Visual Development in Preterm and Full-Term Infants: A Prospective Masked Study

Silvia Weinacht,[1] *Christian Kind,*[2] *Jürgen Schulte Mönting,*[3] *and Irene Gottlob*[1]

PURPOSE. To compare development of visual acuity and binocular vision in preterm and full-term infants in a prospective study that used testers masked to subject's gestational age.

METHODS. Seventy-nine healthy full-term infants, mean gestational age 40 weeks, and 18 low-risk preterm infants, mean gestational age 33 weeks, were examined biweekly between the 44th and 54th weeks of postmenstrual age. Ocular alignment, convergence, fusion, grating acuity, and onset of optokinetic nystagmus (OKN) were assessed at each examination.

RESULTS. The mean postnatal ages of onset of ocular alignment, convergence, fusion, grating acuity to 1.6 cycles per degree, and OKN from temporal to nasal and nasal to temporal were, respectively, 5, 7, 7, 11, 6, and 9 weeks for the full-term and 12, 13, 14, 18, 13, and 16 weeks for the preterm infants. The mean postmenstrual ages of onset for the corresponding parameters were 46, 48, 48, 51, 46, and 50 weeks for full-term and 46, 47, 48, 52, 47, and 49 weeks for preterm infants. The onset of all parameters was earlier in full-term infants than in preterm infants of the same postnatal age ($P \leq 0.0001$). However, no differences were found when the parameters were compared at postmenstrual ages.

CONCLUSIONS. Additional visual experience of preterm infants does not influence development of visual acuity or binocular vision during the first months of life as measured from the time of conception. (*Invest Ophthalmol Vis Sci.* 1999;40:346-353)

Investigations of the effects of prematurity on human development have yielded conflicting results. On the one hand, delays in the development of neurologic functions are potentially attributed to the increased vulnerability and insufficient intrauterine maturation of the premature brain.[1-3] On the other hand, the fact that some functions develop somewhat earlier with age corrected for prematurity in preterm infants has been attributed to the advantage of early additional extrauterine experience during which infants have more environmental stimulations and more self-generated movement.[4,5] The aim of our study was to compare the time frame of development of visual acuity and binocular vision in pre- and full-term infants based on the evaluation of oculomotor responses (visual pursuit and optokinetic nystagmus [OKN]) and orthoptic parameters (ocular alignment, convergence, and fusion).

In healthy infants, visual acuity increases rapidly within the first 3 months of life, as measured by different methods (preferential looking, visual evoked potentials, and OKN).[6] There is general agreement that the acuity of 3-month-old infants is approximately 3 cycles per degree (cpd), but estimates vary by as much as two octaves for 1-month-old infants. Three parameters influence the improvement of visual acuity: the differentiation of the fovea, the myelination of the visual pathways, and the increase in the number of synapses.[7]

In healthy preterm infants, visual acuity measured in behavioral and electrophysiological studies is controversially discussed in the literature. Some investigators[8-10] reported a similar maturation pattern compared with full-term infants of the same postmenstrual age. Others[11-13] showed accelerated visual development in preterm infants, which was attributed to additional visual experience in the premature period. The reported differences between the preterm and full-term infants were small. Van Hof-van Duin and Mohn[11] observed a mean difference of only 0.3 octave across the corrected age range of 1 to 49 weeks. Most reports suggested that after 1 year of age the difference is negligible, although there are two reports of acuities at the lower end of the normal range in previously premature infants at 3 to 4 years.[14,15]

Normal binocular vision requires orthotropic alignment of the eyes and binocular mechanisms for convergence and fusion. Many studies of healthy full-term infants indicate that these different aspects of binocularity approach adult level by 3 to 6 months of age.[16-20]

In most studies that have used corneal reflections from a fixation light to evaluate alignment, infants appeared orthotropic within the first few weeks after birth.[20,21-24] However, in two other studies, both of which used the examiner's face as the fixation target, infants became orthotropic during the third and fourth months of life.[19,25]

The development of convergence is more complex because convergence is driven by at least two cues: disparity detecting and accommodative mechanisms.[26] Slater and Find-

From the [1]Department of Strabismus and Neuro-Ophthalmology, and the [2]Division of Neonatology, Kantonsspital Street Gallen, Switzerland; and the [3]Department of Biomathematics and Statistics, University of Freiburg, Germany.

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Reprint requests: Irene Gottlob, Department of Strabismus and Neuro-Ophthalmology, Kantonsspital Street Gallen, CH-9007 St. Gallen, Switzerland.

