Screening for Retinopathy of Prematurity in Infants Born Before 27 Weeks’ Gestation in Sweden

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Objective: To analyze screening for retinopathy of prematurity (ROP) during a 3-year period in a national cohort of infants born before 27 weeks’ gestation.

Methods: A national prospective study of neonatal morbidity in extremely preterm infants was performed in Sweden between April 1, 2004, and March 31, 2007. Screening for ROP was to start in the fifth postnatal week and to continue weekly until complete vascularization of the retina or until regression of ROP.

Results: The first eye examination was performed no later than the sixth postnatal week in 84.8% of 506 infants, and the last examination was performed at postmenstrual age (PMA) of 38 weeks or later in 96.2% of infants. The mean and median numbers of days between examinations in the total cohort were 8.6 and 7.9 days, respectively (range, 1–27.8 days), and the mean and median numbers of examinations were 12 and 10, respectively. Most infants were treated during a limited period (eg, at PMA of 39 weeks, 75.0% of infants had been treated).

Conclusions: The objective of screening for ROP is timely detection of ROP before reaching treatment criteria, ie, type 1 ROP, according to the Early Treatment for ROP recommendations. In our population of infants born before 27 weeks’ gestation, the first examination could safely be postponed until PMA of 31 weeks because the onset of ROP stage 3 did not occur before then and criteria for treatment were not reached before PMA of 32 weeks. Gestational age at birth and PMA at the time of examination should be considered when deciding when and where the next examination should be performed.

guidelines. The objective of the present article is to evaluate screening routines for ROP among the extremely preterm population in Sweden, with special emphasis on the start, frequency, and termination of screening examinations.

Methods

This study is part of a national population–based project, the Extremely Preterm Infants in Sweden Study. (See “Additional Contributions” on page 171.) All infants born before 27 weeks' gestation and surviving at least until the first eye examination were included during a 3-year period between April 1, 2004, and March 31, 2007.

A national network of screening ophthalmologists was organized to continuously collect and record data from ROP screening. According to the study protocol, screening was to start at postnatal age (PNA) 5 weeks, and infants were to be examined weekly. In infants with no or mild ROP (stages 1 and 2) without progression at the most recent examinations, further examinations were performed each week or every other week from PMA of 35 weeks onward. Examinations were to continue until the retina was completely vascularized (ie, at term) or until regression of ROP. Retrospectively, if regression of ROP and peripheral vascularization were prolonged, an interval between examinations of 1 month or longer was considered the end of screening. To categorize ROP, we used the International Classification of Retinopathy of Prematurity revisited,18 and the Early Treatment for Retinopathy of Prematurity recommendations were followed for treatment.2

After ROP screening was completed, the screening protocol of each infant was sent to Uppsala University Hospital, Uppsala, Sweden, where the findings were entered into a database, which also contained obstetric and neonatal data. Further details about the methods, examination techniques, and logistics are given in previous publications.13-15

Mild ROP was defined as ROP stages 1 and 2 and severe ROP as ROP stages 3 to 5. Postmenstrual age was defined as GA at birth plus PNA (ie, the number of weeks [and days] after birth. Gestational age denotes time from the last menstrual period to birth, estimated by ultrasonographic examination at PMA of 17 or 18 weeks.

The study was approved by the Ethics Committee, Faculty of Medicine, Lund University, Lund, Sweden. No informed consent was needed because the project was considered a quality assuring project and a health register.

Results from statistical analyses and descriptive data for means, medians, percentiles, and quartiles were obtained using commercially available software (Gauss; Aptech Systems Inc, Maple Valley, Washington). All objectives for GA at birth (divided into groups of 22, 23, 24, 25, or 26 weeks) relative to the continuous variables considered were investigated using nonparametric Kruskal-Wallis test. If specified, simple linear regression analyses were also performed using GA at birth as a continuous variable.

Results

The first eye examinations in the total population of 506 infants were performed at mean and median PNAs of 6 and 5 weeks, respectively (range, 4.0-13.6 weeks), and at a mean and median PMA of 31 weeks (range, 27.4-38.1 weeks). With increasing GA at birth, PNA at the first examination was significantly decreased and PMA significantly increased (P < .001 for both).

