OCULAR BIOMETRY IN PRE-TERM INFANTS WITHOUT RETINOPATHY OF PREMATURITY

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SUMMARY

Serial ocular A-scan ultrasound biometry was performed on 100 pre-term infants (less than 32 weeks gestation and/or less than 1500 g) who did not show features of retinopathy of prematurity (ROP) during a screening programme. Axial length increased from 15.38 ± 0.25 mm at 33 weeks post-menstrual age to 16.88 ± 0.59 mm at 41 weeks (rate of growth 0.18 mm/week, $r = 0.99$). The rate of growth appeared to slow down after 40 weeks (term) to 3 months post-term. Male infants had longer eyes and a greater rate of growth than female infants. Axial length (AL) was significantly correlated with birth weight, biparietal and occipito-frontal diameter in the weeks after birth. Between weeks 33 and 41, the anterior chamber depth (ACD) increased from 1.92 ± 0.13 mm to 2.43 ± 0.18 mm, and lens thickness (LT) increased from 3.82 ± 0.33 mm to 3.90 ± 0.13 mm. The largest percentage growth between weeks 33 and 41 occurred in ACD (22%), followed by vitreal length (10%), AL (9%) and LT (2%). These data will help in future studies on the role which ROP plays in the development of ocular growth.

Recently, ocular axial length in infants with stage 4 and 5 retinopathy of prematurity (ROP) was found to be significantly smaller than in normal full-term infants at 5 months chronological age.[1] A previous report had shown that axial length in regressed cicatricial ROP was longer than in controls.[2] Thus ROP may play a role in the normal development of ocular dimensions. Little is known of the post-natal ocular growth in pre-term infants in the weeks following birth. In this report we present ultrasonic measurements of axial length, anterior chamber depth and lens thickness in preterm infants who did not show any signs of ROP, and examine the interaction between axial length and birth weight, biparietal diameter and occipito-frontal diameter.

SUBJECTS AND METHODS

A screening service for ROP in pre-term infants (<32 weeks gestational age and/or <1500 g birth weight) was introduced in the Mersey region of England in April 1989[3] based on the recommendations of the CRYO-ROP trial.[4] Infants born at 32 weeks gestation are screened approximately 6 weeks post-delivery and fortnightly thereafter until signs of ROP regression are noted or until term. Cyclopentolate 0.5% eyedrops are used to dilate the pupils and the fundi examined with indirect ophthalmoscopy.

Since September 1990, ocular A-scan ultrasound biometry has been incorporated into the screening programme. This is performed after the fundal examination, using topical anaesthesia (benoxinate 0.4%) and the Echorule Ultrasonic Biometer (3M Visioncare, Downview, Ontario, Canada). Three or more readings per eye were recorded and averaged for over 95% of the eyes studied.[5] It was not technically possible to do this at every examination because some infants were either too fractious or too ill in incubators to allow for repetitive applanation with the probe.

We present the results in 100 pre-term infants who did not show evidence of ROP using the above screening protocol, and who had serial biometry performed during the screening programme. Biparietal and occipito-frontal diameters were measured using a slide rule caliper. Data on birth weight and gestational age were gathered from hospital records. Gestational age was assessed by early ultrasound and mothers' dates. Statistical analysis (simple linear regression and unpaired t-tests) was carried out with the Macintosh Powerbook 100 PC using the Statview software package.

RESULTS

The mean gestational age of the 100 infants was 29.9 ± 1.3 weeks (range 27–32 weeks), and the mean birth weight was 1430 ± 278 g (range 604–2300 g). The 66 male infants (birth weight 1458 ± 278 g) were heavier than the 34 female infants (1375 ± 273 g), but not significantly so ($p = 0.16$). The average measurements of axial length (AL) at each week from 33 to 41 weeks and at 3 months post-term are presented in Table I. The rate of growth in AL between weeks 33 (15.38 ± 0.25 mm) and 41 (16.88 ± 0.59) was 0.18 mm/week ($r = 0.99$,

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Table I. Ocular axial length in pre-term infants

