A Population-Based Study of the Refractive Outcome in 10-Year-Old Preterm and Full-Term Children

Eva K. Larsson, MD; Agneta C. Rydberg, PhD; Gerd E. Holmström, MD, PhD

Objective: To evaluate the refractive outcome in 10-year-old prematurely born children and in full-term control children.

Methods: Retinoscopy during cycloplegia was performed in 213 prematurely born children from a previous population-based study on the incidence of retinopathy of prematurity and in 217 children born at term. The spherical equivalent, astigmatism, anisometropia, and significant refractive errors (defined as hypermetropia >3 diopters [D], myopia ≤−1 D, astigmatism ≥1 D in 1 or both eyes, and/or anisometropia ≥1 D) were analyzed.

Results: Significant refractive errors were found in 29.6% of the prematurely born and in 7.8% of the full-term children. Prematurely born children had higher prevalences of hypermetropia of more than 3 D, myopia of −1 D or less, astigmatism of 1 D or more, and anisometropia of 1 D or more than those born at term. In the preterm group, the cryotreated children had the greatest risk of refractive errors (16 [64%] of 25 children), with higher prevalences of myopia (<0, ≤−1, or <−3 D), astigmatism (≥1 D), and anisometropia (≥1 D).

Conclusions: Significant refractive errors were 4 times more common in 10-year-old prematurely born children than in full-term controls. Cryotreated children had the highest risk, but prematurity per se was also associated with refractive errors. Ophthalmological follow-up of prematurely born children should, therefore, also include children without retinopathy of prematurity in the neonatal period.

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PREMATURELY BORN children have a higher risk of ophthalmological and neurodevelopmental problems than those born at term. Severe changes are usually diagnosed early in life. Minor lesions, however, may be detected later, in preschool- or school-aged children. Long-term follow-up studies are, therefore, important. Many investigations on the ophthalmological outcome in prematurely born children have been performed, but few have been strictly population based. In Stockholm County, children with a birth weight (BW) of 1500 g or less, born between September 1, 1988, and October 31, 1990, were included in a prospective study on the incidence of retinopathy of prematurity (ROP). The follow-up at 3 years has been reported. Recently, we performed a 10-year follow-up study of various visual functions in the same cohort. A control group of children born at term was also included. The present study reports the refractive outcome in these preterm and full-term children at the age of 10 years, and evaluates the effects of prematurity per se, of ROP, and of cryotreatment on refraction. Longitudinal data with analysis of the development of refractive errors of the prematurely born children will be provided later.

METHODS

In the previous prospective population-based study on the incidence of ROP in Stockholm County, 260 children, with a BW of 1500 g or less and a survival of 8 weeks or more, were included. Of these children, 40% had ROP and 11% underwent cryotreatment. The criterion for treatment was ROP stage 3 in at least 4 contiguous clock hours in zone II, even in the absence of “plus disease.” In the present follow-up study, the prematurely born children and their caregivers were asked by letter whether they wanted to participate in a 10-year ophthalmological follow-up study. The children were located with the help of a 10-digit identification number used in Sweden. From the Swedish National Board of Health and Social Welfare, we obtained a similar number of children born at term (39-41 weeks) with normal BWs (3000-4000 g) who were randomly selected to provide a control group. The

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full-term children were born in exactly the same period and in the same geographical area as the prematures born children. These children and their families were also contacted and asked to participate.

Retinoscopy during cycloplegia was performed by 2 of us (E.K.L. and G.E.H.) 45 minutes after the instillation of a mixture of 0.85% cyclopentolate hydrochloride and 1.5% phenylephrine hydrochloride. Spherical equivalents were calculated. Myopia was defined as less than 0 diopters (D), and moderate or high myopia as less than −3 D. Clinically significant myopia was defined as −1 D or less; hypermetropia was significant when greater than 3 D. Antismetropia was defined as significant when the difference between the eyes was 1 D or more, and high if 2 D or more. Astigmatism was recorded as a negative cylinder, and was defined as significant when 1 D or more and as high when 2 D or more. The axes of astigmatism (≥1 D) were divided as follows: with the rule (0°-15° and 165°-180°), against the rule (75°-105°), and oblique (16°-74° and 106°-164°). A significant refractive error of any kind was defined as hypermetropia of more than 3 D, myopia of −1 D or less, astigmatism of 1 D or more in 1 or both eyes, and/or anisometropia of 1 D or more.