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lay[22] and Aslin and Jackson[21] found partial convergence during the first month of life using the corneal reflection technique assessed by photography. Convergence spasms are often seen in infants younger than 2 months of age, and by 3 to 4 months of age convergence is accurate and consistent in healthy infants.[21-23,27]

Previous studies showed that young infants prefer viewing binocularly orthogonal gratings that are seen as rivalrous by adults, who have normal binocularity, and that between 6 and 16 weeks of age, infants prefer fusible gratings, indicating the onset of sensory binocularity.[17,28,29]

In newborn infants, OKN measured during monocular stimulation by electrooculographic recordings[30] or clinical observation of the eye movements[31] was found to be asymmetrical, showing a higher frequency of beats to stripes moving from temporally to nasally than in the opposite direction. This asymmetry persists in humans with impaired binocular vision.[30-34] In full-term infants, OKN becomes symmetrical to stripes moving in both directions by 3 to 6 months of life.[30-33,35] The concurrent onset of binocularity and symmetrical OKN has led to the speculation that the developmental changes in monocular OKN are linked to the development of binocularly driven cells in the visual cortex.

Little information is available about the development of binocularity in preterm infants. Results from one study[30] in which five preterm infants were tested suggested that the extra period of visual experience appeared to accelerate the maturation of the OKN compared with that of full-term infants. However, the incidence of strabismus in healthy preterm infants is five times higher than in the general population,[36] and patients with strabismus do not develop symmetrical OKN.

In the present study, we evaluated the development of these visual parameters in a group of premature infants and compared the data with those from a large number of full-term infants.

Methods

This research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from parents after the nature and possible consequences of the study were explained. The research was approved by the Institutional Human Experimentation Committee of Kantonsspital St. Gallen.

Patients

Two groups of newborn infants were recruited for the study. The first group consisted of healthy full-term infants ($n = 87$) with a gestational age ranging from 38 to 42 weeks (mean, 40.1 weeks) and a mean birth weight of 3383 g. The second group consisted of preterm infants of low risk ($n = 19$) without neurologic or ocular diseases, with a gestational age ranging from 31 to 36 weeks (mean, 33.5 weeks) and a birth weight greater than 1250 g (mean, 2019 g). All infants were home reared. They were tested biweekly between 44 and 54 weeks of postmenstrual age until the infant showed the presence of each of the examined visual functions. At each examination children were only tested for capabilities that they had not shown at earlier examinations. Postmenstrual age represents the infant's age calculated from the date of the first day of the mother's last menstrual period. Examiners were unaware whether the infants were born at term or were premature. Because premature infants were all born after the 31st postmenstrual week and were at low risk, they were not screened systematically for retinopathy of prematurity. However, the fundus of all infants was examined during the study, usually at the time of the last examination at the postmenstrual age of 54 weeks. At this time, none of the infants showed fundus abnormalities. Simultaneously with fundus examination, 30 minutes after instillation of 0.5% tropicamide and 2.5% phenylephrine (each drop was applied twice 5 minutes apart) retinoscopy was performed in all infants. We decided prospectively to exclude infants with cycloplegic refractions outside a window of 0 and +5 diopters. This resulted in the exclusion of one full-term infant who had hyperopia of 8 diopters. The mean refraction of full-term infants was +2.0 diopters (SD, 0.5 diopters), and the mean refraction of preterm infants was +1.5 diopters (SD, 0.8 diopters). In addition, we decided prospectively to exclude patients demonstrating any ocular pathology. Seven additional full-term infants and one preterm infant were excluded from the study. Two full-term infants had ocular pathology: one had congenital nystagmus and the other strabismus. The other six children (five full-term and one preterm) were excluded due to noncompliance (they missed three or more sessions).

Oculomotor responses involve both subcortical and cortical components and are affected by attention. To control for attention we used scales developed by Prechtl[37] to grade the state of the infant's behavior. The infants were examined in Prechtl's state III, calm "awakeness" with opened eyes, absence of large body movements, and regular respirations. Infants' mothers were asked to come at a time when their children appeared most likely to be in Prechtl's state III, and the examiner had the flexibility to spend sufficient time with each infant so that a complete examination in Prechtl's state III was possible. Therefore, 98% of the orthoptic examinations and 94% of the visual pursuit examinations were completed. However, with OKN testing cooperation was poorer. Here only 67% of the examinations were completed.

Orthoptic and Ophthalmologic Examinations

The orthoptic examination (performed by orthoptists) included ocular alignment, convergence, and fusion. At each examination time two orthoptic examinations were attempted. Every child was examined at least once in Prechtl's state III. If we could not examine an alert child, the mother was asked to wait or to return when the infant was again in Prechtl's state III. Therefore, on each child all the examinations were performed at least once under optimal conditions. Because inattention of infants may negatively influence the results, the "better result" of the two examinations was taken for data analysis. The better result consisted of ocular alignment as opposed to strabismus, full convergence compared with first sign or absent convergence, first sign of convergence versus absent convergence, and present fusion compared with absent fusion. Two examinations were completed for full-term infants in 72%, 72%, 68%, 89%, and 90% and for preterm infants in 79%, 73%, 46%, 100%, and 0% at the five consecutive examinations, respectively. These differences were not statistically significant for the two groups. The difference at the time of the last examination results from the small number of children (nine full-term infants and only one preterm infant, who did not complete the last examination) who had not reached maturity in all orthoptic examinations (ocular alignment, full convergence, and present fusion) at an earlier examination date.

