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# The incidence of visual impairment due to ROP and concomitant disabilities in the Netherlands: A thirty year overview.

*Key-words: Retinopathy of Prematurity (ROP) – visual impairment - concomitant disabilities - incidence*

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## **Abstract**

**Purpose:** Determine the incidence of visual impairment (VI) caused by Retinopathy of Prematurity (ROP) and the concomitant disabilities in preterm neonates born between 2000 and 2009 in The Netherlands.

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

**Results:** Records of 42 infants with VI due to ROP were included. A gradual decrease of gestational age and birth weight but an increase of duration of artificial ventilation, supplemental oxygen administration, bronchopulmonary dysplasia, developmental delay and behavioral abnormalities was found. Compared to the previous study (1994-2000) significantly less children were visually impaired due to ROP (1.84 per 100.000 live births/year vs 3.93 per 100.000 live births/year,  $p=0.000$ ), the incidence of complete blindness decreased from 27.5% to 7.1% ( $p<0.05$ ) and more children were treated (66.7% vs 56.9%, ns). The incidence of concomitant disabilities was again high and did not differ a lot from the previous study.

**Conclusion:** Retrospective study showing a significant decrease in VI due to ROP in the Netherlands. Changes in neonatal care did not result in a decrease of concomitant disabilities. More children were treated for ROP, but still 33% were not.

## **Introduction**

Retinopathy of prematurity (ROP) is still one of the most important causes of partial sight or blindness in premature born infants. In developed countries, ROP accounts for 5.5 to 20% of childhood blindness.<sup>1-4</sup>

The pathogenesis of ROP is multifactorial, but the most significant risk factors for ROP are low gestational age and low birth weight.<sup>5-7</sup> Changes in neonatal care over the past two decades have increased survival of very small and very preterm born infants. This shift was due to introduction of surfactant, increased use of antenatal steroids, resuscitation of infants with lower gestational age, improved nutrition and prophylactic use of indomethacin. Due to this increased survival, a larger number of very preterm infants is at risk not only for visual impairment (VI) caused by ROP but also for non-visual handicaps.<sup>8,9,10</sup> Apart from changes in neonatal care, there have been changes in management of ROP. To reduce the number of adverse outcomes, treatment in the pre-threshold phase was introduced, resulting in an increased number of infants treated for ROP.<sup>5;11;12</sup>

From 1952 onwards, five surveys were carried out in the Netherlands to calculate the number of visually disabled children due to ROP per 100.000 live births per year: 3.24/100.000 from 1952–1964 [Schappert-Kimmijser; survey 1], 2.89/100.000 from 1961-1973 [vd Pol; survey 2], 4.22/100.000 from 1975-1987 [Cats; survey 3], 5.49/100.000 from 1986-1994 [Schalij-Delfos; survey 4] and 3.85/100.000 from 1994-2000 [Termote; survey 5]. The last 3 surveys also included an inventory of concomitant disabilities, showing a marked increase of developmental and behavioral abnormalities. To monitor trends and to determine the incidence of VI caused by ROP as well as the incidence of associated disabilities in these high-risk, vision-impaired children born between 2000 and 2009, a retrospective study was performed [survey 6]. Data of the last 3 surveys were used for comparison, resulting in an overview of more than three decades.

## **Patients and Methods**

Due to privacy regulations and lack of an obligatory registry for children with VI in our country, the access to patient data is limited. Therefore, data retrieval was only possible by collecting the records of all infants with a registered diagnosis of ROP, who are known at one of the Dutch institutes for the partially sighted and blind. This information was obtained by one investigator (AvS).

For comparison the same neonatal and ophthalmological data as in the previous surveys were collected: gestational age (GA), birth weight (BW), visual acuity, treatment for ROP, sex, multiple birth, incidence of bronchopulmonary dysplasia (BPD) and duration of supplementary oxygen administration, artificial ventilation (AV) and admission to the Neonatal Intensive Care Unit (NICU). With regard to concomitant disabilities the same definitions and classifications as described by Termote were used.<sup>13</sup> We considered children to be multiple disabled when they had VI caused by ROP plus one or more of the concomitant disabilities that were listed, excluding BPD as pulmonary function usually improves through the years.

To define VI, the recommendations of the International Association for Prevention of Blindness (IAPB) were used (WHO 1984). Due to limitations in data collection, information on stages of ROP was unreliable and therefore again excluded. As the number of infants with cerebral visual impairment (CVI) increased over the last decade and became the most important cause of VI in prematurely born infants<sup>14</sup>, data on CVI were collected for this survey. They could however not be compared to the previous studies.