Retinopathy of prematurity was divided into mild ROP (stages 1-2) and severe ROP (stages 3-5). Severe ROP was further divided into severe untreated ROP (ROP stage 3 not fulfilling the criterion for treatment) and cryotreated ROP. Right and left eyes were evaluated separately. When anisometropia and significant refractive outcome were analyzed, the premature group was divided into no, mild, untreated severe, and cryotreated ROP.

The study was approved by the local ethics committee at Karolinska Institutet. An independence test of contingency tables was used to compare nominal or ordinal data, and an unpaired t test was used for continuous data. A Wilcoxon matched-pair signed rank test was used to compare the right and left eyes regarding spherical equivalent and astigmatism. A 1-way analysis of variance was used for analyses of the spherical equivalents. Because the sample sizes were unbalanced and the variances were not homogeneous, an analysis of variance model with separate variance estimates was used (Proc Mixed in SAS statistical software). To evaluate the spherical equivalents, gestational age at birth, BW, stage of ROP, and cryotreatment were included in stepwise regression analyses.

Astigmatism and anisometropia were negatively skewed, and data were analyzed using the Kruskal-Wallis analysis of variance by ranks, followed by multiple comparisons between the groups on mean ranks. The P values were then corrected with the Bonferroni procedure. A stepwise logistic regression analysis was also performed to determine the effects of gestational age at birth, BW, stage of ROP, and cryotreatment on anisometropia of 1 D or more (yes or no).

Of the 260 prematurely born children in the prospective population-based incidence study, 12 had been excluded in the previous follow-up studies (7 had died, 4 had ophthalmological or general diseases not related to prematurity, and 1 had moved abroad). The remaining study population at that time consisted of 248 premature-born children. Of those children, 1 had died since the previous follow-up and 1 who had moved abroad during the previous follow-up immigrated at the age of 10 years and could be located again. Moreover, 32 children dropped out during the present study (6 had emigrated, 1 had a protected identity, and 25 denied participation). The remaining study population in the 10-year ophthalmological follow-up, thus, included 216 prematurely born children. Two of these children refused eyedrops and could not undergo refraction during cycloplegia (1 in the group with no ROP and 1 in the group with severe ROP that was not treated). They were excluded from the current study on refraction. Therefore, the total dropout frequency was 13.7% (34/248). Finally, 1 child had bilateral retinal detachments and could not undergo refraction, and was excluded from this analysis. The final population for refraction consisted of 213 prematurely born children. The control group consisted of 217 children born at term.

All children were examined at 10 years ±3 months, except 1 prematurely born child, who was examined at the age of 10½ years. Data on demographic features and ROP stage are given in Table 1.

There was no statistically significant difference between the right and left eyes in analyses of spherical equivalence (P=.12) or astigmatism (P=.63). We, therefore, chose to provide detailed results of the right eyes only.

### RESULTS

The mean spherical equivalent of the right eyes was 0.52 D (range, −20.0 to 5.62 D), and the median value of astigmatism was −0.5 D. The distributions of refractive errors and the axes of astigmatism are given in Tables 2, 3, and 4. Clinically significant myopia (≤−1 D) was detected in 15 (7.0%) of 213 premature children. Regarding anisometropia, the median value was 0.25 D and the distribution is provided in

### PREMATURE GROUP

Table 1. Demographic Data of Children Born Preterm and Full Term

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of REs/LEs</th>
<th>No. With Data for Most Severe ROP</th>
<th>Male-Female Ratio</th>
<th>GA at Birth, wk*</th>
<th>Birth Weight, g*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>217/217</td>
<td>NA</td>
<td>102:115</td>
<td>39-41</td>
<td>3000-4000</td>
</tr>
<tr>
<td>Premature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>213/213</td>
<td>213</td>
<td>102:111</td>
<td>29.1</td>
<td>1166</td>
</tr>
<tr>
<td>No ROP</td>
<td>133/136</td>
<td>130</td>
<td>64:66†</td>
<td>29.8†</td>
<td>1241†</td>
</tr>
<tr>
<td>Mild ROP</td>
<td>44/38</td>
<td>43</td>
<td>22:21†</td>
<td>28.4†</td>
<td>1141†</td>
</tr>
<tr>
<td>Severe ROP, untreated</td>
<td>12/14</td>
<td>15</td>
<td>7:8†</td>
<td>28.3†</td>
<td>1120†</td>
</tr>
<tr>
<td>Cryotreated ROP</td>
<td>24/25</td>
<td>25</td>
<td>9:16†</td>
<td>27.5†</td>
<td>983†</td>
</tr>
</tbody>
</table>

†Data are given according to the eye with the most severe stage of ROP.

