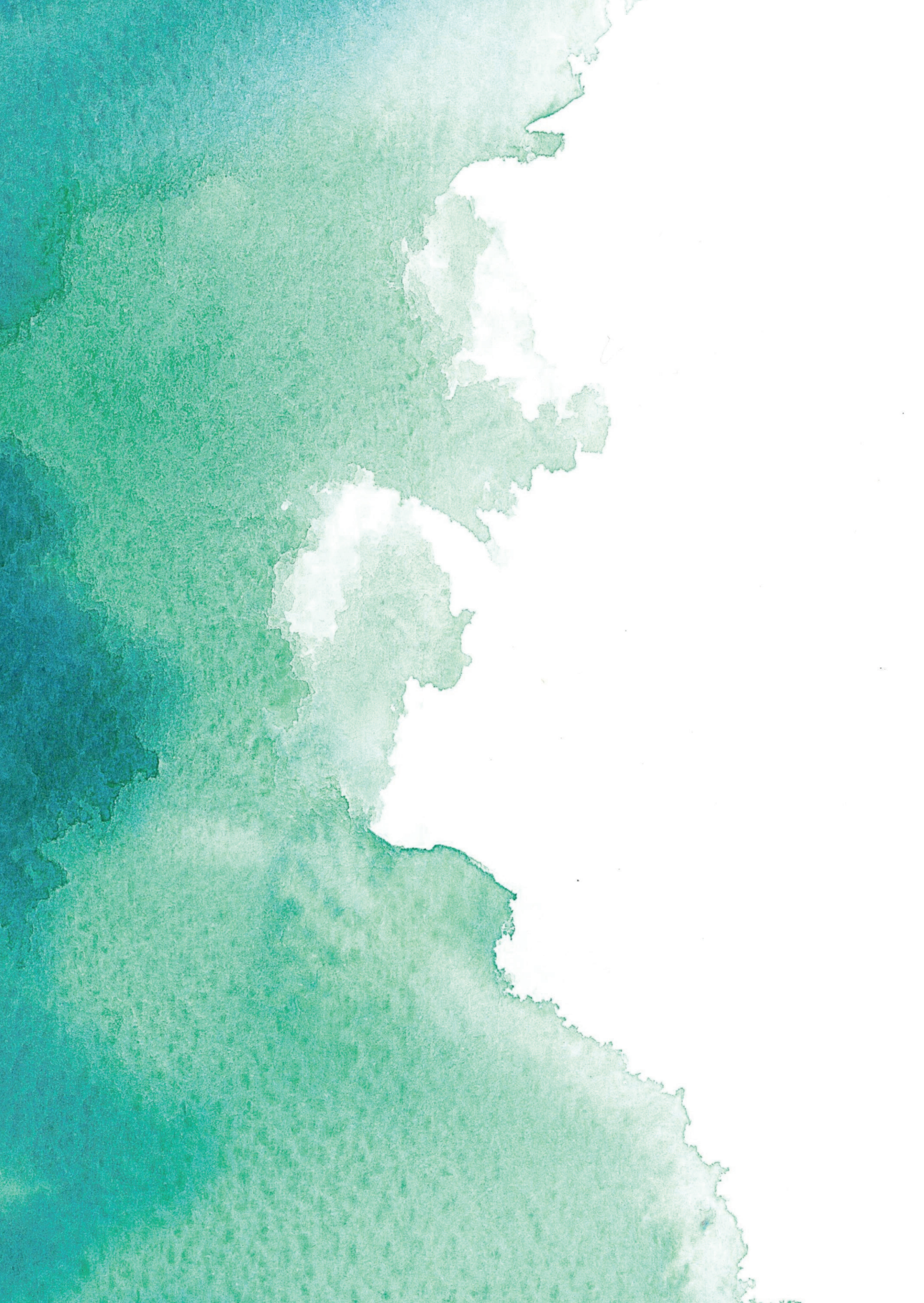

Chapter 6

Cost reduction in screening for Retinopathy of Prematurity in the Netherlands by comparing different screening strategies

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Abstract

Purpose

Evaluate possibilities to reduce the number of infants screened for retinopathy of prematurity (ROP) and investigate costs and number of infants detected of current and alternative screening strategies in the Netherlands.

Methods

Prospective population-based study including clinical data from all infants born in 2017 and referred for ROP-screening (NEDROP-2 study). Cost and effects of screening strategies were evaluated that differed on the criteria gestational age (GA), birth weight (BW) and presence of one or more specific risk factor(s) (RF): mechanical ventilation, sepsis, necrotizing enterocolitis, postnatal corticoids and/or hypotension treated with inotropic agents. RF obtained from the Dutch perinatal registry (Perined).

Results

Of the possible efficient strategies, the annual costs varied from €137,966 (inclusion of BW<700, 63 infants eligible for screening, detection of 17/39 treated ROP) to €492,689 (GA<30 weeks *and* BW<1250 grams, together with infants with GA 30-32 and BW 1250-1500 grams with presence of one more RF, 744 infants eligible for screening, all treated infants detected). Total annual costs of the current Dutch guideline that detects all infants that need treatment for ROP amount to €552,143).

Conclusion

The current Dutch ROP guideline can be improved by implementing new screening inclusion criteria. The most effective strategy detecting all severe and treated infants, reduces the number of screened infants by 24% compared to the current guideline and the overall annual costs by €59,454.

Introduction

Retinopathy of prematurity (ROP) remains the most important cause of visual impairment and blindness in premature infants (1). The majority of ROP cases are mild and regress spontaneously, however timely detection and treatment of a small number of infants with progressive, sight threatening ROP is pivotal to prevent severe and permanent vision loss.

In case of severe ROP and when treatment is required, the gold standard is laser photocoagulation of the peripheral retina (2). Alternatively, intravitreal anti-vascular endothelial growth factor (VEGF) can be considered and its use is increasing worldwide. However, the current Dutch guideline (2013) advises using anti-VEGF in ROP stage 3 in zone I and as last resort treatment only (3). Despite treatment, some infants still progress to retinal detachment, in which the corner stone of management is pars plana vitrectomy (PPV).

Developing a universal ROP screening and treatment guideline is futile, as the risk of progression depends on the overall child's health and strongly correlates with the overall neonatal health and, therefore (regional) neonatal care (4). Therefore, it is crucial that screening and treatment guidelines are based on circumstances of influence per individual country. Most screening programs use gestational age and/or birth weight criteria for inclusion in the screening program (5-8). In addition, some of them include infants with an unstable course (5, 8). Screening programs would benefit from a better defined risk based screening profile to minimise the chance for unwarranted in- or exclusion by solely relying on expert opinion.

In the Netherlands, the first national ROP inventory was the NEDROP (2009)(9). The study revealed, that many babies (1364/1688, 78%) who never developed ROP were exposed to the burden of screening (9). Upon this finding, updated and risk-based screening criteria were included in the new ROP guideline (2013), predictively reducing the number of screened infants by approximately one third, while warranting detection of all infants with severe ROP (10-12).

Yet, since the first inventory, in the Netherlands essential changes in neonatal care were adopted that increase the risk for (severe) ROP. In 2010, the gestational age (GA) in which babies receive active neonatal treatment was lowered from 25 to 24 weeks and in 2014 higher oxygen saturation targets were implemented during the first weeks of life (13). Together with the new screening criteria, these changes called for a second national ROP inventory, resulting in the NEDROP 2, in which incidence, screening logistics, treatment and risk factors of ROP were investigated for the year 2017.

Thus, following increased survival of the most immature infants and the introduction of unfavorable neonatal factors, an increase in infants developing (severe) ROP is expected. Moreover, considering that ROP screening is uncomfortable (14), time consuming and costly, the effectiveness of a screening protocol is increasingly important.

The aim of this study was to analyze if the number of infants requiring ROP screening could be reduced once more. Therefore, the effects and costs were evaluated of the current and other screening strategies.

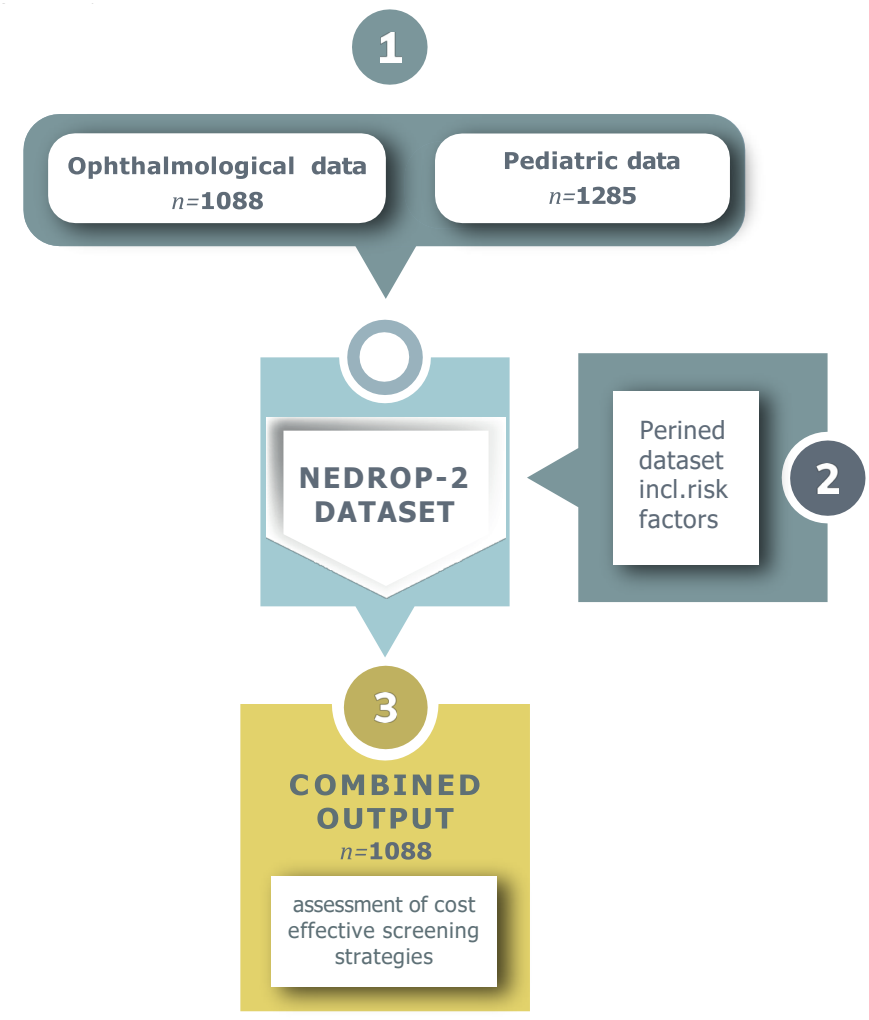


Figure 1. Population flow chart

Methods

This study was initiated and coordinated by the Leiden University Medical Center. Data collection was anonymous, therefore approval of the medical ethical committee was not necessary. For neonatal risk factors a separate existing national register was used, called Perined, containing medical data of 97% of all neonates born in the Netherlands are reported by neonatologists and pediatricians (15). Data from Perined were only recorded after parental approval.

Paediatricians and neonatologists of all hospitals involved in ROP screening in the Netherlands, prospectively reported infants they considered eligible for ROP screening who were born between January 1st and December 31st of the year 2017. They used a coded dataset consisting of date of birth, four digits of the ZIP code, GA, BW and the index number in case of multiple birth (1/2, 2/2, 1/3, etc.). The latest guideline, introduced in 2013, changed inclusion criteria for screening from gestational age (GA) <32 weeks and/ or birth weight (BW) <1500 g to GA<30 weeks and/or birth weight (BW)<1250 grams, and infants with GA 30-32 weeks and/or BW 1250-1500 grams with presence of at least one of the following risk factors: mechanical ventilation, sepsis (defined as clinically ill with positive blood cultures), postnatally administered glucocorticoids, perforated necrotizing enterocolitis, and hypotension treated with inotropic agents (11).