Post-menstrual age (weeks)	33	34	35	36	37	38	39	40	41	52
Axial length (mm)										
Mean	15.38	15.76	15.76	15.98	16.26	16.21	16.54	16.73	16.88	18.23
SD	0.25	0.42	0.38	0.48	0.39	0.53	0.40	0.41	0.59	0.57
No. of eyes measured	26	36	62	68	62	44	49	62	42	22

Table II. Sex differences in axial length in pre-term infants

Post-menstrual age (weeks)	33	34	35	36	37	38	39	40	41	52
Axial length (mm)										
Male	15.42	15.84	15.84	16.02	16.29	16.35	16.64	16.78	17.10	18.41
Female	15.32	15.58	15.58	15.92	16.18	15.98	16.31	16.64	16.59	18.13
p value	0.38	0.10	0.01	0.38	0.30	0.02	0.006	0.20	0.005	0.29

Table III. Biparietal and occipito-frontal diameters in pre-term infants

Post-menstrual age(weeks)	33	34	35	36	37	38	39	40	41	52
Biparietal diameter (mm)	74.2	78.3	78.7	81.8	83.0	85.6	88.1	90.3	91.2	107.0
Occipito-frontal diameter (mm)	108.4	112.0	113.8	119.7	119.5	122.4	125.8	128.6	129.0	143.7
No. of infants measured	12	15	29	28	28	16	21	24	12	3

$p<0.0001$); between weeks 33 and 37 it was 0.20 mm/week and between weeks 37 and 41 it was 0.18 mm/week. The rate of growth between week 33 and 3 months post-term (i.e. week 52) was 0.15 mm/week.

The mean AL of pre-term male infants ($n = 66$) was greater than in female infants ($n = 34$) at all weeks from 33 weeks to 3 months after term (Table II). This difference was statistically significant ($p<0.05$) at weeks 35, 38, 39 and 41. Eyeball length grew at a rate of 0.19 mm/week in the male infants ($r = 0.99$) and 0.16 mm/week in the female infants ($r = 0.97$) from week 33 to 41.

The measurements of biparietal diameter (BPD) and occipito-frontal diameter (OFD) are presented in Table III. The rate of growth of BPD and OFD between weeks 33 to 41 was found to be 2.1 mm/week ($r = 0.99$) and 2.6 mm/week ($r = 0.99$), respectively. The relationship between AL (average of both eyes) and birth weight, BPD and OFD at both 34 weeks and 40 weeks (term) chronological age was determined by simple linear regression analysis and is presented in Table IV. This shows that ocular AL is significantly ($p<0.05$) associated with birth weight, BPD and strongly with OFD ($p = 0.003$) at 35 weeks. These correlations are weaker at 40 weeks yet the relationship persists such that the ocular AL is longer in those with the heaviest birth weight and the larger BPD and OFD during the weeks following birth until term.

Data on anterior chamber depth (ACD) and lens thickness (LT) show a significant increase of 0.05 mm/week for ACD ($r = 0.95$, $p = 0.0001$) and 0.012 mm/week for LT ($r = 0.74$, $p = 0.02$) between weeks 33 and 41 (Table V). The ACD increased from 1.92 ± 0.13 mm at 33 weeks to 2.36 ± 0.15 mm at term, while LT grew from 3.82 ± 0.33 mm at 33 weeks to 3.99 ± 0.10 mm at term (40 weeks).

Table IV. Correlation between axial length and birth weight, biparietal and occipito-frontal diameters at 35 and 40 weeks post-menstrual age

	Axial length					
	35 weeks			40 weeks		
	r	*p* value	*n*	*r*	*p* value	*n*
Birth weight	0.38	0.04	31	0.35	0.07	29
Biparietal diameter	0.41	0.03	27	0.38	0.08	22
Occipito-frontal diameter	0.55	0.003	27	0.66	0.008	22

The percentage growth between weeks 33 and 41 was 9% for AL, 22% for ACD and 2% for LT. Using an approximate calculation of vitreal or posterior segment size [axial length minus (ACD plus LT)], the vitreal length at 33 weeks was 9.64 mm, and 10.64 mm at 41 weeks. This gives a percentage growth of 10% in vitreal length in that time period.

