# Nationwide Inventory of Risk Factors for Retinopathy of Prematurity in the Netherlands

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**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. *(J Pediatr 2014;164:494-8)*.

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

Because oxygen and the extent of the avascular peripheral retina play a key role in the pathogenesis of ROP, factors influencing oxygen levels as well as factors responsible for large areas of avascularity are expected to be associated with an adverse outcome. Low GA, low BW, and factors related to general illness such as length of stay (LOS) on a neonatal intensive care unit (NICU), duration of artificial ventilation, and the administration of supplemental oxygen are established risk factors.[7] Screening and treatment protocols vary by country and may result in differences in incidence and risk factors for ROP. To provide optimal care for premature infants at risk, a nationwide inventory was conducted to provide up-to-date insight on the incidence and potential risk factors for ROP in the Netherlands.

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| BPD | Bronchopulmonary dysplasia | LOS | Length of stay |
| BW | Birth weight | NEDROP | Netherlands Retinopathy of Prematurity |
| CLD | Chronic lung disease | | |
| DOB | Date of birth | NICU | Neonatal intensive care unit |
| GA | Gestational age | ppm | Parts per million |
| IGF-1 | Insulin-like growth factor-1 | ROP | Retinopathy of prematurity |
| iNO | Inhaled nitric oxide | VEGF | Vascular endothelial growth factor |

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## Methods

The Netherlands ROP (NEDROP) study is a multicenter, prospective, approximating population-based study in which investigators analyzed all infants born in 2009 eligible for screening of ROP according to the prevailing guideline: GA <32 weeks or BW <1500 g or preterm birth and treatment with ≥40% supplemental oxygen for more than 3 days. Pediatricians and ophthalmologists of the 103 Dutch hospitals involved in care for premature infants reported all infants entitled for ROP screening to the study center. Ophthalmologists reported all infants actually screened for ROP as well as ROP classification, the presence of "plus disease" (additional signs of active disease), screening schedule, and whether there was need for treatment. ROP was classified according to the International Classification of ROP, the highest stage in either eye being reported.[8]

Data entry in the NEDROP database was coordinated, centralized, and handled by one investigator (A.v.S.). To comply with patient privacy regulations, infants were reported anonymously with initials, zip code, date of birth (DOB), GA, and BW. The NEDROP database was merged with the already-existing Netherlands Perinatal Registry, which is a medical, professional-based registry where pediatricians and neonatologists report their data of neonates born in the Netherlands. Contribution to the Netherlands Perinatal Registry is obligatory for NICUs and high-care centers and voluntary for regional centers of which 50% participate. All infants born with a GA <30 weeks and 85%-90% of infants with GA 30-32 weeks are admitted to a NICU. Yearly, more than 95% of infants born <32 weeks' gestation are reported to the Netherlands Perinatal Registry.

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

### Statistical Analyses

GA and BW are presented as median values with the IQR (25th-75th percentile). The occurrence of risk factors in the study population and the incidence of ROP were tabulated as numbers and percentages. Some of the characteristics such as sex, small for gestational age, duration of artificial ventilation, duration of $O_2$, 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 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 the **Figure**, and clinical characteristics are shown in **Table I**.

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 II**). 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 ROP (OR 2.6, 95% CI 1.1-6.2,