Ophthalmologists provided a separate report on ophthalmological data by use of the same code, together with findings from the conducted ROP examinations: consisting of presence of plus disease, maximum zone and ROP stage per eye, reason for discontinuation of screening and, if applicable modality of treatment. ROP was classified according to the revised International Classification of Retinopathy of Prematurity ((16). For the purpose of comparison with NEDROP 1 study, ROP was categorized into mild (stage 1-2) and severe (stage ≥3) ROP.

Data from the NEDROP 2 database and Perined were merged through the use of the earlier mentioned code (population flow chart fig. 1). For infants for which this merging failed (*n*=141), information on the presence of risk factors was obtained using multiple imputation by predictive mean matching (17) using information on GA, BW, treatment, presence of ROP and when present, maximum ROP stage. In a sensitivity analysis the effect of the imputation was studied by repeating the analyses using the non-imputed data.

Based on these data, various screening strategies were evaluated, using (a combination of) the following inclusion criteria: 1. GA, 2. BW, 3. Combined GA-BW and 4. Combined GA-BW and presence of one or more risk factor (appendix 1). For each of these screening strategies the number of infants eligible for screening, the number of infants per ROP category, and the number of infants treated were assessed.

Subsequently, each strategy is compared to the other strategies that resulted in the same number of infants detected. The screening strategy that screened the lowest number of infants to detect this number of infants is a so-called efficient strategy.

Costs

For all efficient strategies, costs were assessed from a healthcare perspective by including costs of screening and treatment during the first year after birth. Due to this short term time horizon, no discounting was applied. Costs are expressed in 2021 Euros. Cost prices of earlier years have been converted into 2021 price levels by use of the general Dutch consumer price index (18) To obtain the screening costs, the number of examinations per infant were multiplied by the costs per screening. The mean number of screening examinations per infant per ROP category (no, mild and severe ROP), were obtained from the NEDROP 2 data and were 2.3, 4.9 and 10.2 respectively. Costs for screening consist of personnel costs of a nurse and an ophthalmologist and material costs of the eyelid speculum and eye drops amounting to €97 per screening (table 1). Costs of bilateral ROP treatment involve transfer to the treatment center by ambulance with obligatory escort of a resident or neonatologist (€1449) (19) and laser treatment (€3819) for 97% of the patients or vitrectomy (€7245) for the remaining patients (table 1). For unilateral treatment it was assumed that two-thirds of the surgery time of bilateral treatment with associated cost for surgery room and personnel, and the same material and equipment costs as for bilateral treatment was needed.

Effects

The effects of screening are defined as improved visual acuity as a result of early laser treatment compared to no and late treatment (2), according to the Cryotherapy for ROP (CRYO-ROP) and Early Treatment for ROP (ETROP) studies. The CRYO-ROP study compared cryotherapy versus no treatment, the ETROP study compared early laser treatment with late treatment with cryotherapy. This resulted in improved vision of 17.7% and 7.7% respectively, using the adjusted indirect comparison method. Combined, an estimated improved vision of 25.4% was used to analyze outcomes of treatment versus no treatment.

Cost-effectiveness

Costs and effects were combined to assess the cost-effectiveness, expressed as the average costs per infant with improved vision of a screening strategy compared to a situation without screening and treatment. Subsequently, dominant strategies were identified, i.e. efficient strategies for which no (combination of) other strategies exist that result in a higher number of infants with improved vision for lower costs. For these strategies the marginal costs per additional infant with improved vision were calculated, which indicates the amount that have to be paid to find an additional infant compared to the nearest dominant screening strategy that finds a lower number of infants.

Table 1. Costs of retinopathy of prematurity screening and treatment, 2021 euros

Cost item	Amount	Cost price (2021 €)[1]	Cost	Sources
Cost of screening				
Nurse	40 min	€35/hour	€24	Personal communication; Kanters et al. 2017
Ophthalmologist	30 min	€126/hour	€63	Personal communication; Kanters et al. 2017
Eyelid speculum	1	€9.92	€9.92	Tariff of manufacturer
Eyedrops		€0.58	€0.58	Price list national pharmacotherapeutic manual
Total			**€97**	
Cost of laser treatment				
Surgical assistants	2*2 hours	€41/hour	€162	Personal communication; Salary table surgical assistant[2]
Anesthesia assistant	2 hours	€41/hour	€81	Personal communication; Salary table surgical assistant[2]
Anesthetist	2 hours	€126/hour	€252	Personal communication; Kanters et al. 2017
Ophthalmologist	2 hours	€126/hour	€252	Personal communication; Kanters et al. 2017
Neonatologist	0.3 hour	€126/hour	€38	Personal communication; Kanters et al. 2017
Laser equipment[3]	1	€34	€34	Personal communication
Operating room	2 hours	€1500	€3000	Personal communication
Total			**€3819**	
Cost of vitrectomy treatment				
Surgical assistants	2*3.5 hours	€41/hour	€284	Personal communication; Salary table surgical assistant (ref)
Anesthesia assistant	3.5 hours	€41/hour	€142	Personal communication; Salary table surgical assistant (ref)
Anesthetist	3.5 hours	€126/hour	€441	Personal communication; Kanters et al. 2017
Ophthalmologist	3.5 hours	€126/hour	€441	Personal communication; Kanters et al. 2017
Neonatologist	0.3 hour	€126/hour	€38	Personal communication; Kanters et al. 2017
Equipment[3] and disposables	1	€650	€650	Personal communication
Operating room	3.5 hours	€1500	€5250	Personal communication
Total			**€7245**	
Transfer ambulance				
Ambulance (back and forth)	2	€564	€1128	Kanters et al. 2017
Escort resident or neonatologist	2 hours single ride	€80/hour[4]	€319	Kanters et al. 2017
Total			**€1447**	

[1]Cost prices of earlier years have been converted into 2021 price levels by use of the general Dutch consumer price index www.opendata.cbs.nl/statline . Accessed: January 19, 2021

[2] Salarisschalen, premies & vergoedingen, NVZ Cao Ziekenhuizen
https://cao-ziekenhuizen.nl/salarisschalen-premies-vergoedingen

[3] Calculated on the basis of initial purchasing price, yearly use and depreciation, and maintenance and interest costs

[4] Average cost per hour of resident (€34) and (€126), ref Kanters et al. 2017

Results

The NEDROP database included 1285 infants, of which 120 patients died before first screening. Screening was performed in 1088 babies, ROP was found in 305 babies: 259 mild (stage 1-2) and 47 severe (stage≥3). Treatment (all retinal laser photocoagulation) was performed in 39 infants. Initial treatment was bilateral for all infants, by means of laser treatment for 97% of the infants and vitrectomy for the others. Furthermore, in 15% of the children retreatment was necessary, of which 50% with laser treatment and 25% bilateral.

In table 2, the number of infants eligible for screening and infants treated for ROP are presented per screening strategy. The most efficient strategy detecting all infants treated for ROP, includes infants with GA<30 weeks and BW<1250 g *and* GA 30-32 weeks and/or BW 1250-1500 g with one or more risk factors. This would require screening of 744 children, representing a 23.8% reduction in comparison to the current screening guideline. A total of 2662 screening examinations would be performed if the strategy would apply to the NEDROP 2 population, representing a 18.7% reduction compared to the 3274 screenings that need to be carried out according to the current guideline.

In table 3 and fig. 2 the cost-effectiveness is shown of efficient strategies in ascending number of treated infants. For comparison also the current Dutch strategy is shown.

The total annual costs (screening + treatment) of the most efficient strategies vary from €137,966 (strategy 9: BW <700g) detecting 17/39 of the infants treated for ROP to €492,689 (strategy 50: GA<30 weeks and BW<1250 grams or GA 30-32 weeks and/or BW 1250-1500 grams with at least one risk factor) detecting all 39 infants treated for ROP. Only the latter scenario detects all infants with treatment requiring ROP, while reducing annual costs by €59,454 compared to the current guideline. The other strategies are more economically beneficial, however missing children who require treatment would need to be accepted.

Detecting all 39 infants needing treatment would lead to an overall improvement of vision corresponding to an improvement of 9.9 children from no sight (0%) to full sight (100%). The Average Cost per Person with Improved Vision (AC/PIV) ranges from €31,951 (strategy 9: BW <700g) to €49,736 (again strategy 50). The Marginal Costs per additional PIV (MC/APIV), ranged from €32,173 (strategy 9) to €250,028 (strategy 50).

The sensitivity analysis using non-imputed data resulted in the same selection of efficient strategies and comparable cost-effectiveness results (appendix 2).

Table 2. Number of infants eligible for screening and treated for ROP while using different screening inclusion criteria . The most efficient strategies for the different numbers of infants treated for ROP found are shaded. BW, birth weight; GA, gestational age; ROP, retinopathy of prematurity.

	Criteria	Eligible	Treated for ROP
	GA, weeks		
1.	<26	104	21
2.	<27	208	30
3.	<28	348	35
4.	<29	535	38
5.	<30	742	38
6.	<31	885	39
7.	<32	1025	39
8.	<33	1066	39
9.			
	BW, g		
10.	< 700	63	17
11.	< 1000	346	33
12.	< 1100	452	34
13.	< 1200	602	37
14.	< 1250	682	37
15.	< 1300	740	37
16.	< 1500	923	39
17.	< 1600	984	39
18.	< 1700	1022	39
19.	< 1800	1047	39
20.	< 1900	1069	39
21.	< 2000	1074	39
	Combined, GA and BW		
22.	< 29/<1200	428	37
23.	< 29/<1250	452	37
24.	< 29/<1500	528	38
25.	< 30/<1250	545	37
26.	< 30/<1500	707	38
27.	< 31/<1200	542	37
28.	< 31/<1250	601	37
29.	< 31/<1500	805	39
30.	< 32/<1200	578	37
31.	< 32/<1250	643	37
32.	< 32/<1500	871	39

Table 2. Continued

	Combined, GA and/or BW		
33.	< 29/<1200	709	38
34.	< 29/<1250	765	38
35.	< 29/<1500	930	39
36.	< 30/<1200	847	38
37.	< 30/<1250	879	38
38.	< 30/<1500	958	39
39.	< 31/<1200	945	39
40.	< 31/<1250	966	39
41.	< 31/<1500	1003	39
42.	< 32/<1200	1049	39
43.	< 32/<1250	1064	39
44.	< 32/<1500	1077	39
	Combined GA-BW-risk factor*		
			Treated for ROP
45.	<30 weeks and <1250 g and at least one risk factor	402	36
46.	<32weeks and <1500 g and at least one risk factor	564	38
	Combined GA-BW-risk factor		
			Treated for ROP
47.	<30 weeks and/or <1250 g and at least one risk factor	566	37
48.	<32 weeks and/or <1500 g and at least one risk factor	664	38
49.			
50.	< 30 weeks and <1250 g & 30-32 weeks and/or 1250-1500 g and at least one risk factor	744	39
51.	NL < 30 weeks and/or <1250 g & 30-32 weeks and/or 1250-1500 g and at least one risk factor	977	39
52.	escape < 32 weeks and/or <1500 g	1077	39
53.	Lower limit < 30 weeks and/or < 1250 g	879	38

*Risk factors: mechanical ventilation, sepsis, perforated necrotizing enterocolitis, postnatally administered glucocorticoids and hypotension treated with inotropic agents

Table 3. Cost-effectiveness of efficient screening strategies (shaded strategies table 1) and current strategy, €2021