Dutch birth rate figures were obtained from the Central Bureau of Statistics (CBR). Survival rates of premature infants according to gestational age were collected from the Dutch Neonatal Registration. The study was approved by the Medical Ethical Committees of all participating institutes for the partially sighted and blind and children were included when informed consent was obtained.

Data collected for this study (2000-2009) were compared to data from the previous study (1994-2000). Besides, data of the four surveys conducted from 1975 onwards were compared to evaluate which trends in treatment and outcome could be seen.

**Statistical analysis** Clinical data of the four surveys as presented in table 1 were evaluated using the independent samples t-test. The Poisson regression was used to calculate figures on VI caused by ROP in relation to Dutch birthrates and the chi-square test for all other data. Differences with a p-value of <0.05 were considered significant. As all children with VI due to ROP were studied in the subsequent periods, trends could be determined even though the separate values failed to reach significance.

## **Results**

Records of 43 children with VI caused by ROP were found. Informed consent was obtained from 42 parents. No additional infants born between 1994 to 2000 (survey 5) registered with the diagnosis of ROP were found during survey 6.

General and neonatal data of infants diagnosed with ROP in four consecutive periods in The Netherlands are presented in table 1. Compared to the previous study (1994-2000) no significant differences were found. However, a gradual decrease of mean GA and BW over the years was seen. For supplemental oxygen and AV a significant increase was found between survey 3 and 4, but there were no significant changes since the mid-eighties. Not all infants from survey 3 and 4 were admitted to a NICU, so admission days to a NICU were only analyzed for the fifth and sixth period, for which there was no significant difference.

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

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

<sup>1</sup> column 1 vs column 2 p= 0,004, 1 vs 4 p=0.004, 2 vs 3, 3 vs 4 and 2 vs 4 ns

<sup>2</sup> column 1 vs 2 ns, 1 vs 3 p=0.001, 1vs 4 p=0.003, 2 vs 3 p=0.032, 3 vs 4 ns, 2 vs 4 p=0.03

<sup>3</sup> column 1 vs 2 p=0.003, 1 vs 3 p=0.005, 1 vs 4 p =0.004, 2 vs 3, 3 vs 4 and 2 vs 4 ns

<sup>4</sup> column 1 vs 2 p=0.0009, 1 vs 3 p=0.004, 1 vs 4 p=0.004, 2 vs 3, 3 vs 4 and 2 vs 4 ns

<sup>5</sup> column 3 vs 4 ns

Although no significant differences were found in clinical data of children from the present study as compared to the previous study, the proportion of infants with VI caused by ROP in relation to Dutch birthrates decreased significantly (table 2).

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

Period / Number	No. ROP sequelae	No. live births x 10 <sup>5</sup> *	ROP sequelae / 100.000 live births
1952 – 1964 <sup>15</sup> (survey 1)	100	30.9	3.24
1961 – 1973 <sup>16</sup> (survey 2)	89	30.8	2.89
1975 – 1987 <sup>17</sup> (survey 3)	97	23.0	4.22
1986 – 1994 <sup>18</sup> (survey 4)	79	14.4	5.49
1994 – 2000 <sup>13</sup> (survey 5)	46	11.7	3.93
2000 – 2009 (survey 6)	32	17.4	1.84

\*Central Bureau of Statistics for the Netherlands

The average incidence of VI due to ROP is presented column 3 is the result of the fraction of the absolute number of individuals with ROP sequelae (column 1) and the absolute number of individuals born during the study period (column 2). The average incidence of VI due to ROP shows a decrease since the early nineties.

A decline can be seen starting in the mid-nineties. The incidence of VI due to ROP decreased in the period 1994-2000 but failed to reach significance when compared to period 1986-1994 ( $p=0.07$ ).

Comparing our study to survey 4 and 5 a significant decrease of the incidence of VI caused by ROP was found ( $p=0.000$  for both). More specific data on visual acuity are presented in table 3.