*Data are given as mean values for preterm children.

Abbreviations: GA, gestational age; LE, left eye; NA, data not applicable; RE, right eye; ROP, retinopathy of prematurity.
Clinical significant myopia (the axes of astigmatism are illustrated in Tables 2 through 4). Clinically significant myopia (≤−1 D) was found in 5 (2.3%) of 217 control children. The median value of anisometropia was 0.12 D. The distribution of anisometropia is illustrated in Table 5. The overall refractive outcome is given in Figure 1.

CONTROL GROUP

The mean spherical equivalent of the right eyes was 0.64 D (range, −2.25 to 4.00 D), and the median value of astigmatism was 0 D. The distributions of refractive errors and the axes of astigmatism are illustrated in Tables 2 through 4. Clinically significant myopia (≤−1 D) was found in 5 (2.3%) of 217 control children. The median value of anisometropia was 0.12 D. The distribution of anisometropia is illustrated in Table 5. The overall refractive outcome is given in Figure 1.
D), and moderate or high myopia (≤−3 D) (Table 2 and Figure 2).

**Astigmatism**

The control group had significantly less total astigmatism (median value) than the premature group \((P<.001)\). The distribution of astigmatism is given in Table 3. The prevalence of astigmatism of 1 D or more was significantly higher in the premature group than in the control group \((P<.001)\). In the premature group, the cryotreated eyes had the highest prevalence of astigmatism of 1 D or more and 2 D or more.

An oblique axis of astigmatism was more common in the premature group than in the control group (Table 4). No other obvious difference for the axis of astigmatism was found between these groups or in the preterm group.

In a stepwise logistic multiple regression analysis of astigmatism \((≥1\ D)\) in the prematurely born children, gestational age at birth, BW, stage of ROP, and cryotreatment were included as independent risk factors. Cryotreatment was the only significant risk factor for astigmatism \((P<.001)\).

**Anisometropia**

Anisometropia (median value) was significantly greater in the premature group than in the control group \((P<.001)\). Moreover, anisometropia \((≥1\ D)\) was more common in the premature group \((P<.001)\) (Table 5). In the premature group, the cryotreated children had the highest frequency of anisometropia \((≥1\ D)\), especially high anisometropia \((≥2\ D)\).

**Significant Refractive Errors**

Significant refractive errors, defined as hypermetropia of greater than 3 D, myopia of −1 D or less, astigmatism of 1 D or more in 1 or both eyes, and/or anisometropia of 1 D or more, were more common in prematurely born children (63/213) than in children born at term (17/217) \((P<.001)\) (Figure 1). Cryotreated children had the highest risk; those with untreated ROP or those without ROP were also prone to develop significant refractive errors.

![Figure 1. Significant refractive errors in prematurely born and full-term children. A significant refractive error is defined as spherical equivalents of −1 diopter (D) or less or greater than 3 D, astigmatism of 1 D or more in 1 or both eyes, and/or anisometropia of 1 D or more. The prematurely born children were divided into groups according to their eye that had the most severe retinopathy of prematurity (ROP).](https://example.com/figure1)

![Figure 2. Clinically significant myopia (≤−1 diopter [D]) in full-term and prematurely born children (right eyes). ROP indicates retinopathy of prematurity.](https://example.com/figure2)

