Development of Astigmatism and Anisometropia in Preterm Children During the First 10 Years of Life

Eva K. Larsson, MD, PhD; Gerd E. Holmström, MD, PhD

Objective: To assess the development of astigmatism and anisometropia to 10 years of age in preterm children, previously included in a population-based study on the incidence of retinopathy of prematurity.

Methods: Cycloplegic retinoscopies were performed in 198 preterm children at 6 months, 2½ years, and 10 years of age. We analyzed the development of astigmatism of 1 diopter (D) or more and anisometropia of 1 D or more.

Results: The amount and prevalence of astigmatism declined between 6 months and 2½ years of age and then remained stable. We found no difference in the course of astigmatism at different ages with regard to stage of retinopathy of prematurity. The amount of anisometropia increased, but its prevalence remained unchanged. Multiple regression analyses showed that astigmatism of 1 D or more at 2½ years of age and cryotreated severe retinopathy of prematurity were risk factors for astigmatism at 10 years of age, and that anisometropia of 2 D or more at 2½ years of age was a risk factor for anisometropia at 10 years of age.

Conclusions: The development of astigmatism and anisometropia showed a similar course, regardless of stage of retinopathy of prematurity. The retinoscopy findings at 6 months of age were of no value in predicting astigmatism and anisometropia at 10 years of age, but the refraction at 2½ years of age was. Retinoscopy at about 2½ years of age in all preterm children may be useful for detecting astigmatism and anisometropia that will persist in children of school age.

Arch Ophthalmol. 2006;124:1608-1614

Ophthalmological studies of preterm (prematurely born) children have resulted in recommendations that they need follow-up examinations, to find those in need of extra help. However, such follow-up programs are expensive and must be based on accurate knowledge of the prevalences of ophthalmological disorders in preterm and full-term children. Only a few population-based studies of children from birth to school age have been performed in which the children have also been screened for retinopathy of prematurity (ROP) in the neonatal period. The results reveal a higher prevalence of refractive errors in preterm than in full-term children.

In Stockholm County, Sweden, a cohort of preterm children (born September 1, 1988, through October 31, 1990) that was screened prospectively for ROP was followed up with retinoscopies at 6 months, 2½ years, and 10 years of age. The development of spherical equivalent refractive error has recently been reported.

The aim of the present study was to assess the development of astigmatism and anisometropia in this preterm cohort during the first 10 years of life and to determine whether it was related to the stage of ROP. We also wished to discuss which children should be included in a program to follow up refractive errors.

Methods: A previous study by Holmström et al prospec-tively determined the incidence of ROP in preterm children in Stockholm County. The study was population based and included 280 children with a birth weight of 1500 g or less, which was the inclusion criterion. The infants had gestational ages at birth of 24 to 35 weeks. One hundred five children (40.4%) had ROP, and 28 (10.8%) had received cryotherapy. The criterion for treatment was stage 3 ROP in at least 4 contiguous clock hours in zone II, even in the absence of plus disease. All children who fulfilled this criterion were treated. Two hundred forty-eight of the preterm children were followed up ophthalmologically for 3.5 years, and 216 of them were asked to return at 10 years of age. The dropouts have
Table 1. Demographic Data of 198 Preterm Children by ROP Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Group</th>
<th>No ROP</th>
<th>Mild ROP</th>
<th>Untreated</th>
<th>Cryotreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of RE/LE</td>
<td>198/197</td>
<td>121/123</td>
<td>42/36</td>
<td>12/14</td>
<td>23/24</td>
</tr>
<tr>
<td>No. with data for most severe ROP</td>
<td></td>
<td></td>
<td></td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>No. M/F</td>
<td>94/106</td>
<td>57/61</td>
<td>21/20</td>
<td>7/8</td>
<td>9/15</td>
</tr>
<tr>
<td>Gestational age, mean (SD), wk†</td>
<td>29.1 (2.3)</td>
<td>29.8 (2.3)</td>
<td>28.3 (1.8)</td>
<td>28.3 (1.9)</td>
<td>27.5 (2.2)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g†</td>
<td>1162 (221)</td>
<td>1212 (206)</td>
<td>1136 (233)</td>
<td>1121 (192)</td>
<td>988 (200)</td>
</tr>
</tbody>
</table>

*Data are presented as number of children, unless otherwise indicated.
†Data are according to the eye with the most severe stage of ROP.