DISCUSSION

The factors which determine ocular growth are incompletely understood. The change from hyperopia to emmetropia which occurs in early life is associated with considerable alteration in AL, ACD, and both corneal and lenticular refractive power. Gordon and Donzis[6] found that term infants had a mean AL of 16.8 mm, a mean keratometry power of 51.2 dioptres, and a mean lens power of 34.4 dioptres. In this study of 100 pre-term infants (less than 32 weeks gestation and/or less than 1500 g birth weight) without ROP or other ocular disease, we have documented the weekly growth in AL, ACD and LT from weeks 33 to 41 and also at 3 months (52 weeks) post-term.

There was an almost completely linear growth curve in AL ($r = 0.99$) and ACD ($r = 0.95$) from week 33 to 41; the correlation coefficient for LT was less linear but still significant at $r = 0.74$. These results are in agreement with a recent report from Tucker *et al.*[7] for AL, who also found a linear growth in corneal diameter between weeks 25 and 37. Hirano *et al.*[8] have shown that 'premature' infants (defined as <2000 g) have a linear growth in AL for 12 months after birth which then levels off, while 'mature' infants show a linear growth for 4–5 months and after this the growth slows down. Similarly, Harayama *et al.*[9] found an almost linear increase in ocular diameter in the enucleated eyes of 252 undamaged human fetuses (measured by a micrometer) between weeks 12 to 40. It may be deduced that overall growth curves in AL of pre-term and

Table V. Anterior chamber depth and lens thickness in pre-term infants

Post-menstrual age (weeks)	33	34	35	36	37	38	39	40	41	52
Anterior chamber depth (mm)	1.92	2.01	2.07	2.18	2.14	2.24	2.19	2.36	2.43	2.73
SD	0.13	0.12	0.14	0.15	0.25	0.12	0.11	0.15	0.18	0.21
No. of eyes	10	10	32	16	30	14	22	25	23	19
Lens thickness (mm)	3.82	3.90	3.87	3.88	3.90	3.91	3.93	3.99	3.90	3.88
SD	0.33	0.15	0.12	0.11	0.13	0.11	0.11	0.10	0.13	0.13
No. of eyes	10	10	32	16	30	15	22	24	23	20

term babies run a parallel time course – separated by the difference in gestational age.

Larsen,[10] using A-scan biometry, found the AL in 80 term babies was 16.78 + 0.51 mm, and later Blomdahl[11] gave measurements of 16.6 mm in 28 term infants. These figures for term babies correspond well with the pre-term infants in our study at 40 weeks (i.e. term): 16.73 ± 0.41 mm. Forslund[12,13] has shown that when corrected for gestational age, pre-term infants had the same height and weight and the same stage of neurological development at term, 9 and 18 months of chronological age as term babies. Fledelius[14] performed biometry and keratometry in low birth weight and full-term infants when they reached the ages of 10 and 18 years. He found that premature eyes do not 'catch up' with full-term children. The emmetropic 18-year-old AL was 23.29 mm in premature infants and 23.76 mm in term infants; and he comments that 'low birth weight is an impediment to the overall development of the individual'. Our results suggest that premature infants without ROP (when adjusted for gestational age) have the same AL as that reported by others in term infants.

Recently Fledelius[15] reported that the AL of 101 pre-term (<34 weeks gestation and/or <1800 g birth weight) and 25 term infants measured 17.02 ± 0.53 mm and 17.03 ± 0.54 mm respectively at 40 weeks. The group of 101 pre-term infants included 25 with regressed stage 1 and 2 ROP, and the inclusion of these may have altered the data if ROP is shown to play a significant role in ocular growth. The results seem to contradict the earlier assertion of Fledelius[14] that the AL of premature infants failed to 'catch-up' with term infants. He also reported that the ACD was significantly shallower and the LT significantly greater in the pre-term compared with the term infants.

Sorsby and Sheridan[16] measured the sagittal diameter of enucleated cadaver infants, and found that males (17.9 mm) had longer eyes than females (17.7 mm). Larsen[10] observed a significant difference ($p<0.01$) between term male (16.78 mm) and female (16.40 mm) infants using ultrasound biometry, and found that this sex difference persists during childhood into adulthood. We found that eyes of male infants were larger between week 33 to 3 months post-term, and the difference was significant at weeks 35, 38, 39 and 41, with a difference of 0.51 mm at 41 weeks. This occurred despite the fact that there was no significant difference in birth weight although male infants were heavier. It appears too that the growth rate in AL was greater in male infants (0.19 mm/week between weeks 33 and 41) than in female infants (0.16 mm/week). Fledelius[15] likewise found that AL in pre-term male infants was significantly longer than in female infants.