Ocular alignment was measured by the Hirschberg or cover tests, or both. We only analyzed manifest ocular deviations; phorias were not evaluated. During the Hirschberg test an illuminated toy was jiggled at a distance of 1 m from the infant's face to trigger attention and fixation while the positions of the corneal light reflections were observed. A conversion for the Hirschberg test of 20 prisms/mm was used.[38] Because of the infant's large angle kappa (8°-10°), we considered decentered corneal reflections to indicate exotropia only when they were more than midway from pupillary center to nasal pupillary margin.[38]

Convergence was tested by attracting the infant's fixation with an illuminated toy at a distance of 0.5 m. The toy was then moved slowly toward the infant's face while the examiner observed the infant's eyes. Convergence was classified as absent, first sign of convergence (any bilateral adduction), and full convergence (binocular adduction to 12 cm from the face).

Binocular fusion was measured by the four prism base out test. After attracting the infant's fixation with an illuminated toy, the prism was placed base out in front of each eye. Binocular vision was considered to be present when a convergent eye movement was observed with or without a preceding saccadic eye movement. Binocular vision was judged to be absent when no eye movement or only a saccadic eye movement was observed. Although the four prism base out test may show atypical responses in certain subjects,[39] it is fast and simple and therefore was useful in this infant study.

A complete ophthalmologic examination (performed by ophthalmologists) including fundus examination and retinoscopy was performed on each infant. Anterior segments and fundi were normal in all children.

Infrared Eye Movement Recordings

The eye movements were recorded by a corneal reflection tracker,[40] which consisted of a cathode ray tube in which stimuli for visual pursuit and OKN were generated. The infant was placed 30 cm in front of the screen. While the infant was looking at different stimuli, infrared light was directed to the infant's right eye, and the eye movements were recorded by an infrared-sensitive camera. Infrared source and camera were installed over the infant's head, and infrared light was reflected by a hot mirror positioned in the center of a cathode ray tube and directed to the infant's eye. Analysis of the eye movements is based on the measurement of the relative position of the reflected image of the infrared source on the cornea and pupil center.

Grating Acuity

Grating acuity was measured by pursuit eye movement recordings. The stimulus was a square of 9.4° of visual angle on a gray surface of equal luminance. It consisted of gratings moving along a horizontal axis at a constant velocity of 7.5 degrees per second. We tested five different spatial frequencies: 0.1, 0.2, 0.4, 0.8, and 1.6 cpd. Pursuit eye movements were evoked binocularly and were recorded from the right eye. After attracting the infant's attention with a flashing light to the screen, a grating was presented for 38 seconds. If the initial grating elicited a pursuit response, the spatial frequency of the stimulus was increased, otherwise it was decreased. The criterion for presence of the grating acuity for a certain stimulus was if the infant followed this stimulus by saccadic or smooth pursuit at least once over the entire screen (6.2 seconds).

Optokinetic Nystagmus

The stimulus was a vertical grating of 0.5 cpd covering a visual field of 56 × 42° and moving along a horizontal axis at a constant velocity of 30 degrees per second. OKN was evoked monocularly from the right eye by covering the left eye with an orthoptic patch and was recorded during the presentation of stripes moving temporally to nasally and in the opposite direction. OKN was considered present if the typical pattern of slow and fast phase nystagmus was shown in correlation with the displacement of the stimulus. OKN examinations were completed in full-term infants in 48%, 44%, 67%, 77%, and 82% and in preterm infants in 25%, 50%, 56%, 63%, and 87% at the five examination times, respectively.

Statistical Evaluation

Data were analyzed by survival analysis using the time of onset for each parameter and for each infant as variables. Thus, the plotted curves on the figures represent the percentage of subjects showing onset of each visual function at each age. Two estimators for the percentage of infants showing the onset of the parameter of interest up to a certain time were used. They were the nonparametric Kaplan-Meier estimator and the log-logistic fitting. The log-logistic function was preferred to other link functions because it fits the Kaplan-Meier curves best. To compare the parameters of the two groups of infants we used the log rank test.

Results

Between the 44th and 46th weeks of postmenstrual age, 60% of the infants were orthotropic, 36% were exotropic, and 4% were esotropic. The mean postnatal age (SD) of onset of ocular alignment was 5 (0.2) weeks for full-term and 12 (0.6) weeks for preterm infants. The mean postmenstrual age of onset of ocular alignment was 46 (0.2) weeks for full-term and 46 (0.5) weeks for preterm infants. The percentage of infants showing orthotropia at different ages is plotted in Figure 1A for postnatal ages and Figure 1B for postmenstrual ages. The onset of ocular alignment was significantly earlier ($P \leq 0.0001$) in full-term infants compared with preterm infants of the same postnatal ages. However, no statistically significant difference was found when postmenstrual ages were compared ($P = 0.69$).