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Untreated</th>
<th>Cryotreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, mean (SD), g†</td>
<td>988 (200)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LE, left eye; RE, right eye; ROP, retinopathy of prematurity.

In the entire preterm group, the median value of astigmatism declined between 6 months (1.0 D) and 2½ years of age (0.5 D) (P<.001), but remained stable thereafter (0.5 D).

The prevalence of astigmatism of 1 D or more at 6 months, 2½ years, and 10 years are illustrated in Figure 1. In the entire group, the prevalence fell significantly between 6 months and 2½ years of age (P<.001) and then became stable (P=.6). Although no change in the prevalence occurred between 2½ and 10 years of age, 27 children lost their astigmatism, and 14 new cases were seen. The prevalences of astigmatism (≥1 D) declined slightly in the children with no ROP and mild ROP between the examinations at 2½ years and those at 10 years of age, but in the children with cryotreated severe ROP the prevalence increased during this period. However, these differences were not statistically significant.

In the entire preterm group, the median value of anisometropia was present on all 3 retinoscopies. Nineteen of the 216 preterm children, 198 were examined on all 3 occasions and are included in the present study.

Retinopathy of prematurity was classified as none, mild (stages 1–2), or severe (stages 3–5). Severe ROP was further subdivided into untreated and cryotreated severe ROP.

Astigmatism was recorded as a negative cylinder and defined as significant at 1 diopter (D) or more and as high at 2 D or more. The axes of astigmatism (≥1 D) were divided into with-the-rule astigmatism (0°–15° and 165°–180°), against-the-rule astigmatism (75°–105°) and oblique astigmatism (16°–74° and 106°–164°). Right and left eyes underwent separate evaluations. Anisometropia was defined as significant when the difference in spherical equivalent between the eyes was 1 D or more and as high if the difference was 2 D or more. When anisometropia was assessed, the preterm group was divided into no, mild, severe untreated, and severe cryotreated ROP according to their most severely affected eye.

The study was approved by the local ethics committee at Karolinska Institutet, Stockholm, Sweden. Informed consent was received from the families.

STATISTICAL METHODS

The Wilcoxon matched-pair signed rank test and the t test for dependent samples were used to compare astigmatism in the right and left eyes. We used the Friedman test to analyze the median values of astigmatism and anisometropia as well as the axis of astigmatism over time (at 6 months, 2½ years, and 10 years of age). In the analysis of the prevalence of astigmatism on serial examinations, we performed an analysis of variance for repeated measures (the GENMOD Procedure in SAS; SAS Institute Inc, Cary, NC). We performed stepwise logistic regression analyses (combining backward elimination and forward selection methods) to determine the most important risk factors for astigmatism (≥1 D) and anisometropia (≥1 D) at 10 years of age.

RESULTS

There was no statistically significant difference between the right and left eyes in the analyses of astigmatism. Details concerning the 198 right eyes are given below. In the analyses of anisometropia, 197 children were included because retinoscopy could not be performed in the left eye of 1 child at the 2½-year examination. Table 1 shows the demographic characteristics and stage of ROP in the 198 children.

ASTIGMATISM

In the entire preterm group, the median value of astigmatism of 1 D or more at 6 months, 2½ years, and 10 years of age (0.5 D) (P<.001) remained stable thereafter (0.5 D).

The prevalences of astigmatism at 1 D or more at 6 months, 2½ years, and 10 years are illustrated in Figure 1. In the entire group, the prevalence fell significantly between 6 months and 2½ years of age (P<.001) and then became stable (P=.6). Although no change in the prevalence occurred between 2½ and 10 years of age, 27 children lost their astigmatism, and 14 new cases were seen. The prevalences of astigmatism (≥1 D) declined slightly in the children with no ROP and mild ROP between the examinations at 2½ years and those at 10 years of age, but in the children with cryotreated severe ROP the prevalence increased during this period. However, these differences were not statistically significant.

The axes of astigmatism (≥1 D) at the 3 examinations are given in Table 2. In 21 children, astigmatism (≥1 D) was present on all 3 retinoscopies. Nineteen of them had against-the-rule or oblique astigmatism, and no statistically significant change in their axis of astigmatism over time was proved (P=.8).