Strategy	BW<700	GA<26	GA<27	BW<1000	BW<1100	GA<28	GA<30 and BW<1250 and1 RF	GA<29 or BW<1200	GA<29 or BW<1500	GA<30 and BW<1250 or 30-32 and/or 1250-1500 + 1 RF	Current strategy
Strategy number (table 1)	9	1	2	10	11	3	44	32	34	48	49
Infants to be treated for ROP detected	17	21	30	33	34	35	36	37	38	39	39
Number of screenings	370	584	1031	1470	1810	1503	1639	1770	2070	2662	3274
Cost of screening	35,901	56,719	100,145	142,794	175,761	146,012	159,189	171,932	201,037	258,541	317,995
Cost of treatment	91,267	112,742	161,060	177,165	182,534	187,903	193,271	198,640	204,009	209,377	209,377
Cost of retreatment	10,798	13,338	19,055	20,960	21,595	22,231	22,866	23,501	24,136	24,771	24,771
Total costs (€)	137,966	182,799	280,259	340,920	379,890	356,146	375,326	394,073	429,182	492,689*	552,143
No of PIV	4.3	5.3	7.6	8.4	8.6	8.9	9.1	9.4	9.7	9.9	9.9
AC/PIV	31,951	34,270	36,779	40,673	43,989	40,061	41,046	41,932	44,466	49,736	55,738
MC/APIV	31,951	dominated	42,633	dominated	dominated	59,753	dominated	73,806	138,225	250,028	dominated

(A)PIV: additional persons with improved vision

AC, average costs; BW, birth weight; GA, gestational age; MC, marginal costs; PIV, person with improved vision; RF, risk factor; ROP, retinopathy of prematurity

Example of calculation of cost calculation for screening strategy **GA<30 and BW<1250 or 30-32 and/or 1250-1500 + 1 RF:*

Number of screenings:** 47 [number of infants detected with severe ROP in this strategy] * 10.2 [mean number of screening examinations per infant with severe ROP] + 225 [number of infants detected with mild ROP in this strategy] * 4.9 [mean number of screening examinations per infant with mild ROP] + 472 [number of infants without ROP] * 2.3 [mean number of screening examinations per infant without ROP in this strategy] = **2662

Cost of screening :** 2662 [number of screenings] * € 97 [cost of screening] = **€ 258,541

Cost of treatment**: 39 [infants to be treated for ROP detected] * (€ 1447 [cost of transfer ambulance]+0.97 [percentage laser] * € 3819 +0.03 [percentage vitrectomy] * € 7245 [cost vitrectomy]) = **€ 209,377

Cost of retreatment**: 39 [infants to be treated for ROP detected]*0.15 [percentage of infants with retreatment]*(0.5 [percentage vitrectomy]*(0.25 [percentage of infants with bilateral treatment at retreatment] * € 7245 [cost vitrectomy bilateral] + 0.75 [percentage of infants with unilateral treatment at retreatment] * € 5047 [cost vitrectomy unilateral]) + 0.5 [percentage of retreatments with laser]*(0.25 [percentage of infants with bilateral treatment at retreatment] * € 3819 [cost laser bilateral] + 0.75 [percentage of infants with unilateral treatment at retreatment] * € 2557 [cost laser unilateral])) = **€ 24,771

Total cost =** € 258,541 [cost of screening] + € 209,377 [cost of treatment] + € 24,771 [cost of retreatment] = **€ 492,689

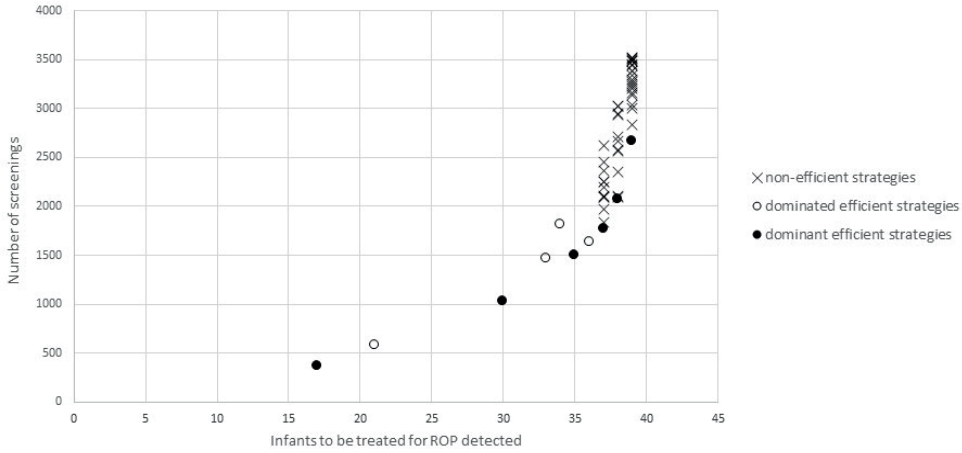
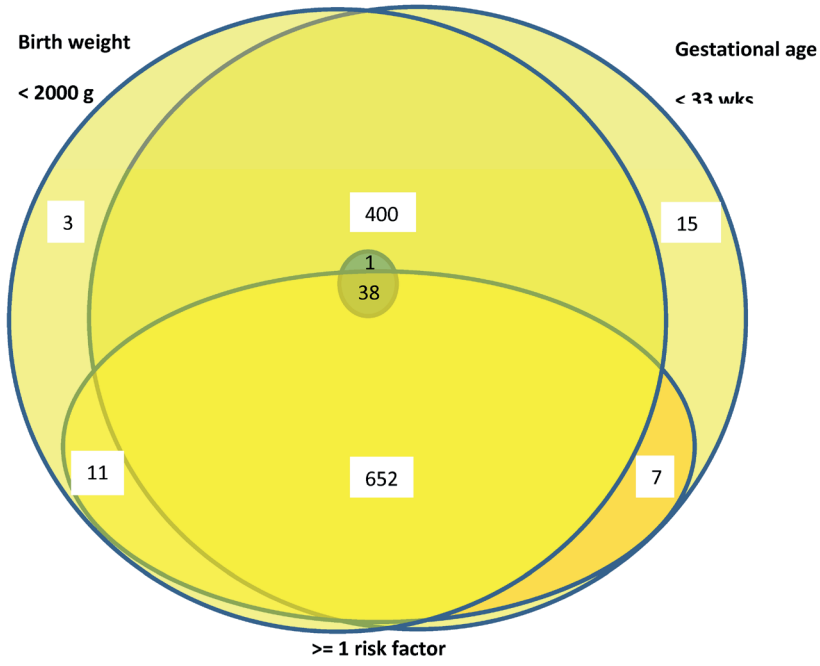


Figure 2. Overview of cost-effective strategies (see table 3)

Appendix 1.



In this diagram the numbers of infants considered eligible for screening with a birth weight < 2000 g, gestational age < 33 weeks, and/or more than one risk factor are presented. In the middle, these numbers are shown for the 39 infants treated for ROP.

Appendix 2. Cost-effectiveness of efficient screening strategies and current strategy based on non-imputed data, 2021 euros

Strategy	BW<700	GA<26	GA<27	BW<1000	BW<1100	GA<28	GA<30 and BW<1250 and1 RF	GA<29 or BW<1200	GA<29 or BW<1500	GA<30 and BW<1250 or 30-32 and/or 1250-1500 + 1 RF	Current strategy
Infants to be treated for ROP detected	16	18	25	28	29	30	31	32	33	34	34
Number of screenings	328	498	901	1288	1592	1345	1442	1560	1838	2348	2880
Total costs (€)	128,805	157,421	239,014	294,820	330,387	312,419	327,916	345,408	378,536	434,087	485,755
No of PIV	4.1	4.6	6.4	7.1	7.4	7.6	7.9	8.1	8.4	8.6	8.6
AC/PIV	31,694	34,431	37,640	41,454	44,853	41,000	41,645	42,496	45,161	50,265	56,248
MC/APIV	31,694	dominated	48,210	dominated	dominated	57,800	dominated	64,939	130,424	218,703	dominated

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

Discussion

In the Netherlands, the retinopathy of prematurity (ROP) guideline can be safely adjusted by lowering the number of infants requiring uncomfortable and time-consuming examinations by 23.8%, without missing treatment requiring ROP. The most efficient strategy detecting all patients with treatment requiring ROP, based on analyses of prospective annual national data, is the one including infants born with GA<30 weeks *and* BW<1250 grams, and infants with 30-32 weeks and BW 1250-1500 grams with at least one defined risk factor (mechanical ventilation, sepsis, necrotizing enterocolitis, postnatal glucocorticoids and treatment with inotropic agents). In the second NEDROP study (NEDROP-2, 2017), no new risk factors were found to be significantly correlated with development of (severe) ROP in the Dutch population (Trzcionkowska et. al., Risk factors for retinopathy of prematurity in the Netherlands: a comparison of two cohorts, Neonatology, 2021). In 2009, the latter strategy also demonstrated to be the most efficient strategy to detect all patients with treatment requiring ROP. However, its implementation was approached with caution as data were based on only one year of ROP data (10), therefore the safer but slightly less efficient GA *and/or* BW criterion was chosen as inclusion criteria. In the present inventory all infants who required treatment were again identified by use of the new strategy which thus, can be considered safe for implementation in the upcoming new guideline.

In developed countries, severe ROP in infants born with GA over 30 weeks is uncommon (20), therefore subjecting more mature infants to stress evoking ROP examinations becomes debatable. However, restricting the criteria is not always possible. It is essential to adjust selection criteria in each country to the national circumstances and screening populations. Particularly in middle income countries, a combination of limited access to neonatal resources and possibly lack of ROP awareness or ophthalmological expertise play a crucial role (21, 22). Therefore, the risk of misdiagnosing patients who require treatment may be too high if our inclusion criteria would be adopted directly.

Nevertheless, not only in the Netherlands investigations are carried out aiming to increase efficiency of ROP screening. In Sweden it was revealed, that in the past decade no infants with GA ≥30.0 weeks were treated for ROP and only ten babies developed ROP stage ≥3, which in all ten regressed spontaneously (5). Therefore, a modification of the inclusion criteria has been proposed from screening babies with GA <31.0 weeks (and an additional selection of more mature infants who are referred by neonatologists based on individual risk assessment) to GA <30.0 weeks, along with individual assessment of high-risk infants. If these criteria would apply in the Netherlands, based on GA solely, a total of 742 infants would have to be screened, two infants less compared to the most effective screening in the present study. However, in our cohort one infant with severe and treatment requiring ROP would have been missed.

If the US guideline would be used in our population (GA<31weeks or BW<1500 g) (8), all infants with severe and treated ROP would have been detected, but at least 60 more infants would undergo screening, resulting in unnecessary discomfort and higher costs. Use of the current UK guideline (GA<32 weeks and/or BW<1501 g) (7) would also provide adequate detection, but would also unnecessarily increase the size of the group to be screened.

The decision whether to accept missing children with severe ROP is on the one hand ethical and on the other hand economical. We have to determine which costs per additional infant with improved vision are acceptable for society. For the efficient treatment strategies, these marginal costs range from €31,951 to €250,028 per additional infant with improved vision. However, we only have an indication of the willingness of the Dutch society to pay for a quality adjusted life year (QALY). In the Netherlands, the willingness to pay for a QALY varies from €20,000 to €80,000 depending on the burden of disease. The most likely threshold for vision loss is €20,000 per QALY according to the iMTA Disease Burden Calculator (23, 24). Therefore, we have to translate improved vision obtained by screening and treatment into QALYs. Assuming a mean visual acuity of 0.20 in non-treated eyes and 0.48 in treated eyes (Dunbar et al. 2009), a yearly gain in utility of 0.10 can be obtained according to the formula of Sharma et al (25). For an average life expectancy around 80 years (Statistics Netherlands 2013) 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, results in incremental cost-effectiveness ratios of €9,809 to €76,754 per QALY for the efficient strategies. For the screening strategy detecting all severe and treatment requiring ROP, therefore, also savings during lifetime due to treatment have to be made to be acceptable for the Dutch situation. These societal cost savings may be obtained by more self-reliance, less or no need of support programs and lower educational costs as these infants with improved vision do not need special education, savings in home modifications and devices and costs for carers.

Strengths & Limitations

This is the second study based on annual national data to study the effectiveness of ROP screening in the Netherlands. The main strength is its repeatability, which allowed consecutive demonstration of safety and benefits of significant reduction in screening. Limitations include the relative short term nature of benefit calculations. We made a rough estimation of longer term effects and costs, but future studies should elaborate on this. Implementation of our results in other countries could be limited due to varying health care costs (i.e. personnel, materials, procedures, etc.), life expectancy and epidemiology of ROP. Moreover the relatively small annual birth number in the Netherlands, increases the importance of centralization of ROP treatment. Therefore perhaps in other countries, transfer to another hospital for treatment might not be necessary. Our calculations and results can be used as framework, but should not be taken on without guarded adjustments.

