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## **The Netherlands retinopathy of prematurity study**

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# Chapter 4

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

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## ABSTRACT

### *Objectives*

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

### *Study design*

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

### *Results*

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

### *Conclusion*

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

## INTRODUCTION

Retinopathy of prematurity (ROP) accounts for 5.5%-20% of childhood blindness in developed countries.<sup>1</sup> Improvement in neonatal care during the past 2 decades has increased the survival of prematurely born infants and lowered the gestational age (GA) and birth weight (BW) of survivors.<sup>2</sup> Several studies demonstrated that this decrease in mortality was accompanied by an increase in significant neonatal morbidities such as severe ROP.<sup>3,4</sup> ROP is a condition confined to the developing retinal vasculature in the prematurely born infant and develops in 2 phases. Vascularization of the retina begins at 16 weeks' and reaches the peripheral retina at 40 weeks' gestation. When infants are born prematurely, the growth of vessels ceases, leaving an incompletely vascularized peripheral retina. Insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are crucial to the normal development of retinal vessels. IGF-1 is produced by the placenta, and preterm birth results in decreased levels of serum IGF-1. Very prematurely born infants cannot produce sufficient IGF-1, and its concentration may be further reduced by sepsis, acidosis, and poor nutrition, which are frequent conditions in those infants. These low levels of IGF-1 are coresponsible for the cessation of retinal vessel outgrowth. The expression of VEGF is regulated by oxygen. ROP can be initiated immediately after premature birth by relative hyperoxia, as supplemental oxygen but also room air increases retinal oxygen saturation to levels far greater than those in utero. Most preterm infants do not get ROP, but in those who do, this hyperoxia suppresses the production of VEGF, resulting in a hypoxic, avascular retina. Subsequently, chronic hypoxia leads to compensatory, excessive VEGF synthesis, causing pathologic neovascularization.<sup>5,6</sup>

Because oxygen and the extent of the avascular peripheral retina play a key role in the pathogenesis of ROP, factors influencing oxygen levels as well as factors responsible for large areas of avascularity are expected to be associated with an adverse outcome. Low GA, low BW, and factors related to general illness such as length of stay (LOS) on a neonatal intensive care unit (NICU), duration of artificial ventilation, and the administration of supplemental oxygen are established risk factors.<sup>7</sup>

Screening and treatment protocols vary by country and may result in differences in incidence and risk factors for ROP. To provide optimal care for premature infants at risk, a nationwide inventory was conducted to provide up-to-date insight on the incidence and potential risk factors for ROP in the Netherlands.

## METHODS

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



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

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

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

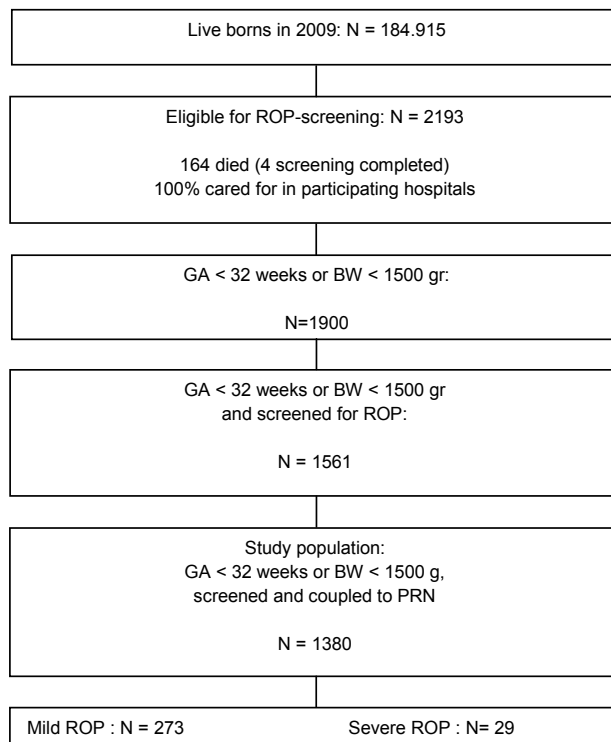
### ***Statistical Analyses***

GA and BW are presented as median values with the IQR (25th-75th percentile). The occurrence of risk factors in the study population and the incidence of ROP were tabulated as numbers and percentages. Some of the characteristics such as sex, small for gestational age, duration of artificial ventilation, duration of O<sub>2</sub>, and LOS on NICU were not filled out for every patient in the Netherlands Perinatal Registry.

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

## RESULTS

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



**Figure 1** Flowchart of the study.





**Table 1** Descriptive statistics

		N	ROP %	
N		1380	302 (21.9)	
Characteristic		N (%)	characteristic +	characteristic –
Female gender		527 (44.7)	20.5	21.7
Extremely low BW (<1000g)		323 (23.4)	51.1	13.0
Small for GA (<P10)		106 (9.0)	23.6	25.9
Multiple birth		404 (29.4)	19.3	23.0
Duration of AV	yes, ≤7 days	360 (30.5)	21.4	
	yes, >7 days	169 (14.3)	53.3	
	No	650 (55.1)	12.6	
Duration of O <sub>2</sub>	yes, ≤28 days	484 (44.9)	16.3	
	yes, >28 days	210 (19.5)	50.9	
	No	383 (35.6)	13.8	
LOS NICU	yes, ≤28 days	789 (67.1)	12.2	
	yes, >28 days	259 (22.0)	51.0	
	No	128 (10.9)	14.1	
BPD		65 (4.7)	58.5	20.1
Patent ductus arteriosus		235 (17.0)	40.9	18.0
Sepsis		404 (29.3)	31.7	17.8
IVH / PVH		207 (15.0)	30.9	12.2
iNO		23 (1.7)	47.8	21.4
Prenatal glucocorticoids		622 (45.1)	19.6	23.7
Postnatal glucocorticoids		78 (5.7)	57.7	19.7
IRDS		663 (48.0)	26.7	17.4
NEC with perforation		27 (2.0)	63.0	21.1
Hyperglycaemia (>8mmol/l)		139 (10.1)	45.3	19.3
Packed cells		549 (39.8)	33.9	14.0

ELBW, extremely low birth weight; IVH/PVH, intra- periventricular hemorrhage; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; SGA, small for GA.

The denominator is 1380 except for some characteristics with missing data: female sex (n = 1180), small for GA (n = 1176), multiple birth (n = 1372), duration of artificial ventilation (n = 1179), duration of supplemental O<sub>2</sub> (n = 1077), and LOS at NICU (n = 1176).

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

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

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

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

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

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

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

IRDS, infant respiratory distress syndrome; PVL, periventricular leukomalacia.

Significant risk factors are in italic.



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

## DISCUSSION

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

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

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

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

There might be doubt whether iNO is correlated to supplemental oxygen use, artificial ventilation, or just following the severity of disease reflected in the time spent at a NICU. However, in this study, iNO continued to be significant after correction for such variables. It is postulated that VEGF is an important mediator in the development of ROP. The relationship between iNO and ROP may be explained by the acutely increased oxygen saturation after the initiation of iNO treatment. This hyperoxia is also present in the retina. High oxygen tensions damage immature retinal capillary endothelial cells, thereby preventing complete vascularization, and cause further downregulation of VEGF, which compromises outgrowth of retinal vessels, thus facilitating the vaso-obliterative first phase of ROP. Because of its rapid effects, iNO therapy is also associated with large fluctuations in arterial pO<sub>2</sub>, another known risk factor for ROP.<sup>23</sup> These fluctuations may cause an imbalance of VEGF and therefore additionally enhance the negative effect on outgrowth of retinal vessels.

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



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

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