The mean (SD) postnatal age of onset of the first signs of convergence was 5 (0.2) weeks for full-term and 11 (0.5) weeks for preterm infants. Full convergence occurred at 7 (0.3) weeks postnatally for full-term infants and at 13 (0.4) weeks postnatally for preterm infants. The mean (SD) postmenstrual age of onset of first signs of convergence was 45.0 (0.2) weeks for full-term, and 45 (0.4) weeks for preterm infants. Full convergence occurred at 48 (0.3) weeks postmenstrually for full-term infants and at 47 (0.4) weeks postmenstrually for preterm infants. The percentages of infants showing first signs and full convergence at different ages are shown in Figure 2. The onset of convergence (first signs and full convergence) was significantly earlier ($P \leq 0.0001$) in full-term infants compared with preterm infants of the same postnatal ages. How-

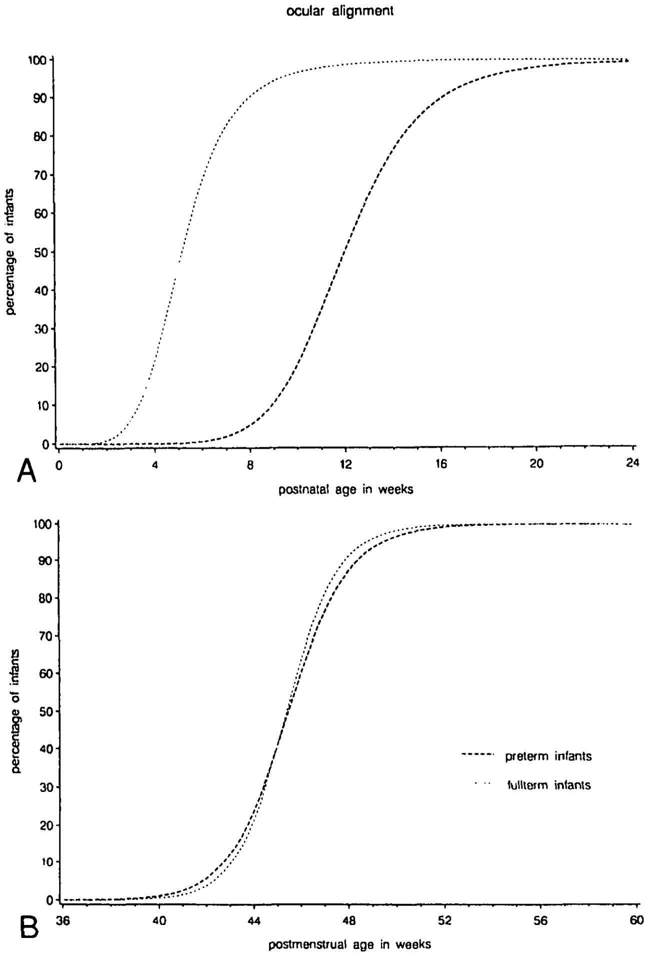

FIGURE 1. Kaplan-Meier curves and log-logistic fitting of percentages of preterm and full-term infants showing orthotropia at different postnatal (**A**) and postmenstrual (**B**) ages.

ever, no statistically significant differences were found when postmenstrual ages were considered (*P* = 0.76 first signs and *P* = 0.12 for full convergence).

The mean (SD) postnatal age of onset of fusion was 7 (0.3) weeks for full-term infants and 14 (0.4) weeks for preterm infants. The mean (SD) postmenstrual age of onset of fusion was 48 (0.3) weeks for full-term infants and 48 (0.4) weeks for preterm infants. We plotted the percentage of infants showing fusion at different ages in Figure 3. The onset of fusion was significantly earlier (*P* ≤ 0.0001) in full-term infants compared with preterm infants based on postnatal ages. However, based on postmenstrual ages no statistically significant difference was found (*P* = 0.80).

The mean (SD) postnatal ages of onset of visual pursuit to stimuli of 0.1, 0.2, 0.4, 0.8, and 1.6 cpd were, respectively, 5 (0.2), 5 (0.2), 5 (0.2), 8 (0.2), and 11 (0.3) weeks for full-term infants and 11 (0.5), 12 (0.4), 12.0 (0.5), 15 (0.6), and 18.0 (0.8) weeks for preterm infants. The mean (SD) postmenstrual ages of onset of visual pursuit to the above stimuli were, respectively, 46 (0.2), 45 (0.2), 45 (0.2), 48 (0.2), and 51 (0.3) weeks for full-term infants, and 45 (0.3), 45 (0.3), 46 (0.3), 48 (0.5), and 52 (0.7) weeks for preterm infants. The percentages of infants showing visual pursuit to the various stimuli at different ages are represented in Figure 4. The times of onset of visual pursuit for all stimuli between 0.1 and 1.6 cpd were significantly earlier for all stimuli (*P* ≤ 0.0001) in full-term infants than in preterm infants based on postnatal ages. However, no differences were found when postmenstrual ages were compared (*P* = 0.56, 0.93, 0.99, 0.65, and 0.90 for stimuli in increasing cpd as above).