In conclusion, two consecutive national inventories on ROP (NEDROP 1 (2009) and NEDROP 2 (2017)) both gave rise to the same preferred screening strategy. The Dutch national guideline for screening will be adjusted accordingly, resulting in fewer infants being exposed to screening examinations. This will reduce healthcare costs further by about 60,000 euro per year. Marginal costs for detecting all these infants might be acceptable for society when QALY gain and savings for society as a result of improved vision are incorporated in the decision.

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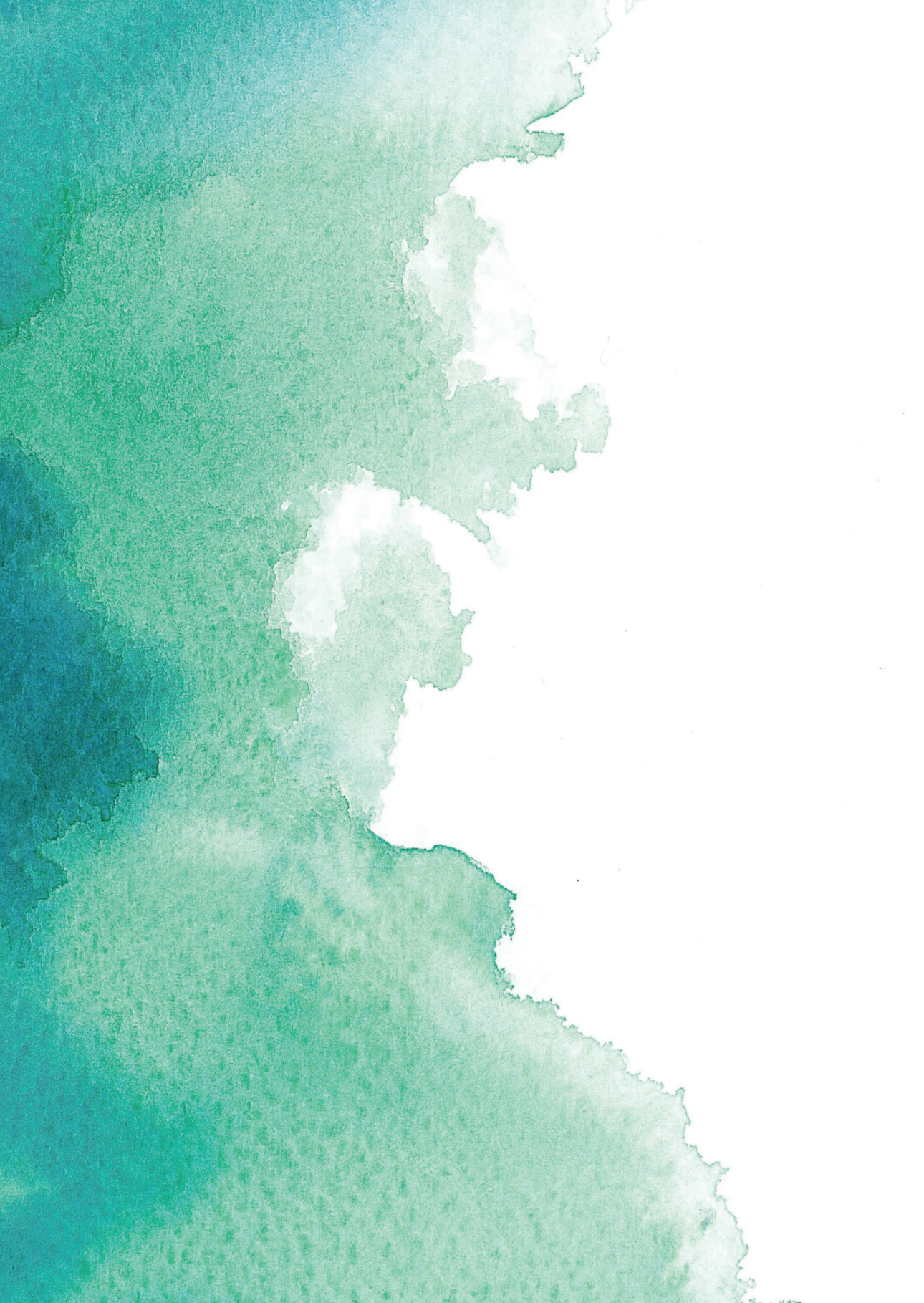

Chapter 7

Visual impairment due to retinopathy of prematurity and concomitant disabilities in the Netherlands

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Abstract

Aim

Determine incidence of visual impairment due to retinopathy of prematurity (ROP) and concomitant disabilities between 2009-2018 in the Netherlands and compare data to four former similar studies. Secondly, monitor if infants were missed for ROP-screening since the adoption of stricter, risk factor guided criteria (2013)

Methods

Retrospective inventory on anonymous data of infants diagnosed with ROP from Dutch visual impairment-institutes. Data including: best corrected visual acuity, ROP-treatment and concomitant disabilities: bronchopulmonary dysplasia, behavioural abnormalities, epilepsy, hearing deficit, developmental delay, cerebral palsy and cerebral visual impairment. During the study period, lower age limit for neonatal life support (2010) and higher oxygen saturation targets (2014) were implemented.

Results

Records of 53 infants were analysed. Visual impairment incidence due to ROP was 2.02 per 100.000 live births (2000-2009: 1.84, p=0.643). Compared to earlier periods (1975-2000), a significant decrease was observed. The incidence of concomitant disabilities remained stable. Mean gestational age (GA) continued to decrease to 26.6±1.9 weeks (2000-2009: 27.4±2.0 weeks, p=0.047). All patients met the screening inclusion criteria.

Conclusion

The incidence of visual impairment due to ROP and concomitant disabilities between 2009-2018 has not increased, despite lower GA and higher oxygen saturation targets. None of the infants were missed for ROP screening following introduction of more restricted screening inclusion criteria.

Introduction

Retinopathy of prematurity (ROP) continues to be a leading cause of preventable blindness in premature infants(1). ROP rates vary among countries, as they are strongly dependent on both neonatal and ophthalmological care. Currently, the highest incidence is seen in rapidly developing economies, mainly due to improvements in neonatal care in combination with limited awareness of pathophysiology and consequences of ROP and ophthalmological resources(2). But also in high income countries, including the Netherlands, the number of infants developing severe ROP (sROP) is increasing as more infants at risk survive(3-7).

From 1975 onwards, four Dutch periods were carried out to evaluate the incidence of visual impairment due to ROP and incidence of accompanying disorders(8-10). Each study demonstrated a decrease in gestational age (GA) and birth weight (BW) of the affected patients compared to the previous period. Regarding the incidence of visual impairment, the first two inventories (1: 1975-1987 and 2: 1985-1994) showed an increase, however from 1994 onwards (3: 1994-2000 and 4: 2000-2009), a gradual but significant decrease was observed. This decrease in visual impairment was however not accompanied by an equal decline in accompanying disabilities. Period 4 revealed, that two-thirds of the children with visual impairment due to ROP were multiply disabled – defined as visual impairment with presence of one or more concomitant disabilities – illustrating the high vulnerability of this population.

During the present study period (2009-2018) several changes were implemented in neonatal care in the Netherlands that likely increased the risk for sROP. Firstly, GA for active neonatal treatment was lowered from 25.0 to 24.0 weeks (2010), which resulted in more extremely premature infants surviving the neonatal period(4). Second, following an interim meta-analysis of the NeOProM group of studies (2014)(11), higher oxygen saturation targets were accepted in most Dutch neonatal intensive care units (NICUs) because they warrant better survival. In 2013 a new screening and treatment guideline was implemented following a national inventory on ROP in the Netherlands (NEDROP, 2009)(12, 13), with narrowed risk factor guided screening inclusion criteria that focus on infants with the highest risk of ROP (14, 15).Safety monitoring of the guideline has not taken place until now. Finally, the Early Treatment for ROP (ETROP) criteria were emphasized in the guideline, possibly leading to treatment decisions at earlier stages (more infants requiring treatment) and therefore, improved treatment outcome(16).

All these policy changes are expected to influence the incidence and outcome of (severe) ROP. Thus, it is pivotal to periodically monitor potential sequelae and if necessary, adjust current policies. Together with previous periods, the present and fifth inventory on visual impairment due to ROP and concomitant disabilities provides insight into over four decades

of ROP sequelae in the Netherlands. Secondly, the purpose is to verify the safety of the 2013 ROP guideline, by determining if infants who were registered in the Dutch institutes for the visually impaired and blind, were missed for screening as they did not fit the new, more restricted inclusion criteria (table 1).

Table 1. Inclusion criteria for ROP screening according to the previous and present Dutch guideline. In 2013 gestational (GA) and birth weight (BW) were lowered and risk factors* were included: mechanical ventilation, sepsis, necrotizing enterocolitis, postnatal corticosteroids and hypotension treated with cardiotonic agents.

Guideline	Previous (1997)	Present (2013)
GA/BW	<32.0 weeks and/or <1500 grams	<30.0 weeks and/or <1250 grams
Additional criterion	-	30.0-32.0 weeks and/or 1250-1500 grams and presence of ≥1 risk factor*

Materials & Methods

This study was initiated by the Leiden University Medical Center. Data from the present, 9-year study period were compared to the previous (2000-2009) and earlier periods going back to 1975. For comparison, an identical approach towards data analysis was chosen.

Ophthalmologists of the Dutch institutes for the visually impaired and blind provided anonymized data of patients born between January 1st 2009 and December 31st 2017 (2009-2018), who were referred to their center with the diagnosis of visual impairment due to (severe) ROP as the main reason for referral (regardless of visual acuity at time of admission). A one year overlap with the previous period (period 4) for the year 2009 was calculated as data collection in all periods was conducted in the final year of the study period. Therefore, it could not be guaranteed that all infants who became visually impaired due to ROP were already registered at the VI institutes at time of the former inventory. According to the General Data Protection Regulation (GDPR)(17) and the local medical ethical committee, informed consent was not required, as no personalized data (for example birth year) were provided.

Visual impairment was defined as visual acuity (best corrected visual acuity, BCVA) of <0.3 in the best eye, according to the recommendations of the International Association for Prevention of Blindness (WHO, 1984) (18). The referrals also included infants who did not meet the WHO criteria for visual impairment and blindness, as the institutes also provide a rehabilitation program to children with ROP who have an increased risk of developing

visual complications due to neonatal risk factors and because of borderline visual acuity (VA), cerebral visual impairment or unilateral blindness.

Ophthalmological data were collected on VA and treatment for ROP. In many cases data on age of VA examination and VA test method were not provided. If an infant was incapable for reliable VA assessment, VA was designated unknown. In other cases, VA was categorized as follows: not partially sighted or blind: VA>0.3, partially sighted: VA 0.1-0.3, socially blind: VA 0.1-1/60, practically blind: VA <1/60-light perception (LP), completely blind VA: no LP. Information on anatomic and =refractive status could not be obtained or was unknown in many cases and therefore excluded from the study. In the Netherlands, the Early Treatment for ROP (ETROP) criteria apply for ROP treatment. According to the Dutch guideline, anti-VEGF was used only for ROP stage 3 with plus disease in zone I and as last resort treatment. Neonatal data consisted of: GA, BW, sex, multiple birth and neonatal treatment. Due to the GDPR however, obtaining details on treatment was challenging compared to period 1-4. For example, in up to 70% of all cases, information about the duration of supplemental oxygen or mechanical ventilation were missing and therefore excluded from this study. Regarding concomitant disabilities, presence of bronchopulmonary dysplasia (BPD, defined as the need for supplemental oxygen at 28 days of life), behavioral abnormalities (classification according to the Diagnostic and Statistical Manual of mental disorders), epilepsy, hearing deficit (defined as bilateral hearing loss≥40dB), developmental delay (defined as at least 6 months disparity with a comparable age group with no improvement in relation to earlier assessment, according to the Dutch adaptation of the Reynell-Zinkin developmental scales for visually handicapped children (19)), and neurological handicap (defined as treated hydrocephalus, posthemorrhagic ventricular dilatation, cerebral palsy and cerebral visual impairment) were recorded.. Infants were considered multiply disabled when they had visual impairment caused by ROP and one or more concomitant disabilities, except for BPD as quality of life improves in adolescence and young adulthood. because pulmonary function usually improves over time (20). To calculate incidences Dutch birth rates were used as denominator. Birth rate data were collected from the Central Bureau of Statistics for the Netherlands(21) and survival rates were obtained from the Dutch national perinatal registry, Perined(22).