In the stepwise logistic multiple regression analysis of astigmatism (≥1 D) at 10 years of age, we included independent risk factors the gestational age at birth, birth weight, stage of ROP (including cryotreated severe ROP), and astigmatism of 1 D or more at 6 months and 2½ years of age. In the univariate analyses, all of the risk factors were significant. However, in the multiple regression analysis, only cryotreated severe ROP and the presence of astigmatism at 2½ years of age were independent risk factors for astigmatism at 10 years of age (Table 3).

We calculated the sensitivity and specificity for various cutoff points of astigmatism at 2½ years of age for astigmatism of 1 D or more at 10 years of age (Table 4).
The prevalences of anisometropia at 6 months, 2½ years, and 10 years of age are given in Figure 2. During the study, the prevalence remained stable apart from individual variations. Anisometropia disappeared in some cases and developed in others (Table 5). Therefore, of the 8 children with anisometropia of 1 D or more and less than 2 D at 6 months of age, 7 no longer had it at 2½ years of age. Of the 6 children with anisometropia...
of 1 D or more and less than 2 D at 2½ years, only 1 child was still anisometropic at 10 years of age. However, in the 7 children with high anisometropia (≥2 D) at 6 months of age, 6 continued to have high anisometropia (≥2 D) during the study, and in the 11 children with high anisometropia at 2½ years of age, 9 had anisometropia of 2 D or more at 10 years of age.

In a stepwise logistic multiple regression analysis of anisometropia of 1 D or more at 10 years of age, we included gestational age at birth, birth weight, the stage of ROP (including cryotreated severe ROP), and anisometropia of 1 D or more at 6 months and 2½ years of age. In the univariate analyses, all of the risk factors were statistically significant. However, in the multiple regression analysis, the presence of anisometropia of 2 D or more at 2½ years of age (P<.001) was the only independent risk factor for anisometropia at 10 years of age (Table 6).

The sensitivity and specificity for detecting anisometropia of 1 D or more at 10 years of age at various thresholds of anisometropia at 2½ years of age are given in Table 7.

### Table 3. Results of Stepwise Multiple Regression Analysis of Risk Factors for Astigmatism (≥1 D) at 10 Years of Age

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotreatment</td>
<td>9.8 (3.2-30.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Astigmatism ≥1 and &lt;1.5 D at 2½ y</td>
<td>5.3 (2.0-14.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Astigmatism ≥1.5 and &lt;2 D at 2½ y</td>
<td>23.7 (5.1-109.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Astigmatism ≥2 D at 2½ y</td>
<td>39.4 (6.9-224.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; D, diopter; OR, odds ratio.

### Table 4. Sensitivity and Specificity of Thresholds of Refraction at 2½ Years of Age for Astigmatism (≥1 D) at 10 Years of Age

<table>
<thead>
<tr>
<th>Threshold of Refraction</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>No. of Cases of Astigmatism Missed at Age 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.75 (59)</td>
<td>75.6</td>
<td>82.1</td>
<td>10</td>
</tr>
<tr>
<td>≥1 (54)</td>
<td>65.9</td>
<td>82.8</td>
<td>14</td>
</tr>
<tr>
<td>≥1.5 (21)</td>
<td>36.5</td>
<td>96.2</td>
<td>26</td>
</tr>
<tr>
<td>≥2 (10)</td>
<td>19.5</td>
<td>98.7</td>
<td>33</td>
</tr>
</tbody>
</table>

Abbreviation: D, diopter.

In the present population-based study, we analyzed the development of astigmatism and anisometropia in preterm children during their first 10 years of life. The amount and the prevalence of astigmatism were found to decrease between 6 months and 2½ years of age and remained stable thereafter. The amount of anisometropia increased between 2½ and 10 years of age, but the prevalence was stable during the entire study, although there were individual variations. No significant difference in the course of refractive development was detected for the various subgroups of previous ROP. The presence of astigmatism and anisometropia at 2½ years of age were the strongest risk factors for having astigmatism and anisometropia at 10 years of age. Moreover, cryotreated severe ROP was a significant risk factor for astigmatism at 10 years of age.

Of the original preterm cohort, 198 (79.8%) of 248 children underwent refraction at 6 months, 2½ years, and 10 years of age and were included in a study of the course of refraction. The development of spherical equivalents in the same population has also been reported. Only a few population-based studies of the refractive outcome at school age have been performed in preterm children who had been screened for ROP, and even fewer have been performed on the development of refraction. Most of the hospital-based studies discuss the development of spherical equivalents, and hardly any have longitudinally evaluated the development of astigmatism in preterm children.