The mean (SD) postnatal ages of onset of OKN were 6 (0.3) weeks for full-term and 13 (0.6) weeks for preterm infants when stripes moved from temporal to nasal and 9 (0.3) weeks for full-term and 16 (0.6) weeks for preterm infants when stripes moved in the opposite direction. The mean (SD) postmenstrual ages of onset of the OKN were 46 (0.3) weeks for full-term infants and 47 (0.5) weeks for preterm infants when stripes moved from temporal to nasal and 50 (0.3) weeks for full-term infants and 49 (0.6) weeks for preterm infants when stripes moved in the opposite direction. The percentage of infants showing OKN to stripes moving in the two directions are shown in Figure 5. The onset of OKN in either direction was significantly earlier (*P* ≤ 0.0001) in full-term infants than in preterm infants of the same postnatal age. However, no statistically significant differences were found when postmenstrual ages were compared (*P* = 0.61 for temporal to nasal and *P* = 0.74 for nasal to temporal).

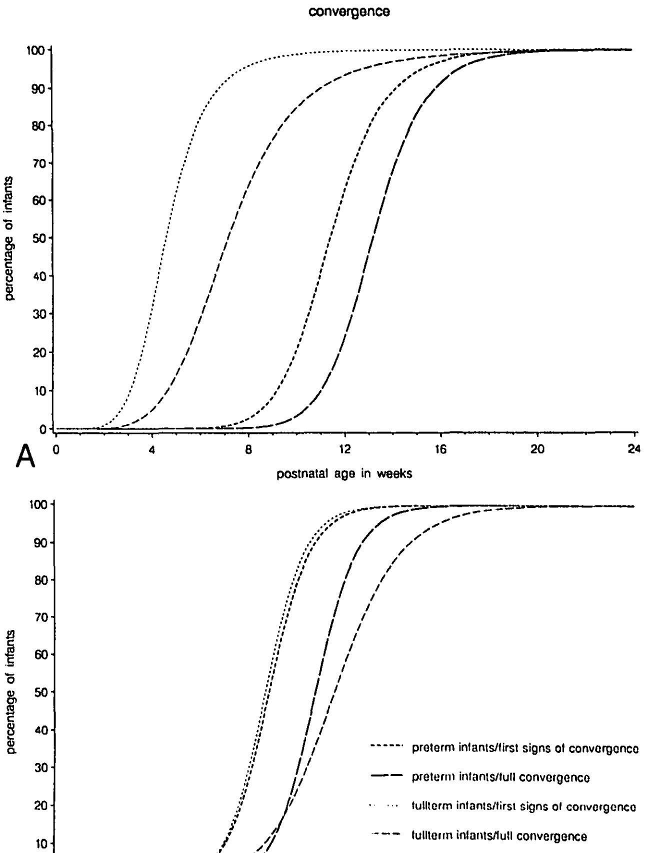

FIGURE 2. Kaplan-Meier curves and log-logistic fitting of percentages of preterm and full-term infants showing first signs of convergence and full convergence at different postnatal (**A**) and postmenstrual (**B**) ages.