Statistical analysis was performed using SPSS Statistics software version 23.0 IBM Corp., Armonk, N.Y., USA. Clinical data were evaluated using the chi-square test and independent samples t-test. The incidence of visual impairment in relation to Dutch birth rates was analyzed using Poisson regression analysis. For the purpose of comparing infants with visual impairment to the previous periods, the total study population was used as denominator. Differences with a p-value <0.05 were considered significant.

Results

General data

Records of 53 infants referred to Dutch institutes for the visually impaired with the (presumed) diagnosis of visual impairment due to ROP were obtained. All children were born with GA<30.0 weeks and/or BW<1250 g and would have therefore been included for ROP screening according to the new screening criteria. Mean population GA and BW continued to decrease to 26.6±1.9 weeks (period 4: 27.4±2.0, p=0.047) and 823±323 g (vs. period 4 p=0.349, period 1 p=0.003) respectively. The incidence of male gender and multiple birth did not change. Other general and neonatal data of the children in the current (period 5, 2009-2017) and previous periods (periods 1-4) are presented in table 2.

Visual impairment

Thirty-two of the 53 infants (60.4%) were registered as visually impaired based on VA<0.3, representing a nonsignificant decrease since period 4 (2000-2009) (32/42=76.2%, p=0.103). Compared to period 3 however, in which 46/51 (90.2%) infants had VA<0.3, the incidence was significantly lower (p=0.02).

The absolute number of live births in the Netherlands with GA<25.0 weeks was more than three times higher (n=573) than in period 4 (188). Contrarily, the number of infants born GA>25.0 did not change. In relation to the overall birth rate, the incidence of visual impairment due to ROP was 2.02 per 100.000 (table 3), representing a non-significant change since period 4 (p=0.643). Yet compared to period 3 and 2, a notable difference was observed (p=0.005 and <0.001 respectively).

In two patients details about VA were unknown. One preverbal child with ROP stage 5 in both eyes was categorized as completely blind. For the other children, the distribution per category has not changed since period 4 (table 4). Though the absolute number of completely blind infants (no light perception, LP) was nearly three times as high compared to period 4, the increase was not significant (p=0.119). Moreover, the number of blind children VA<1/60-LP (practical blindness), showed a parallel threefold decrease. Nineteen infants were not partially sighted or blind, of which 16 had VA >0.3 and three were unilaterally blind. Within this group, ten were treated for ROP, two had stage 2 ROP but were also diagnosed with cerebral visual impairment and in six infants, the details about the course of ROP were unknown. Of all children registered with diagnosis of ROP, eight children (15.1%) had cerebral visual impairment of which three had VA>0.3, four were partially sighted (VA0.1-0.3) and one was blind (VA<1/60-LP).

Treatment

ROP treatment was performed in 35 children (66.0%) using retinal laser photocoagulation (*n*=29, 82.9%), combined laser and intravitreal anti-vascular endothelial growth factor (VEGF) therapy (*n*=1), laser and cryotherapy (*n*=1), anti-VEGF (*n*=1), pars plana vitrectomy (*n*=1) and cryotherapy (*n*=2). Eighteen infants (34.0%) were not treated for ROP of which 9/53 (17.0%) had a VA<0.3 (period 4: 14/42 (33.0%) untreated of which ten (23.8%) VA<0.3). Within this group, three children were included of which data on ROP treatment were unknown. Only compared to period 2 (and earlier), treatment was performed more often (*p*=0.01).

Concomitant disabilities

The incidence of concomitant disabilities found in infants with ROP also seems to have reached a plateau (table 5). Though the absolute number of infants with behavioral abnormalities and a hearing deficit nearly halved, the difference did not reach statistical significance (*p*=0.092 and 0.157 respectively). The number of children with at least one concomitant disability was 45 (84.9%) (period 4: 73.8%, *p*=0.179) and is high for all infants with GA<30 weeks (table 6).

Table 2. Neonatal data of infants with VI caused by ROP in five consecutive periods

	Period 1 1975-1987	Period 2 1986-1994	Period 3 1994-2000	Period 4 2000-2009	**Period 5** **2009-2018**
No. infants	76	87	51	42	**53**
Male (%)*	47	58	59	74	**51**
Mean GA (weeks) †	28.7 ± 2.7	27.5 ± 2.5	27.7 ± 2.4	27.4 ± 2.0	**26.6 ± 1.9**
Mean BW (gram) ‡	1128 ± 331	1071 ± 385	942 ± 306	912 ± 385	**823 ± 323**
Multiple birth (%)	19	21	31	31	**28**

* Gender cohort 4 vs. 5 *p*=0.056 (Chi^2 Test)

† GA cohort 4 vs. 5 *p*=0.047 (Mann Whitney U Test), 1 vs. 5 *p*=0.023

‡ BW cohort 4 vs. 5 *p*=0.349 (Mann Whitney U Test), 1 vs. 5 *p*=0.003

Table 3. Visual impairment* caused by ROP (sequelae) in relation to overall birth rates in the Netherlands.

Period	Years	No. ROP sequelae	No. live births x 10^5	ROP sequelae / 100.000
1	1975-1987	97	23.0	4.22
2	1986-1994	79	14.4	5.49
3	1994-2000	46	11.7	3.93
4	2000-2009	32	17.4	1.84
5	**2009-2018**	**32**	**15.8**	**2.02**

In the present study 32/53 of the registered infants were visually impaired.

* defined as visual acuity <0.3 in the best eye

Table 4. Proportion of infants with different categories of VA determined by vision of the best eye and absolute number of infants treated in period 5 in relation to visual outcome with the number of non-treated infants in brackets.

	Period 1 1975-1987	Period 2 1986-1994	Period 3 1994-2000	Period 4 2000-2009	Period 5 2009-2018	*p* 4 vs. 5	**Treated Period 5 (*n*)**
Inclusion (years)	13	9	7	9	**9**		
No. Infants *n*	76	87	51	42	**53**		
VA per category % (*n*)							
Unspecified	5.1% (4)	-	-	-	**3.8% (2)**	**0.243**	**2 (0)**
Not partially sighted or blind (VA>0.3)*	2.0% (2)	10.3% (9)	9.8% (5)	23.8% (10)	**35.8% (19)**	**0.109**	**10 (9)**
Partially sighted (VA 0.1-0.3)	34.3% (26)	31.0% (27)	25.5% (13)	38.1% (16)	**30.2% (16)**	**0.372**	**11 (5)**
Socially blind (VA<0.1-1/60)	12.1% (9)	10.3% (9)	11.8% (6)	14.3% (6)	**9.4% (5)**	**0.355**	**4 (1)**
Practically blind (VA<1/60-LP)	8.1% (6)	21.8% (19)	25.5% (13)	16.7% (7)	**5.7% (3)**	**0.119**	**2 (1)**
Completely blind (VA=0)	38.4% (29)	26.4% (23)	27.5% (14)	7.1% (3)	**15.1% (8)**	**0.119**	**6 (2)**
ROP treatment (%)	24.4	43.9	56.9	66.7	**66.0**	**0.529**	**35**

LP, light perception; ROP, retinopathy of prematurity; VA, visual acuity.

* Including infants with unilateral blindness. Period 5: *n*=3 (11.8%)

Table 5. Concomitant disabilities in infants with visual impairment caused by ROP in five consecutive periods in the Netherlands (%). (*p*-value chi-square test)

	Period 1 1975-1987	Period 2 1986-1994	Period 3 1994-2000	Period 4 2000-2009	**Period 5 2009-2018**	***p*** **4 vs. 5**
No. infants	76	87	51	42	**53**	
BPD	26.3	45.9	60.4	76.2	**71.7**	**0.621**
Behavioral abnormalities	9.2	21.8	46.9	40.0	**26.4**	**0.092**
Epilepsy	5.3	6.9	16.3	0	**7.5**	**0.157**
Hearing deficit	5.3	2.3	8.2	12.5	**5.7**	**0.157**
Developmental delay	35.5	47.1	52.9	65.0	**69.8**	**0.933**
Neurological handicaps	30.3	49.4	45.1	42.5	**30.2**	**0.621**
Multiple disabled	39.5	58.6	68.2	66.7	**75.5**	**0.935**

* Definitions. BPD (bronchopulmonary dysplasia): the need for supplemental oxygen at 28 days of life; Behavioral Abnormalities: according to the Diagnostic and Statistical Manual of mental disorders; Hearing Deficit: bilateral hearing loss ≥40dB; Developmental Delay: >6 months disparity with a comparable age group with no improvement in relation to earlier assessment, according to the Dutch adaptation of the Reynell-Zinkin developmental scales for visually handicapped children; Neurological handicap (defined as treated hydrocephalus, posthemorrhagic ventricular dilatation, cerebral palsy and cerebral visual impairment); Multiple Disabled: VI caused by ROP and one or more concomitant disabilities, excluding BPD as quality of life improves in adolescence and young adulthood.

Table 6. Visual impairment (VI) caused by ROP in relation to estimated number of survivors and percentage of infants with concomitant disabilities in patients with VI, both in relation to GA.

	VI caused by ROP %(n) *					Concomitant disabilities %(n)	
GA (weeks)	**Period 1 '75-'87**	**Period 2 '86-'94**	**Period 3 '94-'00**	**Period 4 '00-'09**	**Period 5 '09-'18**	**Period 4 '00-'09**	**Period 5 '09-'18**
23	-	-	-	-	6.25 (1)	-	100 (1)
24-25	10.4 (11)	12.5 (11)	3.1 (9)	2.4 (10)	2.1 (21)	69 (7)	81 (17)
26-27	3.3 (40)	4.3 (36)	1.3 (23)	0.9 (19)	0.7 (18)	79 (15)	89 (16)
28-29	0.8 (26)	0.4 (10)	0.3 (10)	0.2 (9)	0.2 (8)	78 (7)	100 (8)
30-31	0.2 (13)	0.2 (8)	0.1 (6)	0.03 (2)	0.05 (5)	50 (1)	60 (3)
>32- <37	0.01 (12)	0.01 (7)	<0.001 (2)	<0.002 (2)	-	50 (1)	-
Total	**102**	**72**	**50**	**42**	**53**	**73.8 (31)**	**84.9 (45)**

* Numbers of estimated survivors obtained from the Netherlands Perinatal Registry

Discussion

This is the fifth consecutive inventory on incidence of visual impairment due to ROP in the Netherlands, providing a national overview of more than four decades. Between 2009-2018, records of 53 children were obtained, who were referred to Dutch institutes for the visually impaired or blind because of visual impairment due to ROP. All children were eligible for screening according to the new risk-based and more stringent inclusion criteria. Thus, though fewer infants were subjected to screening examinations, no infants with visual impairment due to ROP were missed because they no longer fitted the criteria, confirming the safety of the 2013 guideline. Monitoring of the safety of a newly implemented guideline is of utmost importance and evaluation should be repeated continuously as neonatal policies are changing over time and may differ between countries. Therefore each country should evaluate its own ROP screening guideline repeatedly and if necessary modify it. Countries with comparable ROP populations to the Netherlands evaluated their guidelines recently: American guidelines were updated, New Zealand guidelines remained unchanged and modifications of the Swedish guidelines were proposed based on 10 year data from the Swedish register(23-25).