In the present population-based study, significant refractive errors were almost 4 times more common in 10-year-old prematurely born children (29.6%) than in those born at term (7.8%). Cryotreated children had the highest prevalence (16/213) of 25 children), but prematurity per se was also an important risk factor for refractive errors (34 [26.2%] of 130 children). The prematurely born children had a higher prevalence of hypermetropia \((>3\ D)\) and clinically significant myopia \((≤−1\ D)\) than those born at term, and moderate or high myopia \((≤−3\ D)\) was found only in the preterm group. Astigmatism and anisometropia were also more frequent and more marked in the preterm group. The cryotreated children had the highest prevalence of myopia \((<0, \leq−1, \text{and } ≤−3\ D)\), astigmatism, and anisometropia. Regarding hypermetropia, however, the findings in the cryotreated children were similar to those in the other preterm children. The refractive errors in the cryotreated children did not explain all the differences between the control and premature groups. We also found differences in the distribution of refractive errors between the control group and the prematurely born children without ROP (ie, prematurity per se). The latter group had a higher frequency of hypermetropia of greater than 3 D, myopia of less than −3 D, astigmatism, and anisometropia than children born at term.

Several researchers have evaluated refraction in prematurely born children of similar ages as in the present study. However, the findings are difficult to compare because of differences in epidemiological features and methods. Some studies have been hospital based, while others have been population based. To our knowledge, only 3 population-based studies, apart from this one, have been performed on 10-year-old children who had also been screened for ROP in the neonatal period (Table 6). The overall results of refraction in our pre-

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**COMMENT**

In the present population-based study, significant refractive errors were almost 4 times more common in 10-year-old prematurely born children (29.6%) than in those born at term (7.8%). Cryotreated children had the highest prevalence (16/213) of 25 children), but prematurity per se was also an important risk factor for refractive errors (34 [26.2%] of 130 children). The prematurely born children had a higher prevalence of hypermetropia \((>3\ D)\) and clinically significant myopia \((≤−1\ D)\) than those born at term, and moderate or high myopia \((≤−3\ D)\) was found only in the preterm group. Astigmatism and anisometropia were also more frequent and more marked in the preterm group. The cryotreated children had the highest prevalence of myopia \((<0, \leq−1, \text{and } ≤−3\ D)\), astigmatism, and anisometropia. Regarding hypermetropia, however, the find-

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maturely born children seem to compare best with the findings of Fledelius.10

The present study was strictly population based regarding children born preterm and at term. The groups were not masked to the examiner, but there was no reason to expect this as a source of bias. The 2 study groups were born in the same period and in the same geographical area and were examined in exactly the same way, which ensured an accurate comparison between the groups. Such a comparison was more difficult in the other long-term population-based studies10,12,13 for the following reasons: one13 had no control group, a cycloplegic refraction technique, which may underestimate refraction than in the present study. This could be because of their photorefractive technique. Fledelius10 reported the prevalence of myopia induced by severe ROP (threshold disease)38 than in our study. In their study, cryotreatment was given at a more advanced stage of ROP (threshold disease)38 than in our study. At that stage of the disease, the treatment and the disease per se may affect ocular growth to a greater extent and, therefore, explain the high prevalence of myopia in both groups. Whether the high prevalence of myopia in the cryotreated children in the present population was due to the treatment or the severe ROP per se cannot be established because all eyes fulfilling the criteria for treatment in the neonatal period were treated.

A higher prevalence of myopia in prematurely born children without ROP than in those born at term has also been reported.10,13,39 In the present study, prematurity per se seemed to have the greatest effect on myopia of less than −3 D, which could be due to a disturbance in ocular growth and refractive development, as previously reported.11,13,32,37,40-43

In the present study, significant hypermetropia (>3 D) was more common in prematurely born children than in full-term children, unlike in some previous reports.24,34,45 In a comparison with the 3 population-based studies, O’Connor et al14 found a similar prevalence of hypermetropia of greater than 3 D. Darlow et al12 however, reported a lower frequency of hypermetropia of 1 D or more than in the present study. This could be because of their photorefractive technique, which may underestimate refractive errors, and measurements of refraction without cycloplegia. Fledelius10 reported the prevalence of myopia, but did not comment on hypermetropia.

In the present study, prematurity per se seemed to be of importance for significant hypermetropia. However, like Darlow et al,12 we found no difference in the prevalence within the premature group and, like Ricci,46 we found that cryotreated children had the same prevalence of hypermetropia as children without ROP. The normal process of emmetropization is thought to be disrupted in the development of myopia in prematurely born children.1,27-46 It remains to be determined whether this also accounts for the higher prevalence of significant hypermetropia, as found in the present study.