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

Period	1975 – 1987 survey 3	1986 – 1994 survey 4	1994 – 2000 survey 5	2000 – 2009 survey 6
No. Infants	76	87	51	42
Visual acuity unspecified	5.1%			
Not partially sighted or blind (VA>0.3) <sup>+</sup> 1	2%	10.3%	9.8%	23.8%
Partially sighted (VA 0.1 – 0.3)	34.3%	31.0%	25.5%	38.1%
Socially blind (VA < 0.1 - ≥ 1/60)	12.1%	10.3%	11.8%	14.3%
Practically blind (VA < 1/60 – LP)	8.1%	21.8%	25.5%	16.7%
Completely blind (VA = 0) <sup>2</sup>	38.4%	26.4%	27.5%	7.1%
Treatment of acute ROP <sup>3</sup>	24.4%	43.9%	56.9%	66.7%

<sup>+</sup> = infants with unilateral blindness and infants whose vision is expected to deteriorate in the future

LP= light perception

VA= visual acuity

<sup>1</sup> 1 vs4 p= 0.000, 2 vs 4 p= 0.043

<sup>2</sup> 1 vs 4 p=0.000, 2 vs 4 p=0.010 and 3 vs4 p=0.012

<sup>3</sup> 1 vs 2 p=0.013, 1 vs 3 p=0.000, 1 vs 4 p=0.000, 2 vs 4 p=0.014

In the current study there were 32 of 42 infants (76.2%) with VI, compared to 46 of 51 children (90.2%) in survey 5, representing a non significant decrease. In more detail, our survey shows a significant decrease of completely blind children due to ROP compared to the previous period (7.1% vs 27.5%; p=0.012) as well as a significant increase of children who did not fulfill the WHO criteria for VI at the moment of inclusion in this study (23.8% vs 9.8%; p=0.043). Eight children (19%) were diagnosed with CVI: 2 not partially sighted or blind, 4 partially sighted, 1 socially and 1 practically blind. The number of children who were treated for ROP significantly increased since period three, but there was no significant increase between period 5 and 6.

Infants were treated with laser (n=16), cryo (n=1), laser + cryo (n=2), cerclage (n=1), cerclage + laser (n=1), cerclage + cryo (n=1), vitrectomy + lensectomy (n=2), vitrectomy + laser (n=2), vitrectomy + laser + lensectomy (n=1) or bevacizumab (n=1). Most common therapy used was laser (79%).

Fourteen infants (33.3%) of the present study had not been treated against 22 (43.1%) in the previous study. Four of the untreated children in this study had a final VA > 0.3 at least in one eye.

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

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

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

<sup>1</sup> period 1 vs 2 p=0.009, 1 vs 3 p=0.000, 3 vs 4 p= 0.016

<sup>2</sup> 1 vs 2 p= 0.028, 1 vs 3 p= 0.000, 1 vs 4 p= 0.000, 2 vs 3 p= 0.000, 2vs 4 p= 0.027, 3 vs 4 ns

<sup>3</sup> 1 vs 3 p= 0.049 and 3 vs 4 p=0.007

<sup>4</sup> 2 vs 4 p=0.024

<sup>5</sup> 1 vs 4 p=0.003

<sup>6</sup> 1 vs 2 p=0.013

<sup>7</sup> 1 vs 2 p=0.015 , 1 vs 3 p=0.0011 vs 4 p=0.001

In the previous study a significant increase in behavioral abnormalities was seen, but this tendency did not extend to the current study. A gradual increase of children with BPD, developmental delay and hearing deficit can be observed, but differences did not reach significance. The number of infants with neurological handicaps and a multiple disability increased significantly between survey 3 and 4 but was quite stable afterwards.

When the population was split up for GA, the incidence of VI caused by ROP based on the estimated number of survivors as well as the incidence of concomitant disabilities in period 5 and 6, was the highest in children under 30 weeks and concerning VI, increased as GA decreased (table 5). The five infants with unilateral blindness (n=1) or VA > 0.3 (n=4) were also included in this analysis, because this was also done in the previous studies.

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

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

\* Numbers of estimated survivors were derived from The Netherlands Perinatal Registry

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

## **Discussion**

We performed a retrospective study on the incidence of VI due to ROP in preterm infants born between 2000 and 2009 in the Netherlands. The incidence presented in this study must be considered as a minimum incidence because there is no obligatory national registry for VI, children may be missed and there is always a possibility that children born in the study period will become visually impaired at a later age. However the same applied for earlier studies and no additional infants of the previous periods were found during our current search. Data were compared with three earlier Dutch studies starting in 1975 (survey 3, 4 and 5), thus providing an overview of more than thirty years.