The decrease in population GA we found in our study is most likely a consequence of the policy change (2010), which lowered the age of active neonatal treatment for extreme preterm infants. Since the previous period (period 4) a more than 3-fold increase in live births with GA<25.0 weeks was observed. As expected and corresponding to the previous Dutch periods, the largest number of infants with visual impairment due to ROP was in infants with the lowest GA. Moreover, since 2014, higher, and in regard to ROP

more unfavorable, oxygen saturation targets were accepted in most Dutch NICUs. For (retinal) blood vessel development hyperoxic circumstances in the first weeks of life are detrimental, because they can lead to arrest of angiogenesis and obliteration of already developed vessels. Thus, together with the higher survival of extremely preterm infants, the incidence of sROP was expected to increase accordingly. A recent retrospective study on ROP treatment the Netherlands confirmed this concern: twice as many infants were treated for ROP in the period 2013-2016 compared to 2010-2013(3), (4). Fortunately, we did not observe an analogous increase in visual impairment: 32/53 (60.4%) infants became visually disabled representing a nonsignificant decrease since period 4 (32/42, 76.2%, p=0.103). Also among overall live births in the Netherlands, the rate was similar to the last period (table 3). Thus, despite unfavorable neonatal factors, the incidence of visual impairment due to ROP remained relatively stable. Nevertheless, future inventories are of importance to determine no further ROP sequelae due to this policy change, especially considering that in the last cohort (period 5, 2009-2018), only half of the group was born after 2014.

Most infants were treated with laser. Only two were treated with anti-VEGF, which can be attributed to the low number of infants with ROP in zone I, being the criterion for this treatment following the Dutch guideline. The number of untreated infants in the present period remained unchanged (34.0%) compared to the previous (33.3%). Respectively nine (17.0%) and eight (19.0%) of them became visually impaired.

The proportion of children with visual impairment developing at least one nonvisual disability increases with decreasing GA (table 6). The association of prematurity and neurodevelopmental disabilities has previously been widely described(26-29), as well as the correlation between severity of ROP and neurodevelopment(30). Several studies discuss that the possible cause of sROP and decreased brain development may be the same, namely IGF-1 deficiency, and that both disorders therefore may be correlated with one another. . Low IGF-1 concentration levels following preterm birth suppress retinal vessel outgrowth and restoration, contributing to both phases of ROP (31-33). IGF-1 is also essential for the developing brain, i.e. axon maturation, myelinization of the brainstem and development of cerebellar neurons (34). Another explanation for a possible relationship between sROP and brain injury may be that during admission on the NICU preterm infants are extensively exposed to adverse events that all have negative effects on both the developing retina and brain. Glass et al presented delayed white matter maturation and lower cognitive and motor scores in infants with sROP compared to those without(35). However, no significant differences in the rate of cerebral palsy, hearing or visual impairment were found. Two studies, by Drost et al and Sveinsdóttir et al, using magnetic resonance imaging show an association between (severe) ROP and significantly smaller white matter and cerebellar and brainstem volumes for which in both conditions a deficiency in the insulin-like growth factor protein is presumably responsible(36, 37). Moreover, both studies report on poorer

outcome in infants who have developed (severe) ROP. The risk for developmental delay remains high, even in children born moderately preterm. In our cohort, we also observed a trend toward less infants with cerebral palsy and/or behavioral abnormalities, however the overall prevalence of nonvisual disabilities has not changed significantly since the last period and neither did the number of infants with at least one or more concomitant disability (table 5 and table 6).

We compared the Dutch ROP data to several studies from other countries. A global overview of visual impairment due to ROP in 2010 was presented by Blencowe et al. in which the incidence of visual impairment in high income countries was estimated 14.5 per 100.000 live births(1). In a large Swedish cohort, a much lower incidence was presented of 1.3 per 100.000 live births from 2004 to 2015(24). Contrary to our study however, the Swedish data were collected prospectively and moreover, strict inclusion criteria applied: all infants born in a foreign country or with potential other causes of visual impairment than ROP (among which cerebral visual impairment) were excluded. If our criteria would apply to the Swedish cohort, the incidence would increase to 3.3 per 100.000 births. A study from New Zealand was, correspondingly to ours, based on retrospective data from a national registry for blind and low vision children. Over the 22-year study period, 2.8 per 100.000 new-born infants became visually impaired due to ROP(38). Moreover, a notable decrease in visual impairment was found since the implementation of the ETROP treatment criteria in 2005, from 3.4 to 1.8 per 100.000 births.

Treatment of ROP was comparable to the New-Zealand study, in which 22.2% of infants with visual impairment due to ROP were not treated(38). In the Swedish inventory, only 5.9% was untreated, however it was identified that in 35.3% of the population, visual impairment was avoidable because treatment was performed untimely or suboptimal(24). It therefore cannot be emphasized enough that timely identification of treatment warranting ROP stages is essential to allow further decrease in the incidence of visual impairment due to ROP. For this, ongoing surveillance and monitoring of national guidelines is necessary.

It is challenging to compare the incidence of visual impairment caused by ROP, to the incidence in other countries due to different study designs and accessibility of data. By combining the results from the past 3 Dutch periods into a 24-year period, we find a comparable 2.4 per 100.000 incidence in the Netherlands (table 3). Overall, our five Dutch periods demonstrate a gradual decrease in visual disability due to ROP over the past three decades and a slight but nonsignificant increase since 2009.

Main limitations of our study include the retrospective study design and newly introduced strict privacy laws (GDPR), which made it challenging to obtain more detailed data on neonatal risk factors or the course of ROP. Of the two infants with unknown VA it was

not possible to determine if data were missing or if they were too young to assess VA. Furthermore, it is possible that there are infants who are not yet referred to the institutes. Therefore, the visual impairment incidence found in this inventory should be considered a minimum and ongoing future surveillance is necessary. Yet, the institutes are well known among Dutch ophthalmologists and they provide easy access for referral. It therefore is likely that the data from this study give a valid representation of visual impairment due to ROP in the Netherlands.

In conclusion, this study emphasizes the necessity for periodic evaluation of ROP guidelines and long term surveillance of outcome parameters in prematurely born infants. In the Netherlands no infants were missed for screening based on the new inclusion criteria, illustrating the safety of the national ROP guideline. Despite improvements in neonatal care, the number of infants with concomitant disabilities did not change. visual impairment due to ROP remained low despite a lower GA and higher oxygen saturation targets.

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The authors declare that there is no conflict of interest.

Contribution
K. Trzcionkowska: investigation, funding acquisition, formal analysis, writing – original draft, writing review & editing; **J.U.M. Termote**: writing review & editing; **M.M. van Genderen**: recourses, writing review & editing; **M.J. de Vries**: recourses, writing review & editing; **A.J. van Sorge**: recourses, writing review & editing; **N.E. Schalij-Delfos**: supervision, writing review & editing;

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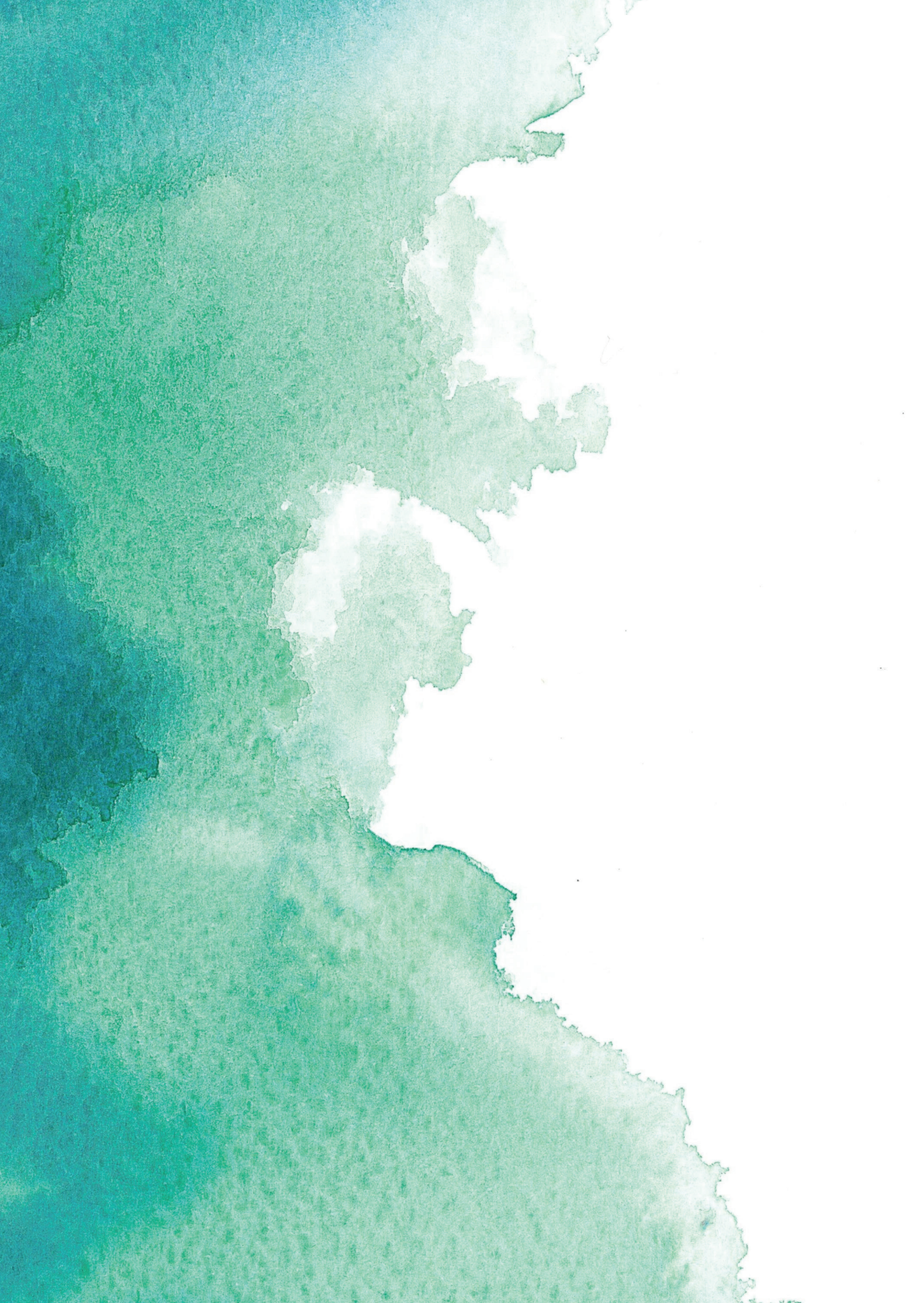

Chapter 8

English summary
Conclusions
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English summary

In this thesis, the results of the second national Dutch inventory on retinopathy of prematurity (NEDROP 2) are presented. Crucial changes in the national ROP screening guideline (2013) required monitoring and dependable present-day data in order to provide for a new, up to date guideline. The three principal aims of the study were to gain insight in current ROP demographics in the Netherlands, evaluate the influence of neonatal policy changes on the number of infants with severe ROP and treatment and assess the safety of the adjusted screening criteria in the Dutch ROP guideline (2013), and investigate possibilities for further restriction of these screening inclusion criteria, allowing to subject less infants to burdensome ROP examinations, under the condition that no treatment requiring ROP is missed.

Following the first NEDROP (NEDROP 1, 2009), a new ROP guideline was established in 2013 including more stringent inclusion criteria for ROP screening. Shortly after the implementation, concerns were raised when an increase was observed in the number of infants with severe ROP. A retrospective inventory was carried out, to evaluate the incidence of severe ROP and to determine the number and outcome of treatment before and after introduction of the new guideline (period 2013-2016 compared to 2010-2013) (**chapter 2 and 3**). The study revealed that twice as many infants were treated and the number of retinal detachments doubled since the new ROP guideline. It was hypothesized that on one hand, better awareness of the Early Treatment of ROP (ETROP) criteria contributed to more ROP being categorized as indicative for treatment. On the other hand, the alarming increase could be explained by the neonatal policy changes (i.e. reduced age limit for active life support treatment and higher oxygen saturation targets in the first weeks after birth).