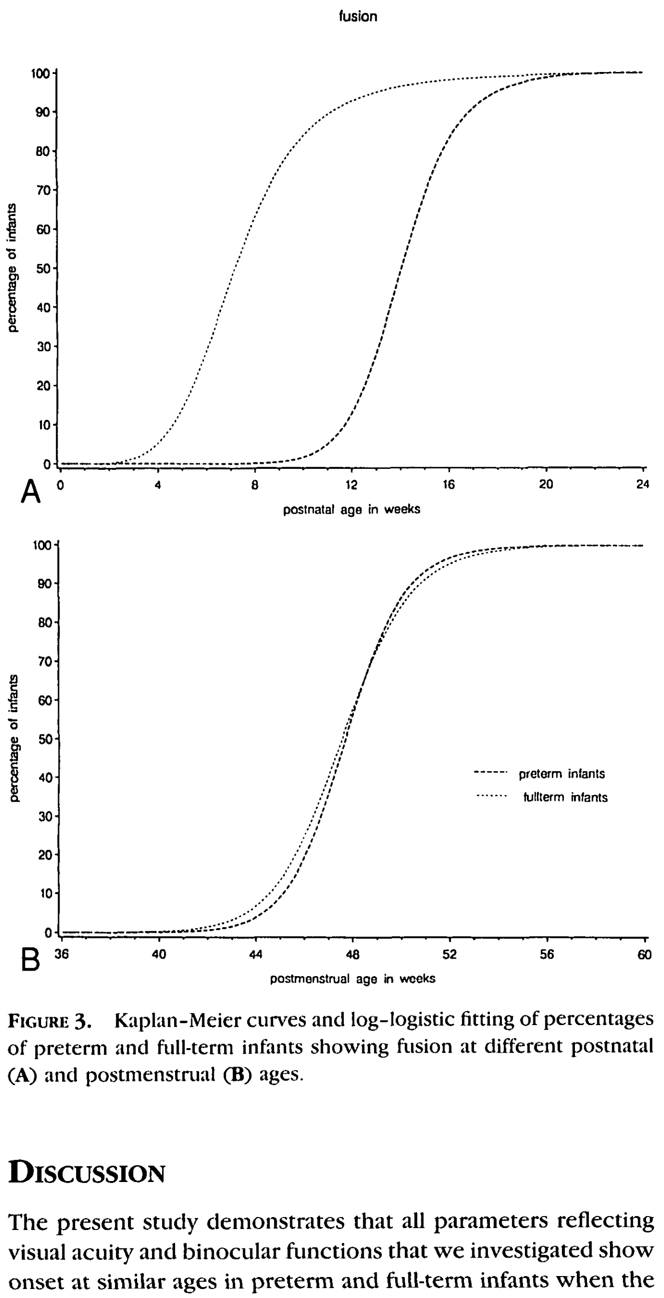

FIGURE 3. Kaplan-Meier curves and log-logistic fitting of percentages of preterm and full-term infants showing fusion at different postnatal (A) and postmenstrual (B) ages.

DISCUSSION

The present study demonstrates that all parameters reflecting visual acuity and binocular functions that we investigated show onset at similar ages in preterm and full-term infants when the comparison is based on age from conception.

These results indicate that at least with respect to visual functions, prematurity and the associated additional visual experience do not appear to confer a developmental advantage. However, our data only apply to low-risk preterm infants. Preterm infants born at gestational ages less than 31 weeks or with perinatal complications may show a different visual development. With our methods we could not confirm other studies[11-13] suggesting an accelerated development of grating acuity. We are in agreement with studies showing no differences between grating acuity of low-risk preterm and full-term infants.[8-10] With regard to parameters of binocular vision, little was known about the influence of prematurity. To our knowledge, our present study is the first one to analyze parameters reflecting binocular vision in preterm infants compared with full-term infants. We could not document an acceleration of the development of ocular alignment, fusion, and convergence in premature infants. In contrast to Roy et al[30] who analyzed the gain (ratio of the velocity of the fast phase of the OKN and of the stimulus) of the OKN (another indicator of binocularity), we could not find differences in the OKN development between preterm and full-term infants. However, our evaluation was based on the onset of OKN and not on the gain.

Our results indicate that at least in the first 3 months of life, clinical examinations of prematurely born infants should be adjusted for the date of conception. Investigations of several developmental milestones[38] showed that correction for preterm birth should be applied during the first year of life. However, at 2 years of age the developmental milestones[41] of the premature children were equal to or better than those of children born at term. With regard to visual function, the results of comparisons between premature and full-term children during the first year of life[8-13,30] are inconclusive. Further studies investigating visual function at later ages than in our study would be interesting.

The large number of full-term infants we evaluated offered the opportunity to investigate the normal visual development in the first 3 months of life and to compare them to the results of other studies. Because mean refractive values of normal neonates were found to be hyperopic,[42] we decided prospectively to exclude infants with cycloplegic refractions outside of a window of 0 and +5 diopters. In this study we used tropicamide for cycloplegia. The cycloplegic effect of this drug is known to be only minimally less than cyclopentolate.[43]

We demonstrated that ocular alignment based on observations of corneal reflections of a fixation light occurred in full-term infants at a mean age of 5 to 6 weeks after birth. Our results are in agreement with several other studies in which the same examination technique was used.[21-23] Archer et al[19] investigated a large group of infants with the Hirschberg test and found the occurrence of orthotropia later than in our study. They found that approximately 50% of the infants were orthotropic at 2 months of age, whereas in our study at 2 months of age almost 100% were orthotropic. Differences may be explained by the difficulty in measuring ocular alignment with the Hirschberg test in children. In addition, we examined most children twice, and the "better result" (consisting of ocular alignment as opposed to strabismus) of the two examinations was taken for data analysis. This could also explain the earlier development of orthotropia in our study. In agreement with results of Archer et al,[19] we found that most of the children were exotropic or orthotropic at 4 weeks of age. Therefore, a convergent squint at this age should raise a high suspicion of pathology and prompt close follow-up examinations.