Over the years there has been an increase of survival of smaller and more immature infants due to changes in neonatal care.<sup>19</sup> From 1975 till now mean GA and BW of infants with VI due to ROP in the Netherlands gradually decreased. Although we found no significant changes in neonatal data in infants with VI in the present study compared with the former one, we found a decrease in VI due to ROP. It seems reasonable to assume that improvement in neonatal care might contribute to a better visual outcome of these preterm neonates. An important limitation is that we could not have more insight in detailed information about the neonatal period. From other Dutch studies covering approximately the same period we can learn more about general changes that have taken place. Two

Dutch cohort studies from *Hoogerwerf*<sup>20</sup> and *Groenendaal*<sup>21</sup> demonstrated an improvement in outcome. *Groenendaal et al* analyzed two cohorts of inborn preterm neonates (1997-2001) and (2002-2006) with a GA of 25–29.9 wks and found an improved survival but no increase in the number of infants treated for severe ROP. The study from *Hoogerwerf et al* focused on changes in the incidence and risk factors responsible for the development of ROP and compared two cohorts of prematures born in the time period of 1991-1995 and 2001-2005. They found an increase in the use of antenatal steroids and surfactant and a decrease in duration of AV, supplemental O<sub>2</sub> administration and NICU admission as well as a decrease in incidence of ROP. Most of these changes were not reproducible in our study. However, we included only those infants that were referred to one of the Dutch institutes for the visually impaired and were supposedly the most critically ill neonates. We speculate that more subtle improvements in neonatal care are responsible for the decrease of the incidence of VI caused by ROP and of completely blind children. Furthermore there was an increase in infants treated for ROP (from 56.9 to 66.7%). The Early Treatment criteria (ETROP) were introduced in the early phase of this survey resulting in a larger number to treat and an expected reduction of adverse outcomes.<sup>3;11;12</sup> Besides, the former study resulted in a campaign for more awareness of necessity to treat timely and for potential visual problems on the long term. Earlier referral to the institutes together with changed treatment criteria could be an additional explanation for the significantly higher number of infants with a VA > 0.3 found in the current study and the significant decrease in VI due to ROP. Although more infants received treatment in the current study, still 33 % did not of which 10 had a VA < 0.3. *Haines et al*<sup>22</sup> also distinctly described that, even after implementation of screening guidelines, some children developed VI due to non-adherence to the screening protocol.

Studies from the UK on VI due to ROP as a proportion of childhood VI, covering the same period<sup>4;23</sup> show a tendency that compares favorably with our surveys. A study of *Schiariti et al*<sup>1</sup>, demonstrated an increase of ROP as well as severe ROP without changes in the rate of VI when comparing neonates born in 1992-1996 and 1997-2001. *Slidsborg et al*<sup>5</sup> found a more than twofold increase in the incidence of treated ROP cases born in Denmark from 2001 to 2005, compared with 1996-2000. This increase was most pronounced for the smallest infants. The number of infants with VI or blindness caused by ROP was stable. These studies also attribute the decline of VI due to ROP to a more complete ophthalmic surveillance, earlier treatment and improvement in neonatal care.

Compared to the earlier Dutch surveys, again most children with VI caused by ROP were surviving preterm neonates < 30 wks of gestation. This group of infants also showed the highest incidence of concomitant disabilities. Although a substantial number of infants had 1 or more concomitant disabilities (73.8%), no significant changes were found compared to the study of Termote. Inexplicably, no children with epilepsy were registered in the present study. BPD, developmental delay and hearing deficit gradually increased whereas behavioral abnormalities, multiple disabilities and neurological handicaps decreased minimally. A Dutch study of *van Baar et al*<sup>24</sup> showed a clear association between preterm birth and multiple disabilities at 5.5 years of age in 157 children born before 30 weeks GA. One or more disabilities were found in 75%. Several other studies conclude that the survival rate for extremely preterm born infants has improved over the past decade, but that the

overall prevalence of neurodisability after preterm birth has not fallen thus supporting the findings in our study.<sup>8;9;10</sup>

This overview over more than 30 years shows a decrease in GA and BW and a gradual increase in AV and supplemental oxygen administration with a turning point in the early nineties when novel treatments such as surfactant treatment, high frequency oscillation (HFO), postnatal steroids and inhaled NO were introduced. The incidence of VI caused by ROP decreased over the past thirty years with the most obvious change seen in the last period. Additional changes in neonatal care such as antenatal steroids and antenatal antibiotics together with earlier treatment for ROP could be an explanation. However, these changes did not result in a decrease of concomitant as well as multiple disabilities.

Although more children were treated, still 33% were not. Therefore, it can not be emphasized enough that timely screening, follow up and treatment as well as close collaboration of all professionals involved in the care of these at risk neonates should be our aim for the future to further decrease the number of children with VI caused by ROP. As long as GA and BW of survivors decline, it seems a more difficult task to diminish the number of multiple disabled children.

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