In 71.1% (360 of 506) of infants, examinations were started during or before the fifth postnatal week, as recommended, and in 84.8% (429 of 506) of infants, examinations were started before the seventh postnatal week. Ninety-nine percent of infants had their first examination before PNA of 11 weeks. For PMA, the first examination was performed before the 31st week in 47.6% of infants and before the 35th week in 99.0% of infants. Only 5 infants had their first examination as late as between PMAs of 35 and 38 weeks.

For age at last eye examination, 6 infants who died before screening was terminated and 99 infants who were treated for ROP were excluded from the analyses. The last eye examination in the remaining 401 infants was performed at mean and median PNAs of 18 and 16 weeks, respectively (range, 7.6-42.6 weeks), and at mean and median PMAs of 44 and 42 weeks, respectively (range, 34.4-67.4 weeks). The PNA and PMA at the last examination were significantly decreased with increasing GA at birth (P < .001). Postmenstrual age at the last exami-

Table 1. Postmenstrual Age (PMA) at the Last Examination in 401 Nontreated Infants

<table>
<thead>
<tr>
<th>ROP</th>
<th>No. of Infants</th>
<th>Mean</th>
<th>5th Percentile</th>
<th>50th Percentile</th>
<th>95th Percentile (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>135</td>
<td>40.4</td>
<td>36.3</td>
<td>40.0</td>
<td>44.3 (34.4-61.6)</td>
</tr>
<tr>
<td>Mild</td>
<td>189</td>
<td>44.0</td>
<td>39.0</td>
<td>42.7</td>
<td>52.1 (36.0-67.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>77</td>
<td>48.1</td>
<td>39.4</td>
<td>47.7</td>
<td>63.4 (38.6-66.6)</td>
</tr>
<tr>
<td>Total</td>
<td>401</td>
<td>43.6</td>
<td>38.1</td>
<td>41.6</td>
<td>54.6 (34.4-67.4)</td>
</tr>
</tbody>
</table>

Abbreviation: ROP, retinopathy of prematurity.

Six infants who died before screening was terminated were excluded.

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nation in infants with no, mild, or severe ROP is given in Table 1. In 96.2% of infants, the last examination was performed at PMA of 38 weeks or later. Ninety-nine percent of infants had their last examination in the 36th week or later. Only 5 infants had their last examination before the 36th week. Among infants treated for ROP, the last examination was performed at mean and median PMAs of 49 and 48 weeks, respectively.

The mean and median numbers of examinations in the total population (503 infants with available information) were 12 and 10, respectively (range, 1-30). The number of examinations decreased significantly with increased GA at birth (P < .001) (Figure 1). The mean and median numbers of days between examinations in the total cohort were 8.6 and 7.9 days, respectively (range, 1-27.8 days). The mean interval between examinations was 2 weeks or less in 95.4% of infants and 3 weeks or less in 99.6% of infants.

For evaluation of the start of screening, we analyzed PMA at onset of ROP stage 3 (Table 2) and at the first treatment for each week of GA at birth (Table 3). Data on the right eyes only are presented, as a high degree of symmetry between stages of ROP in the 2 eyes was previously reported (P < .001). Analyses showed a significant reduction of PMA with decreasing GA at birth for onset of ROP 3 and for the first treatment (P < .01 for both).

Table 2. Postmenstrual Age (PMA) at the Onset of Retinopathy of Prematurity (ROP) Stage 3 in 157 Right Eyes Relative to Gestational Age (GA) at Birth

<table>
<thead>
<tr>
<th>GA at Birth, wk</th>
<th>No. of Right Eyes</th>
<th>PMA at the Onset of ROP Stage 3, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st Percentile</td>
</tr>
<tr>
<td>22</td>
<td>4</td>
<td>32.3</td>
</tr>
<tr>
<td>23</td>
<td>29</td>
<td>31.6</td>
</tr>
<tr>
<td>24</td>
<td>46</td>
<td>31.7</td>
</tr>
<tr>
<td>25</td>
<td>49</td>
<td>32.0</td>
</tr>
<tr>
<td>26</td>
<td>29</td>
<td>33.4</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>31.7</td>
</tr>
</tbody>
</table>

Table 3. Postmenstrual Age (PMA) at the First Treatment in 96 Right Eyes Relative to Gestational Age (GA) at Birth