In the present study, the amount and prevalence of astigmatism declined during the first 2½ years of life, unlike the study by Theng et al, who found an increase in astigmatism during the first 3 years of life in preterm children. This difference may be partly owing to a greater dropout rate in their study. The decrease in astigmatism in our study accorded with the findings in studies of growing children. However, in the present study, the prevalence of astigmatism remained stable from 2½ to 10 years of age, unlike studies of normal children. The differences in the development of astigmatism between these 2 groups of children may be caused by an arrest in the normal process of emmetropization, ie, disturbances in ocular growth such as changes in axial length, an increase in corneal curvature, a shallower anterior chamber, and a thicker lens, which have been described in preterm children.

Dobson et al assert that it is important to detect astigmatism at an early age and prescribe eyeglasses for prevention of amblyopia. In the present multiple regression analysis, the presence of astigmatism at 2½ years of age was a risk factor for astigmatism at 10 years, but the presence of astigmatism at 6 months of age had no apparent effect on astigmatism subsequently. Children with astigmatism of 2 D or more at 2½ years of age ran a 40-times-higher risk of developing astigmatism than those without. However, those with astigmatism of 1 D or more but less than 1.5 D also ran a significantly higher risk of developing astigmatism at 10 years of age.

Although not statistically significant, the prevalence of astigmatism in cryotreated eyes increased between 2½ and 10 years of age. This was in accordance with the American Cryotherapy for Retinopathy of Prematurity Trial. Quinn et al reported an increase in the prevalence of astigmatism during the first 10 years of life in cryotreated eyes and untreated eyes with threshold ROP. A higher frequency of astigmatism in cryotreated eyes at 10 years of age, compared with untreated eyes, was also shown, which would suggest that cryotreatment may affect the long-term growth of the eye. This finding could not be evaluated in the present study because all of the children fulfilling the criteria for treatment had been treated.

The prevalence of against-the-rule astigmatism was higher at younger ages for preterm children, as is the case.
in a normal population of children, but the prevalence remained high and was more common at 10 years of age than was with-the-rule astigmatism, unlike the findings in the latter group.22,28 The prevalence of oblique astigmatism was also higher than in a normal population of children28 and showed no change during the study. These findings may be of importance for follow-up examinations of preterm children with astigmatism, because against-the-rule and oblique astigmatism are risk factors for amblyopia.29,30

The prevalence of anisometropia (≥1 D) remained the same during the study, as in studies of children in the normal population,31,32 although it was higher than in full-term children at all 3 examinations.7,8 The amount of anisometropia, however, increased slightly, unlike in the studies of the normal population.31,33,34 Abrahamsson and Sjostrand35 reported that high anisometropia (≥3 D) at 1 year of age will probably persist, which was also the case in the present study, in which children with high anisometropia (≥2 D) remained anisometropic during the study. This was confirmed by the multiple regression analysis in which anisometropia of ≥2 D or more at 2½ years of age was the only significant risk factor for anisometropia of ≥1 D or more at 10 years of age.

In the preterm cohort, the children with cryotreated severe ROP had the highest prevalence of anisometropia.22,28
opia on all 3 retinoscopic examination results, and also the highest prevalence of high anisometropia (≥2 D). Moreover, no change in prevalence occurred during this period, which suggests that the process of emmetropization had already been disturbed early in life.

Many aspects must be taken into account when discussing ophthalmological follow-up examinations of preterm children. Recently, the American Cryotherapy for Retinopathy of Prematurity Trial published a report of their 15-year follow-up of eyes with cryotreated and threshold ROP. They emphasized the need for regular follow-up examinations of these children because retinal detachment and other ROP-related complications may occur after 10 years of age. In our cohort, children with cryotreated severe ROP had the highest prevalence of refractive errors during the first 10 years of life, which also favors follow-up of such children. However, we found no difference in the prevalences of refractive errors at 10 years of age between the eyes without ROP and those with mild or untreated severe ROP, and no difference in the course of refractive development as regards astigmatism and anisometropia (present study) or the spherical equivalent. Therefore, apart from cryotreated severe ROP, the stage of ROP should not be used as a criterion for follow-up examinations of refractive errors in our population.