Astigmatism was significantly more common in prematurely born children than in full-term controls in the present study, in accord with the study by Fledelius.10 Darlow et al,12 however, found a lower prevalence, which may be explained by their photorefractive technique. O’Connor et al14 did not study astigmatism.

The degree of astigmatism in prematurely born children increases with the severity of ROP.49 In the present study, the stage of ROP and cryotreatment per se were

<table>
<thead>
<tr>
<th>Source</th>
<th>Age, y</th>
<th>Definition</th>
<th>Children, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fledelius,10 1996</td>
<td>7-10</td>
<td>Mean spherical equivalent (RE/LE)</td>
<td>0.71/0.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>=−0.25 D, all</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>No ROP</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROP</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astigmatism =1 D</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anisometropia =2 D</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>=−0.5 D</td>
<td>14/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(better/worse)</td>
<td></td>
</tr>
<tr>
<td>Darlow et al,12 1997</td>
<td>7-8</td>
<td>=1 D</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Astigmatism =1 D</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0 D, all</td>
<td>22.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No ROP</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROP stage 1</td>
<td>16.7</td>
</tr>
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<td></td>
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<td>ROP stage 2</td>
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<tr>
<td></td>
<td></td>
<td>ROP stage 3/4</td>
<td>80.0</td>
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<tr>
<td>O’Connor et al,13 2002</td>
<td>10-12</td>
<td>=1 D</td>
<td>18</td>
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<td>20.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROP stage 3/4</td>
<td>80.0</td>
</tr>
</tbody>
</table>

Abbreviations: D, diopter; LE, left eye; RE, right eye; ROP, retinopathy of prematurity.
identified as risk factors for astigmatism of 1 D or more in univariate analyses. However, in the following step-wise logistic regression analysis, only cryotreatment remained an independent risk factor. This is in accord with the findings by Kent et al.\textsuperscript{37} who found that children with ROP stage 3 had significantly more severe astigmatism only when the cryotreated and laser-treated eyes were included. Quinn et al.\textsuperscript{22} compared cryotreated eyes with untreated eyes with threshold ROP, and found a tendency for a higher frequency of astigmatism of 1 D or more in treated than untreated eyes, at the age of 10 years, indicating that cryotreatment per se may induce astigmatism. We are unable to evaluate this question because all children fulfilling our criteria for treatment underwent cryotreatment.

The prevalence of anisometropia (≥ 1 and ≥ 2 D) in the prematurely born children in the present study was significantly higher than in the full-term children, in accordance with the findings by Fledelius.\textsuperscript{10} Anisometropia is not mentioned in the 2 other population-based studies.\textsuperscript{12,13} Gallo and Lennerstrand\textsuperscript{20} found a lower prevalence in 5- to 10-year-old prematurely born children, but their study was retrospective and based on medical records.

In the group of prematurely born children in the present study, the cryotreated children had the highest frequency of anisometropia, as noted by others.\textsuperscript{31,32} However, it remains uncertain whether the high prevalence of anisometropia in the cryotreated children was due to the treatment or the more severe ROP.

Theoretically, the dropout group can be a source of bias, but the low dropout frequency in the present study (13.7% [34/248]) minimized this risk. In comparing the 3 population-based studies, Darlow et al\textsuperscript{12} had an even smaller dropout group of 9% of all survivors. Fledelius\textsuperscript{10} reported the refractive outcome for 48%, and O’Connor et al\textsuperscript{13} for 53%, of their original populations. In the present study, the significance of the results would not have changed if the estimated refraction of the dropout group had been included in the analyses.

In conclusion, refractive errors were more common in prematurely born children than in those born at term. Altogether, 29.6% of prematurely born and 7.8% of full-term children had some kind of significant refractive error. The mean spherical equivalents were similar in both groups, but the distribution of refractive errors differed. The prematurely born children had a higher prevalence of hypermetropia (> 3 D) and clinically significant myopia (≤ 1 D). Astigmatism and anisometropia were more common and more severe in premature children. Moreover, 26.2% of prematurely born children without ROP (i.e., prematurity per se) had significant refractive errors. We, therefore, recommend that guidelines for follow-ups of prematurely born children include not only cryotreated or laser-treated children or children with previous severe ROP but also those without ROP in the neonatal period.

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