<table>
<thead>
<tr>
<th>GA at Birth, wk</th>
<th>No. of Right Eyes</th>
<th>PMA at the First Treatment, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st Percentile</td>
</tr>
<tr>
<td>22</td>
<td>4</td>
<td>32.9</td>
</tr>
<tr>
<td>23</td>
<td>21</td>
<td>32.1</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>32.1</td>
</tr>
<tr>
<td>25</td>
<td>28</td>
<td>34.0</td>
</tr>
<tr>
<td>26</td>
<td>13</td>
<td>34.3</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>32.1</td>
</tr>
</tbody>
</table>

Our study evaluating ROP screening in extremely pre-term infants born before 27 weeks’ gestation in Sweden shows that there was good compliance with the screening protocol among participating colleagues. The first eye examination was performed no later than in the sixth post-natal week among 84.8% of infants, the last examination was performed at PMA of 38 weeks or later among 95.4% of infants, and the screening interval was 2 weeks or less among 95.4% of infants. This discussion will further analyze our results and their implications for the start, frequency, and termination of screening examinations.

The study protocol prescribed ROP screening from the fifth postnatal week onward. In 15.2% of infants, the first eye examination was performed later than the sixth postnatal week, but the first examination was markedly delayed in only 6 infants (1.2%) (ie, they had their first eye examination at PMA of ≥35 weeks or at PNA of ≥11 weeks). One of these 6 infants was not referred from the neonatologist, and 5 infants were transferred to other hospitals before the start of ROP screening, which might explain the delay. One of the latter 5 infants subsequently developed ROP stage 3 but did not reach treatment criteria until 4 weeks later. Our findings emphasize the importance of scheduling further eye examinations in the receiving hospital before transfer of an infant, a fact that is highlighted in American and British guidelines for ROP screening.

The objective of ROP screening is timely detection of severe ROP and initiation of treatment at the correct time. It seems reasonable that timing of the first eye examination should be designed to detect at least 99% of severe ROP. In accord with Palmer et al, it was previously shown that onset of severe ROP correlates significantly with PMA but not with PNA. In the present study, the most immature infants had earlier onset of ROP stage 3 than the less immature ones but never before PMA of 31 weeks (Table 2). Treatment was also performed earlier among the most immature infants but not before 32 weeks in this study (Table 3). Hence, starting ROP screening at PMA of 31 weeks would identify all extremely pre-

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term infants with ROP stage 3 in our population, and this would be before they reached treatment criteria.

British guidelines recommend that ROP screening should start at PNA of 4 to 5 weeks among infants born at 27 to 32 weeks' gestation and at PMAs of 30 to 31 weeks among infants born before 27 weeks' gestation at birth. Moreover, American guidelines recommend that the first screening examination should be performed at PMA of 31 weeks or at PNA of 4 weeks, whichever is later. Consequently, all infants with a GA younger than 27 weeks will have their first examination at PMA of 31 weeks. However, recommendations for the most immature infants (GAs, 22-23 weeks) should be considered tentative rather than evidence-based guidelines because of few survivors. In the present study with a high proportion of infants born in the earliest weeks of gestation, we confirm that it should not be necessary to start ROP screening of infants born before 27 weeks' gestation earlier than at PMA of 31 weeks, which would also enable timely treatment of ROP (Table 4).

Screening intensity is important for timely detection of severe ROP. As mentioned previously, no infant in our study population reached treatment criteria before PMA of 32 weeks (Figure 2). Furthermore, 50.0% of infants were treated between PMAs of 35 and 39 weeks (ie, the 25th and 75th percentiles). During this period, efficient screening intensity is crucial. Moreover, it was previously shown that infants in our population had a high risk (20%) of developing severe ROP that fulfilled the criteria for treatment. This risk was closely related to GA at birth and was almost halved for each week of increase in GA at birth: 80% of infants with GA of 22 weeks at birth were treated, 43% with GA of 23 weeks, 31% with GA of 24 weeks, 16% with GA of 25 weeks, and 7% with GA of 26 weeks.

Consequently, screening intensity is particularly important in the most immature infants up to PMA of at least 39 weeks. This is a fact that needs to be considered before discharge or transfer of these infants to other hospitals where treatment is unavailable.

Based on our findings reported herein and in accord with opinions expressed by Donahue and Elder, we recommend that degree of infant immaturity (ie, GA at birth) and PMA at the time of each examination should be considered when deciding when the next examination should be performed. We also believe that these risk factors should be included in screening guidelines to avoid intervals between examinations that are too long, leading to increased risk of treatment failure and poor visual outcome. To date, neither American nor British guidelines consider degree of immaturity at birth or PMA at the time of examination in their recommendations about screening intervals.