In **chapter 4**, the results of a retrospective study are presented on visual impairment (VI) due to ROP between 2009-2018. The incidence of VI and other concomitant disabilities (i.e. neurological handicaps, developmental delay) remained stable, despite the further decrease in mean gestational age (GA) and unfavourable neonatal risk factors in the present population. All babies met the new inclusion criteria, validating safety of the ROP guideline during the past decade. Together with the results of four earlier inventories from 1975 onwards, this study provides an overview of more than four decades on VI due to ROP in the Netherlands.

Due to the strict Dutch privacy regulations, an ongoing national ROP registry yielding continuous up-to-date data on incidence and treatment outcome is not available. With the aim to obtain insight in present-day ROP incidence and organisation of screening and treatment in the Netherlands, a national prospective inventory was initiated (**chapter 5**). In 2017, 1287 infants were eligible for ROP screening of which 84% was screened by

ophthalmologists. Compared to NEDROP 1 (2009) this is a 28.4% decrease in number of screened infants which can be attributed to the restricted inclusion criteria. Overall incidence of ROP remained stable, but the number of infants with severe ROP and ROP treatments increased. Despite this, less infants advanced to end stage ROP (retinal detachment) indicative of better treatment outcome (6.1% in 2017 vs. 20% in 2009). Additionally, quality indicators in the 2013 guideline led to more timely executed screening examinations and less loss to follow-up after hospital transfer

In order to assess validity and safety of the 2013 risk-based inclusion criteria. To obtain current risk factors, the NEDROP 2 database was matched with Perined, the Dutch neonatal registry, Perined, in which the majority (97%) of clinical data and treatments of Dutch newborns during hospital admission is recorded. Analysis after coupling revealed no new risk factors other than those already included in the present guideline: mechanical ventilation, sepsis, necrotizing enterocolitis, postnatal glucocorticoids and hypotension treated with inotropic agents. The study, presented in **chapter 6**, revealed no new factors other than those already included in the guideline, wavering the need to adapt the risk factors in the upcoming guideline. Furthermore, for infants with a GA <26.0 weeks with a high-risk profile, defined as treatment with postnatal steroids and for perforated necrotising enterocolitis, the risk to develop any ROP is almost equal to severe ROP.

Based on these data, different potential future screening strategies were analysed on sensitivity and cost-effectiveness of which the results are discussed in **chapter 7**. The most effective strategy, detecting 100% of treatment requiring ROP, will reduce the number of screened infants by 24% compared to the current strategy, lowering annual screening costs by €59.454.

Conclusions

This thesis shows that national inventories provide valuable data to improve level of care. Outcomes of NEDROP 1 led to implementation of quality indicators in the national screening guideline for ROP in 2013. The second NEDROP study proves these measures to be effective.

Key lessons deducted from the prospective national inventory NEDROP-2 include: the increase in number of infants with high risk ROP since the implementation of new neonatal policy guidelines has led to a doubling in ROP treatment in the Netherlands. This increase was accompanied by a considerable increase in number of retreatments and retinal detachments.

Simultaneously, while more infants developed severe ROP, less infants were included for ROP screening examinations since the 2013 guideline. We confirmed that all infants screened after implementation of the 2013 guideline met the new screening criteria and were examined according to protocol, confirming safety of the national guideline in the present day population.

Despite lower gestational age and unfavorable neonatal risk factors, the incidence of visual impairment due to ROP and concomitant disabilities remained stable since the previous inventory (2009-2018 vs. 2000-2009).

The overall incidence of ROP within the screened population remained stable, but the number of infants with severe ROP nearly doubled (3.3% vs. 1.8%). Quality indicators led to more timely executed screening examinations and less loss to follow-up after hospital transfer.

NEDROP-2 (2017) showed a 28.4% decrease in number of screened infants compared to 2009, which can be attributed to the implementation of new risk factor based screening inclusion criteria (2013). Current risk factors (mechanical ventilation, sepsis, necrotizing enterocolitis, postnatal glucocorticoids and hypotension treated with inotropic agents) can be safely implemented in the upcoming guideline. It was also found that the risk to develop any ROP is almost equal to severe ROP for infants with a GA <26.0 weeks with a high-risk profile, defined as treatment with postnatal steroids and for perforated necrotising enterocolitis.

Finally, our results provided viable data for an even more cost-effective screening strategy being: GA<30 weeks **and** (2013 guideline: and/or) BW 1250 grams and the subgroup with GA 30-32 weeks and/or BW 1250-1500 gram with presence of at least one of the earlier mentioned risk factors. This will predictively reduce the number of screened infants by 24%, lowering annual screening costs by €59.454.

Future recommendations

Future registration

Periodical monitoring of the content and safety of guidelines is imperative due to continuous discoveries and developments in medical care. This is particularly relevant with regard to retinopathy of prematurity (ROP). During the past decades, tremendous advances in neonatal care led to a drastic increase in survival of extremely premature babies in developed countries. For this purpose, present-day demographic details of the population at risk should at least include gestational age (GA), birth weight (BW), risk factors and, if present, ROP staging and treatment outcome. Furthermore awareness of neonatal treatment guidelines is crucial. Ideally, these data should be assessed continuously and prospectively.

However, due to strict privacy regulations (General Data Protection Regulation, GDPR, applied since April 2016), no such ROP registry exists in the Netherlands. The NEDROP studies served as an interface, but only to provide for data for the years in which they were conducted (2009 and 2017). Furthermore, systemic neonatal risk factors are recorded in Perined, a medical professional-based registry of neonatal data during hospital stay, reported by pediatricians and neonatologists. The registry generates dependable data on neonatal care in the Netherlands as it is obligatory for neonatal intensive care units (NICU's) and high-care centers. However, information in Perined on ROP is not always equally reliable as in the majority of cases, ROP develops after discharge from the NICU, after the hospital admission data have usually already been recorded in the Perined database. Therefore, insight on the associated risk factors of ROP can only be obtained by coupling a separate ROP registry (in this case, NEDROP) with Perined. For this coupling, a code consisting of patients' date of birth, zip code, gestational age and birth weight are required, causing two major obstacles: firstly, 100% matching is never achieved due to errors and unknown data, and secondly, the privacy of patients cannot be completely warranted as the code is made of personal data, prohibiting studies such as the NEDROP from being carried out in the future following the GDPR.

A promising initiative called the European registry on ROP (1) has been established, which is an extended version of the German ROP registry that already exists since 2012. It is an international, multicenter, observational registry, in which data of infants treated for ROP are collected and analyzed. These combined data are expected to provide for long term results (i.e. visual function and other outcomes) on a large scale. However, while pseudonymization allows to avoid the earlier discussed privacy issues, there is a lack of information on the complete premature population at risk, and the incidence of ROP and severe ROP within the screened population, organization of screening and risk factors for ROP remain unknown. For the future, we urge for collection of data of all babies that roll into ROP screening program (also those that do not develop ROP), respecting current privacy regulations. This

could be enabled by the introduction of automatic pseudonymization, allowing for extensive and thorough follow-up, even after hospital transfer.

Treatment

It is of great importance to investigate and optimize ROP treatment strategy. The "golden standard" of ROP treatment remains laser photocoagulation. Due to technical challenges and adverse side effects however, intravitreal anti-VEGF is increasingly used as an alternative. Nevertheless, important questions on safety, timing and modality remain uncertain (see introduction), posing ethical questions for widespread use. Furthermore, despite extensive studies, the exact role of oxygen in ROP is still unclear, therefore i.e. optimal oxygen saturation targets in mechanical ventilation and cut-off hemoglobin levels for packed cells transfusion are still unknown. A promising finding by Lopriore et al. poses to treat premature anemia with autologous placental or umbilical cord blood (UBC) instead of commonly used adult donor blood (2). Newborn babies have a predominance of fetal hemoglobin (HbF) at birth, which gradually declines and finally disappears by 1-2 years of age. It also has a greater affinity to oxygen compared to adult (HbA), shifting the oxygen-dissociation curve to the left. This physiological mechanism enables the fetus to gradually receive oxygen from the maternal into the placental circulation. In turn, following transfusion with HbA during the first weeks after birth (phase 1 of ROP, GA<32 weeks), tissue oxygen delivery automatically increases and contributes to the development of ROP (3). A physiological (and most logical) alternative to avoid this transfusion-induced non-physiological hyperoxia would be the use of UCB. Currently, the main limitation of this therapy is the low volume of blood collection from the small preterm placentas. Allogenic UCB drawn from term neonates could give a solution, although safety regarding appropriate serological typing and transfusion-associated morbidity and mortality needs further pursuit.

Early intervention

Consultation of neonatologists and ophthalmologists on the ROP risk profile and intervention in neonatal treatment of screened babies starts relatively late as screening programs for ROP do not start before 5 weeks postnatal age or 31 weeks postmenstrual age, whichever comes first. This means that, in the early weeks of life, high risk for ROP is not incorporated in neonatal treatment. The placenta reflects early maternal and fetal condition, previous to the neonatal period. It is readily available shortly after birth, and can be very easily obtained. The placenta provides excellent opportunities to investigate histology, inflammation, angiogenesis and immune profile of the fetal and maternal elements in the placental microenvironment. This can provide new insights on the etiology and pathophysiology of ROP and may ultimately offer options for intrauterine treatment to reduce the risk of ROP development. Finally, it creates the opportunity to incorporate the high risk profile in the personalized treatment approach by neonatologists during the first phase of ROP. With the aim of further investigation of these promising modalities, the ophthalmology, neonatology

and pathology departments at the Leiden University Medical Center initiated the project 'placenta as a predictor for ROP (PAP for ROP)' of which results are expected in the near future.

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Dutch summary

Prematurenretinopathie (ROP) is, ondanks uitgebreid onderzoek, invoering van verschillende maatregelen en nieuwe behandelmogelijkheden, nog steeds een belangrijke oorzaak van blind- en slechtziendheid bij te vroeg geboren (premature) kinderen. Deze ernstige gevolgen zijn grotendeels vermijdbaar, mits de aandoening tijdig wordt opgespoord en zo nodig, tijdig behandeld. In Nederland en andere landen met een hoge welvaart maakt de zorg voor pasgeborenen (neonatologie) voortdurend een belangrijke vooruitgang door, waardoor de overleving van extreem premature baby's toeneemt. Hiermee stijgt ook het aantal kinderen dat risico loopt om ernstige ROP te ontwikkelen.

ROP is een aandoening van de bloedvaten van een nog onvolgroeide retina (netvlies). Vele factoren spelen een rol bij het ontstaan van ROP, maar de belangrijkste zijn zwangerschapsduur en geboortegewicht. Andere geassocieerde factoren zijn onder te verdelen in een aantal subgroepen: demografische factoren (bv. geslacht, etniciteit); factoren die een rol spelen bij de oxygenatie (bv. het aantal dagen kunstmatige beademing, de mate van longrijping); geassocieerde aandoeningen (sepsis, necrotiserende enterocolitis (NEC), intraventriculaire bloedingen (IVH)); biochemische factoren (bv. fluctuaties in zuurstofspanning, acidose, hyperglycaemie); systemische behandeling (bv. bloedtransfusies) en maternale factoren (bv. leeftijd, pre-eclampsie).

Deze risicofactoren zijn veelal onderling gerelateerd en mede afhankelijk van bijkomende morbiditeit bij de prematuriteit. De verschillen in niveau van neonatale zorg, overlevingskansen en inclusie criteria voor screening verklaren de verschillen in incidentie van ROP per land of regio. Het is hierdoor niet mogelijk om een universeel screeningsprotocol op te stellen omdat de verschillen groot kunnen zijn. In Nederland werd in 2009 de eerste landelijke studie naar ROP geïnitieerd (Nederlandse studie prematurenretinopathie, NEDROP 1), met als doel inzicht te verkrijgen in de landelijke situatie en op basis van deze resultaten een evidence-based richtlijn te realiseren. Hierbij namen alle Nederlandse oogartsen, neonatologen en kinderartsen deel, die betrokken zijn bij de zorg voor prematuren. Doel van deze nationale, prospectieve inventarisatie was inzicht te krijgen in veranderingen in de neonatale zorg, de incidentie van ROP, de risicofactoren, de criteria voor en resultaten van behandeling, logistiek en effectiviteit van het proces van screening en de invloed van overplaatsing.