We showed the first signs of convergence at a mean postnatal age of 4.8 weeks and of full convergence at a mean postnatal age of 7.4 weeks in full-term infants. These findings are in agreement with previous studies,[21,22,44,45] which found systematic and reliable changes in convergence and accommodation to be present after 6 to 8 weeks postnatally. Thorn et al,[24] on the other hand, found the onset of full convergence at a later age (13.7 weeks). Because Aslin[21] showed that stimulus velocity influences convergence capability, differences in the velocity of the target approaching the infant's face may explain the different results.

Although the four prism base out test can be difficult to perform in infants, in our experience it was shown to have a good test-retest reliability and reproducibility when performed by experienced examiners. We found a mean age of onset of fusion to be at 7.5 weeks after birth in full-term infants. In

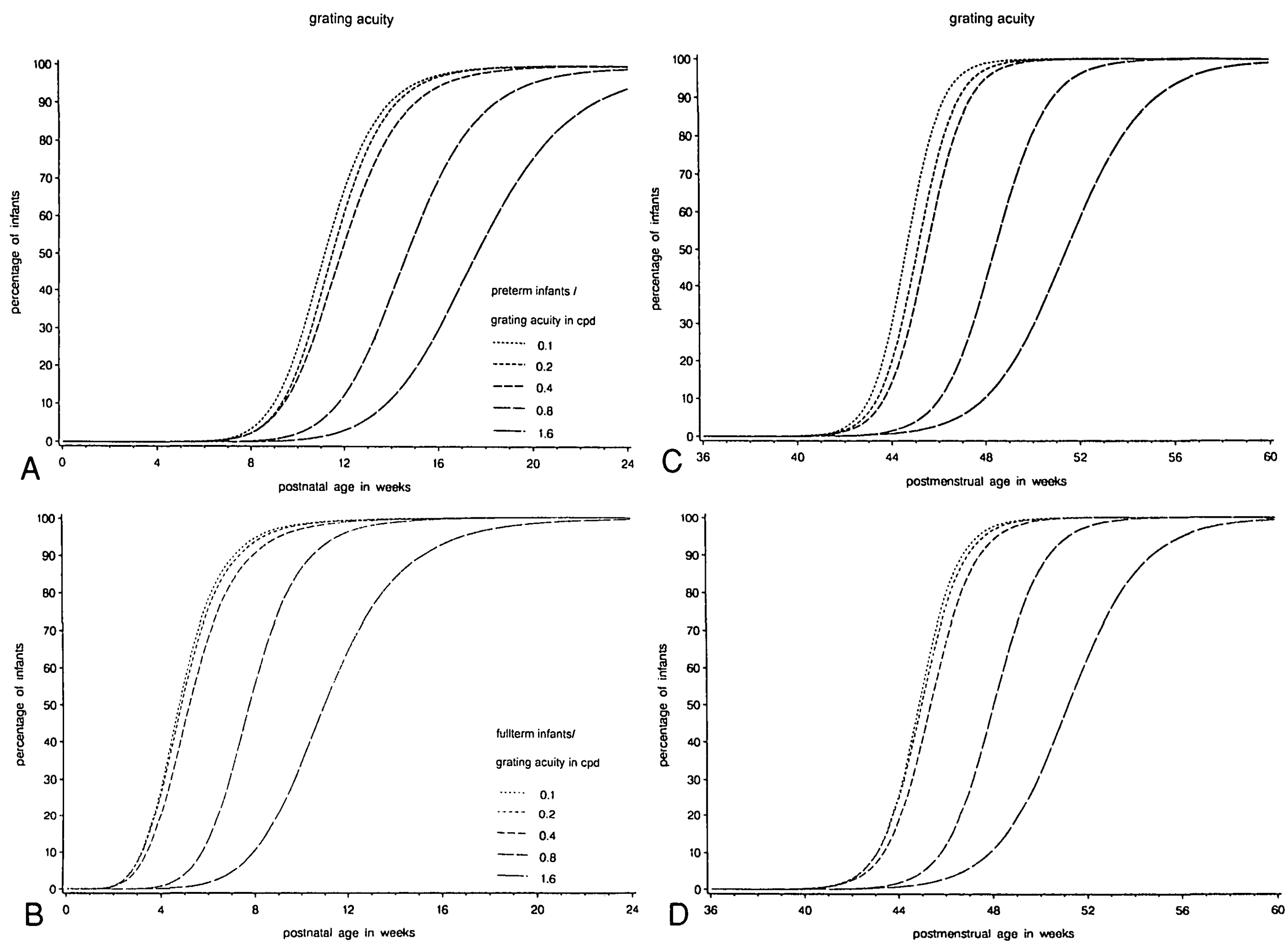

Figure 4. Kaplan-Meier curves and log-logistic fitting of percentages of preterm and full-term infants showing visual pursuit (grating acuity) to stimuli of 0.1 cpd to 1.6 cpd at different postnatal (**A**, preterm infants; **B**, full-term infants) and postmenstrual (**C**, preterm infants; **D**, full-term infants) ages.

agreement with previous studies,[17,24,28,29] we found the onset of fusion at an age similar to that of full convergence. However, we found the onset of convergence and fusion at an earlier age than the above-mentioned studies, in which investigators found a mean age of onset of fusion at 13.7 weeks of age. These differences may be explained by methodical differences. Fusion was investigated in those studies by preferentially looking for fusible versus rivalrous gratings and in our study by the four prism base out test. In addition, in our study we evaluated data that were the better result of two orthoptic examinations.