At present, there is no consensus in the literature about termination of screening for ROP. The present study was not designed to study regression of the disease; therefore,
we cannot draw extensive conclusions from our findings. As expected, examinations continued longer among the most immature infants, who have the highest risk for ROP requiring treatment. In 96.2% of the study group, screening was terminated at PMA of 38 weeks or later, and only 5 infants (1.0%) had the last examination before PMA of 36 weeks. Of these 5 infants, one at onset of ROP after PMA of 36 weeks progressed to ROP by PMA of 36 weeks. The other 4 had GA at birth of 26 weeks, developed no ROP, and received their last examination at PMAs of 34 to 35 weeks.

Subgroup analyses from the CRYO-ROP19,23 indicate that, in case of no previous ROP, the risk of developing sight-threatening ROP is minimal once vascularization has extended into zone III and that 50% of eyes did so by PMA of 36 weeks. In our study, 7 of 31 infants with onset of ROP after PMA of 36 weeks progressed to ROP stage 3. Two of these infants were treated; one had onset of ROP at PMA of 38 weeks and developed ROP stage 3 in zone III, and the other had ROP stage 3 in zone II. Consequently, our data are in line with the American9 and British10 guidelines stating that, if there is no previous ROP, the risk of developing sight-threatening ROP is minimal once the retinal vessels have entered zone III. However, it must be emphasized that such judgment requires an experienced ophthalmologist with sufficient knowledge of ROP screening and a thorough examination of the periphery of the retina. If there is any uncertainty about the findings, further examination is recommended.

For infants with ROP stage 2, we believe that they should be followed up until regression or at least until the risk of developing treatment-requiring ROP has passed. In our study, all infants had been treated by PMA of 47 weeks. This is in accordance with findings by Reynolds et al.20 who reported that 99% of eyes developing serious ROP (defined as prethreshold ROP, threshold ROP, and any stage of ROP with plus disease) will have done so by PMA of 46.3 weeks. Hence, the risk of progression to treatment criteria should be minimal after PMA of 46 weeks.

Screening for ROP necessitates extensive resources, as illustrated in our study of extremely immature infants, among whom the mean number of examinations was 12, with some infants having up to 30 examinations. Although it has been shown that screening for ROP is cost-effective,4,5 it is our responsibility to continuously evaluate the screening program to reduce costs and, most importantly, to avoid unnecessary and stressful examinations in infants. By postponing the first screening examination until PMA of 31 weeks, a few examinations in about 65% of these extremely preterm infants will be avoided, and costs of screening will be reduced.

In conclusion, this national study of extremely immature infants at the limit of viability has provided us with new information. Based on our findings, we propose modifications of guidelines for ROP screening of infants born before 27 weeks’ gestation.

We recommend postponing the first examination until PMA of 31 weeks, which will reduce costs and several stressful examinations in the youngest infants. Because GA at birth and PMA at onset of ROP are correlated with severity of ROP and with progression to treatment criteria, we also recommend that GA at birth and PMA at the time of examination should be considered when deciding when and where the next examination should be performed.

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Author Contributions: Drs Kallen and Holmstrom had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


**Ophthalmological Numismatics**

Victor Deneffe’s (1835-1908) interests in medicine were wide-ranging; as a result, ophthalmology was generally a side interest. Nevertheless, after completing his medical degree and a special doctorate at Ghent in 1864, he was appointed Professor of Ophthalmology at his alma mater in 1899, in addition to serving sequentially as professor of surgical pathology, theoretical obstetrics, and operative medicine. In the 1890s, Deneffe organized a campaign against trachoma, in part because he had the disease. Among his many publications are ophthalmic research studies as well as a number of works dealing with the history of ophthalmology, including *Chirurgie antique: Les oculists Gallo-Romains au IIIe siècle* (1893). Following his retirement, he donated his extensive collection of antique ophthalmic and surgical instruments to the University of Ghent, now housed in the Museum of the History of Sciences.

In 1905, a lifetime commemorative uniface plaquette measuring 41 × 68 mm was struck in bronze in Deneffe’s honor by the artist Domien Van Den Bossche. It was presented to Deneffe by his students and friends for his 70th birthday. The plaquette depicts Deneffe’s clothed bust facing left.

Courtesy of: Jay M. Galst, MD, Clinical Associate Professor, New York Medical College, and Peter van Allen, PhD, Associate Curator, American Numismatic Society.

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