In the present cohort, a previous refractive error was a risk factor for subsequent ones. However, retinoscopic examination findings at 6 months of age did not predict refractive errors at 10 years of age. The findings in the American Cryotherapy for Retinopathy of Prematurity Trial indicated that no change occurred in myopia after 1 year of age in preterm children without ROP or with nonthreshold ROP. In the present cohort, the children were not examined at 1 year of age, but retinoscopic findings at 2 1/2 years of age significantly predicted future myopia, as well as astigmatism and anisometropia (present study). At 2 1/2 years of age, it is still possible to prevent amblyopia and prescribe eyeglasses to improve the development of vision. Therefore, we recommend that all preterm children have follow-up examinations at about this age.

Recommendations for thresholds of refractive errors for follow-up examinations are necessarily based on the economic resources of the local community. The sensitivity and specificity of various cutoff thresholds for spherical equivalents at 2 1/2 years of age have been reported elsewhere (ie, Holmstrom and Larsson [2005]9). Thresholds of less than 0.5 D or of less than 0 D spherical equivalents were suggested for such follow-up examinations. In the present study of astigmatism and anisometropia, we found it more difficult to find a threshold with both high sensitivity and high specificity (Tables 4 and 7). A cutoff at 0.75 D or more or 1 D or more for astigmatism would have the highest sensitivity and specificity, but 10 and 14, respectively, of the 41 children with astigmatism at 10 years of age would still have been missed. The levels of sensitivity for anisometropia were poor, probably because of the large number of cases who lost their anisometropia and new cases of anisometropia (Table 5) during the study. Nine (82%) of the 11 children with high anisometropia (≥2 D) at 2 1/2 years of age showed no change at 10 years of age and therefore should be followed up. However, other studies have found a correlation between visual outcome and a lower degree of anisometropia. This would suggest that the cutoff of anisometropia should be at a lower level, such as 1 D or more or 1.5 D.

Preterm children, regardless of the stage of ROP, run a higher risk of developing refractive errors than those born at term. In this population-based study, we found that a refractive error at 2 1/2 years of age predicts that refractive error will also be present at 10 years of age. Although the children who underwent cryotherapy had the highest prevalence of refractive errors, the course of refractive development was similar in all subgroups of preterm children. Recommendations for follow-up examinations must include all aspects of visual function, ie, visual acuity, contrast sensitivity, and visual fields, as well as the refraction, strabismus, and perceptual problems. All preterm children should be included in such follow-up examinations for refractive error, irrespective of the ROP stage.

Submitted for Publication: March 2, 2006; final revision received May 10, 2006; accepted May 14, 2006.

Correspondence: Eva K. Larsson, MD, PhD, Department of Ophthalmology, Uppsala University Hospital, 751 85 Uppsala, Sweden (eva.larsson@gon.uu.se).

Financial Disclosure: None reported.

Funding/Support: This study was supported by Stiftelsen Synftramjandets Foundation for Research and the Crown Princess Margaretha Foundation for Visually Impaired.

Acknowledgment: We thank Elisabeth Berg, Department of Humanities, Informatics and Social Sciences, Karolinska Institutet, for her valuable advice about the statistical analyses, and the Swedish National Board of Health and Social Welfare, for their help.

REFERENCES


2. Schalij-Delfos NE, de Graaf ME, Treffers WF, Engel J, Cats BP. Long term follow

Table 7. Sensitivity and Specificity of Various Thresholds of Refraction at 2 1/2 Years of Age as Regards Anisometropia (≥1 D) at 10 Years of Age

<table>
<thead>
<tr>
<th>Threshold of Anisometropia at Age 2 1/2 y, D (No. of Eyes)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>No. of Cases of Anisometropia Missed at Age 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5 (44)</td>
<td>81.2</td>
<td>82.9</td>
<td>3</td>
</tr>
<tr>
<td>≥0.75 (26)</td>
<td>75.0</td>
<td>92.3</td>
<td>4</td>
</tr>
<tr>
<td>≥1 (17)</td>
<td>62.5</td>
<td>96.1</td>
<td>6</td>
</tr>
<tr>
<td>≥1.5 (12)</td>
<td>56.2</td>
<td>98.3</td>
<td>7</td>
</tr>
<tr>
<td>≥2 (11)</td>
<td>56.3</td>
<td>98.9</td>
<td>7</td>
</tr>
</tbody>
</table>