We demonstrated that visual acuity of 1.6 cpd measured by pursuit eye movement recordings is reached at a mean postnatal age of 11.2 weeks in full-term infants. Based on pursuit eye movement recordings, our results show a lower grating acuity than the average age-matched values measured with the preferential looking technique.[8–10] This may be because of methodical differences. Visual pursuit was only considered present if the infant followed the stimulus for at least 6.2 seconds However, no defined fixation time is required in the preferential looking technique. In addition, pursuit eye movements involve an oculomotor response that may be controlled at a different cortical level than preferential looking. Another method used to assess visual acuity in infants involving the oculomotor system is the determination of OKN eye movements. Although with this method stimuli-related variations are found,[6] results are in a comparable range to those found in our study with pursuit eye movements.

The examination of the OKN confirmed the known asymmetry of monocular-elicited OKN in infants younger than 3 months of age, appearing earlier in the temporonasal direction. Most studies showed the OKN to become symmetrical at approximately 3 months of age.[33,35] We found the mean onset of OKN if stimuli moved from nasal to temporal only at the beginning of the third month of age (mean postnatal age in full-term infants: 9.3 weeks). In the infants tested with OKN until 14 weeks of age, we observed still an obvious difference between the OKN response to stimuli from nasal to temporal direction and response to stimuli from temporal to nasal direction. With our method, the appearance of OKN and of OKN symmetry seems to be later than reported in the literature.[33,35] This may be because of the fact that we used a smaller stimulation field, whereas full field stimulation was used in the studies above.

In conclusion, our results indicate that the development of parameters reflecting visual acuity and binocular vision is similar in healthy preterm and full-term infants, when infants of the same postmenstrual age are compared. Normative data obtained for full-term infants are an appropriate standard also

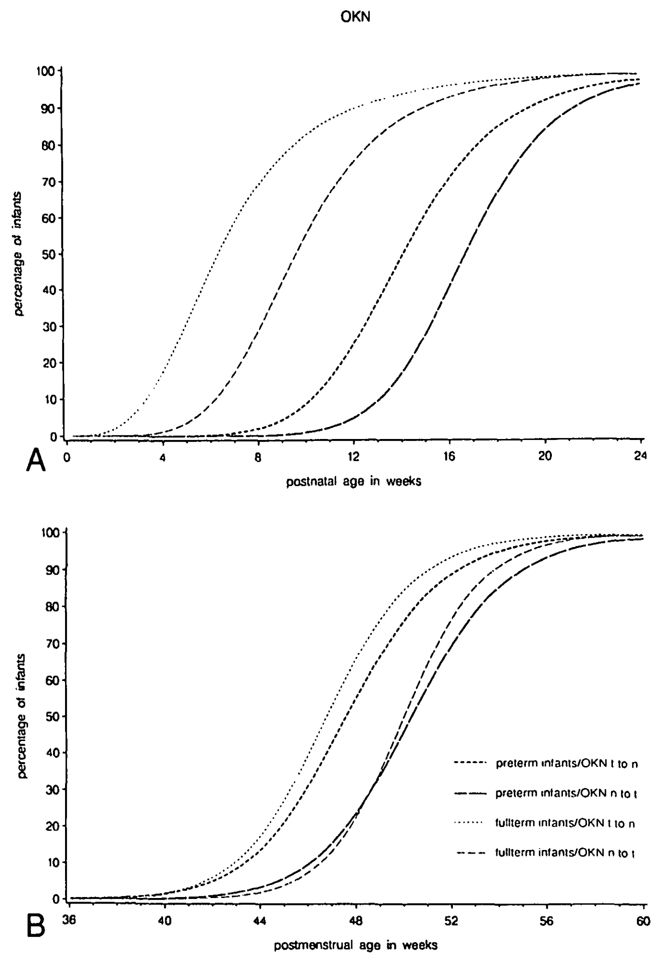

FIGURE 5. Kaplan-Meier curves and log-logistic fitting of percentages of preterm and full-term infants showing OKN to stripes moving in nasal to temporal (n to t) and temporal to nasal (t to n) direction at different postnatal (A) and postmenstrual (B) ages.

for preterm infants as long as the preterm infant's corrected age is used for comparison in the first months of life. Our results contradict the hypothesis that early visual experience gained by preterm infants positively influences the development of visual acuity or binocular functions.

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