De studie leidde tot de invoering van een nieuwe landelijke ROP-richtlijn in 2013. Een belangrijk doel hiervan was het verminderen van het aantal te screenen kinderen met een laag risico op ROP, onder de voorwaarde dat geen ernstige ROP werd gemist. Om dit te realiseren werd de screeningsindicatie bij alle kinderen geboren met een zwangerschapsduur (AD) <32 weken en/of geboortegewicht (GG) <1500 gram verlaagd naar de leeftijd van AD <30 weken en/of GG <1250 gram. Kinderen geboren met AD 30-32 weken en/of GG 1250-

1500 gram hadden enkel nog een screeningsindicatie bij aanwezigheid van tenminste een van de volgende risicofactoren: kunstmatige ventilatie, sepsis, NEC, hypotensie behandeld met cardiotonica en/of postnatale behandeling met corticosteroïden. De NEDROP studie toonde verder aan dat de Early Treatment for ROP-criteria (ETROP), waarbij de focus van behandelindicatie verschoven is van uitbreiding van ROP in klokuren naar aanwezigheid van plus-disease, nog onvoldoende werden toegepast en dat het risico op niet gescreend worden aanzienlijk groter was bij kinderen die overgeplaatst werden naar een ander ziekenhuis. Hierop zijn de ETROP-behandelcriteria nogmaals benadrukt en werden toetsbare kwaliteitsindicatoren voor logistieke processen opgenomen in de nieuwe richtlijn.

In het afgelopen decennium is het risico op (ernstige) ROP in ons land toegenomen, mede door cruciale veranderingen in neonataal beleid. Zo worden sinds 2010 prematuren vanaf een zwangerschapsduur van 24 weken i.p.v. 25 weken actief na de geboorte opgevangen en behandeld en zijn in 2014 de zuurstof saturatiegrenzen in de periode tot 36 weken na de geboorte in de meeste neonatale intensive care units verhoogd. **Hoofdstuk 2 en 3** beschrijven de resultaten van een retrospectieve landelijke inventarisatie naar behandeling van ROP, waaruit de gevolgen van bovengenoemde veranderingen, en de zorgen van Nederlandse kinderoogartsen worden bevestigd: het aantal behandelingen en blinde ogen ten gevolge van ROP verdubbelde in de periode 2013-2016 ten opzichte van 2010-2013. Mogelijke oorzaken hiervoor waren een absolute toename van het aantal kinderen met verhoogd risico op (ernstige) ROP en het aangepaste zuurstofsaturatiebeleid.

Parallel aan deze toename van het aantal kinderen met ernstige ROP, komen zoals eerder gezegd sinds 2013 op basis van de nieuwe richtlijn minder kinderen in aanmerking voor ROP screening. Doel van het in **hoofdstuk 4** gepresenteerde onderzoek was om na te gaan of er sinds het nieuwe screenings protocol kinderen waren die blind- of slechtziend geworden waren door ROP, maar die niet binnen de nieuwe criteria vielen en hierdoor onterecht niet gescreend en dus gemist waren. Hiervoor werden de data geanalyseerd van kinderen geboren tussen 2009-2018 uit de Nederlandse Instituten voor visueel gehandicapten. Het betreft een vervolg op vier eerdere overeenkomstige studies, waarmee in totaal een overzicht van meer dan veertig jaar blind- en slechtziendheid door ROP in Nederland is gerealiseerd. In de huidige periode werden 53 kinderen geïdentificeerd die aangemeld waren met de diagnose ROP. Ondanks een verdere daling in de gemiddelde zwangerschapsduur, geboortegewicht en de eerdergenoemde ongunstige neonatale factoren, bleef het aantal kinderen met een visuele beperking door ROP stabiel ten opzichte van de vorige studie (2000-2009). Ook de incidentie van bijkomende handicaps (bijvoorbeeld doofheid, neurologische uitval, ontwikkelingsachterstand) verschilde niet significant ten opzichte van de eerdere studies. Alle 53 aangemelde kinderen voldeden aan de nieuw geïntroduceerde inclusiecriteria voor screening op ROP en zijn volgens protocol gescreend.

Vanwege alle cruciale veranderingen en om de veiligheid van de huidige richtlijn, de invloeden van de genomen maatregelen en actuele ROP-incidentie in Nederland te vast te stellen is de tweede nationale studie geïnitieerd: de NEDROP 2. Om dit te realiseren is wederom aan alle betrokken Nederlandse neonatologen en kinderartsen gevraagd om alle kinderen geboren in 2017, die volgens hen in aanmerking kwamen voor ROP-screening, aan te melden. De (kinder)oogartsen gaven vervolgens de oogheelkundige gegevens van de ROP-screening via een formulier door, waarna de twee data, indicatie en daadwerkelijke screening, aan elkaar werden gekoppeld. Net als in 2009 is 100% deelname van alle screenende en behandelende ziekenhuizen gerealiseerd.

In totaal werden 1287 kinderen aangemeld door neonatologen en kinderartsen, waarvan er 1087 (84.4%) zijn gescreend. Bij 307 kinderen is ROP vastgesteld, waarvan bij 49 stadium 3 of hoger en bij 36 type 1 ROP (behandelindicatie). In totaal zijn 39 kinderen behandeld, allen primair door middel van laserbehandeling van het netvlies (panretinale lasercoagulatie). Bij drie van hen was uiteindelijk sprake van progressie tot netvliesloslating (1 bilateraal ROP stadium 5, 2 unilateraal stadium 4a/4b). Samenvattend is in 2017 een screeningsreductie van 28.4% gerealiseerd en is de incidentie van ROP onder kinderen geboren met een AD <32 weken ongeveer gelijk gebleven. Opvallend echter is de toename in het aantal kinderen met ernstige ROP (stadium 3 of hoger) en het meer dan verdubbelde aantal ROP-behandelingen. Tegelijkertijd zijn van alle kinderen met ernstige ROP in 2009, 6/30 (20%) blind of slechtziend geworden door ROP versus 3/49 (6%) in 2017. Van alle overgeplaatste kinderen is 7.8% niet gescreend, in 2009 was dit nog 23.5%. Maar hoewel de kwaliteitsindicatoren tot een aanzienlijke verbetering hebben geleid ten opzichte van het jaar 2009, verschilt het risico op uitval in vergelijking met niet-overgeplaatste kinderen niet statistisch significant (2.4 vs. 1.1%, p=0.2).

Helaas wordt een forse toename van het aantal te behandelen kinderen gezien, waarvoor meerdere verklaringen zijn: enerzijds worden meer jongere kinderen in leven gehouden en neemt het risico op ernstige ROP onder prematuren toe door neonatale beleidsveranderingen. Anderzijds is de implementatie van de ETROP-criteria verbeterd, waardoor kinderen in een eerder stadium behandeld worden. En hoewel de resultaten van behandeling ten opzichte van het jaar 2009 zijn verbeterd, is het van groot belang dat deze lijn ook in de toekomst wordt vastgehouden om een nog grotere daling van het aantal kinderen dat blind of slechtziend wordt door ROP te realiseren. Concluderend heeft de succesvolle implementatie van de in 2013 geïntroduceerde richtlijn tot de afname van bijna een derde gescreende kinderen geleid. Hierbij is hoge detectie van ernstige ROP gewaarborgd en zijn de resultaten van ROP-behandeling (aantal kinderen met netvliesloslating) verbeterd.

In **Hoofdstuk 5** worden de neonatale risicofactoren opnieuw geanalyseerd, met als doel het evalueren of de huidige richtlijn, waarin een deel van de inclusiecriteria berust op specifieke risicofactoren, nog actueel is. De analyse is mogelijk gemaakt dankzij de koppeling van de

NEDROP-2 data aan de Nederlandse neonatale registratie (Perined). In Perined worden alle klinische gegevens van op Nederlandse neonatale intensive care units (NICU's) opgenomen pasgeborenen geregistreerd. De eerder geïdentificeerde risicofactoren – reeds opgenomen in de huidige richtlijn – werden opnieuw bevestigd. Er werden geen nieuwe risicofactoren gevonden, waarmee de huidige richtlijn voorts als veilig en betrouwbaar kan worden beschouwd.

ROP screeningsonderzoeken zijn stressvol voor het kind en tijdrovend voor de oogarts. Met een steeds groter wordende risicopopulatie is het in toenemende mate van belang de richtlijn kritisch te beoordelen op mogelijkheden tot veilige, verdere reductie van het aantal screeningsmomenten bij kinderen met een laag risico op ernstige ROP. **Hoofdstuk 6** beschrijft een uitgebreide analyse van diverse inclusiecriteria, op basis waarvan een nieuw screeningsmodel tot stand is gekomen met de volgende criteria: GA<30 weken **en** BW<1250 gram en kinderen met GA 30-32 weken en/of een BW 1250-1500 gram met de eerder beschreven factoren. Dezelfde strategie kwam ook in 2009 als meest kosteneffectief naar voren, maar wegens het grote verschil met de oude richtlijn, is toen gekozen voor minder stringente criteria (zie richtlijn 2013). Nu deze voor een tweede keer als kosteneffectief *en* veilig is geïdentificeerd, wordt de strategie als betrouwbaar beschouwd. De nieuwe screenings inclusiecriteria zullen opgenomen worden in de eerstvolgende ROP richtlijn, waarvan de implementatie in 2023 wordt verwacht. Hiermee zullen ten opzichte van het huidige protocol naar verwachting 24% minder baby's gescreend worden terwijl 100% detectie van ernstige ROP met behandelindicatie gewaarborgd blijft. Op jaarbasis leidt dit tot een kostenreductie van €59.454.

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Curriculum vitae

Kasia (Katarzyna) Trzcionkowska werd geboren op 14 maart 1990 te Warschau, Polen. In hetzelfde jaar verhuisde zij met haar moeder naar Nederland en groeide zij op in Haarlem. Voortkomend uit een muzikale familie, speelde zij sinds haar vijfde levensjaar viool. Dit bracht haar o.a. bij het Kennemer Jeugd Orkest waar zij lid en aanvoerder was en meerdere landelijke concoursen won. Na het behalen van haar VWO-examen aan het College Hageveld in Heemstede, begon zij – na een reis door Australië – aan haar studie geneeskunde aan de universiteit Maastricht. In deze tijd werd zij bestuurslid van AIESEC Maastricht en verkozen tot AIESEC Ambassadeur in Peru.
Met oogheelkunde kwam zij in aanraking tijdens het coschap bij Eyescan in Sittard, onder begeleiding van Drs. Marianne van den Maegdenbergh. Hierna deed zij ook haar keuzecoschap, semiarts- en wetenschapsstage in de oogheelkunde. In april 2016 werd zij aangenomen voor het promotieonderzoek naar prematurenretinopathie in het LUMC, de NEDROP 2. Dit onderzoek zette zij voort na haar afstuderen tot arts in februari 2017.

De resultaten van het onderzoekswerk werden gepresenteerd op meerdere binnen- en buitenlandse congressen, waaronder European Paediatric Ophthalmological Society EPOS in Riga, Letland en The Association for Research in Vision & *Ophthalmology (*ARVO) in Vancouver, Canada, waarbij meerdere onderscheidingen werden toegekend, waaronder een travel grant (reisbeurs). Haar onderzoek leidde tot de nieuwe Nederlandse richtlijn prematurenretinopathie, die in november 2023 is geïmplementeerd.

Per 1 februari 2020 is Kasia in opleiding tot oogarts in het LUMC (opleiders prof. dr. N.E. Schalij-Delfos en prof. dr. G.P.M. Luyten).