A review of the literature on AL in premature babies reveals that while several authors have addressed this topic, there are few or no data available on the week-by-week measurement of eyeball length in the weeks after birth. The studies of Hirano *et al.*,[8] Yamamoto *et al.*[17] and Tucker *et al.*[7] all show the linear growth curves but measurements at individual weeks are lacking. Both Grignola *et al.*[18] and Gordon and Donzis[6] provide approximate data, e.g. Grignola uses descriptions such as 7 and 8 months gestation, while Gordon pooled results between weeks 30 to 35, 35 to 39, and 39 to 41. We have presented more precise data than previous publications on AL between 33 to 41 weeks and at 3 months post-term (52 weeks chronological age). These data were gathered from infants who satisfied the criteria laid down for ROP screening, and therefore differ from other published reports in the selection of subjects for study. Our results therefore pertain to a specific subset of premature infants.

AL of the infants in this study increased from 15.38 mm at 33 weeks to 16.88 mm at 41 weeks chronological age, and was 18.23 mm at 3 months post-term (52 weeks chronological age). The average weekly growth from 33 to 41 weeks was 0.18 mm/week. The rate of growth rate between 33 weeks and 3 months was 0.15 mm/week. These observations are very similar to those of Fledelius.[15] We also studied the growth curves during two specific time intervals. This was performed because the mean time at which babies with stage 3 threshold ROP require treatment is 37 weeks.[4] We wondered whether there might be a different rate of growth before and after 37 weeks. The rate of AL growth reduced from 0.20 mm/week between weeks 33 and 37 to 0.18 mm/week between weeks 37 and 41. This suggests that there is a slight reduction in the rate of ocular growth after week 37. It may be that the period of maximum ocular growth in the weeks following birth in pre-term infants coincides with the period of maximum retinal vascular abnormalities noted in ROP.

We were able to show a significant association between AL at 35 weeks and birth weight, as well as both the OFD and BDP measurements at 35 weeks. This trend appeared to hold up when assessed at 40 weeks, although the relationships with both birth weight and BDP were of only borderline significance ($0.05<p<0.10$). This suggests that the greater the time interval after birth, the weaker the effect of birth weight on ocular development, and indicates that other external and internal factors play a more important role in ocular growth. Fledelius also found a weak but significant correlation between birth weight and AL at 40 weeks in pre-term infants.[15] Overall, eyeball length was best correlated with OFD, indicating that head

Table VI. Anterior chamber depth, lens thickness and vitreal length as a percentage of axial length

	Post-menstrual age (weeks)			Emmetropic adult males[19]
	33	40	52	
Anterior chamber depth	12.5	14.1	15.0	16.0
Lens thickness	24.8	23.8	21.3	16.1
Vitreal length	62.7	62.1	63.7	67.9
Axial length (mm)	15.38	16.73	18.23	23.42

length is a good indicator of AL size. Larsen[19] observed a significant correlation between AL and head circumference, head length and head width in 40 emmetropic adults. Both Hirano *et al.*[8] and Harayama *et al.*[9] in pre-term infants, and Blomdahl[11] in term infants, found a significant relationship between AL and birth weight.

ACD increased from 1.92 mm at 33 weeks to 2.36 mm at 40 weeks, while LT grew from 3.82 mm to 3.99 mm during the same time period. These measurements are quite comparable with those obtained by Larsen[10] in 80 newborn term infants, and those of Fledelius[15] in pre-term infants at 40 weeks, but less than the term infants in his study group. As a result, the estimated vitreal length at 40 weeks in the present study (10.38 mm) is again similar to that given by Larsen. It appears that the relative growth of the different ocular dimensions in pre-term infants in the weeks after birth is in keeping with intrauterine growth up to term for AL, ACD, LT and vitreal length – at least in the sagittal plane.

The percentage change in the various parameters measured shows that AL increased by 9%, ACD by 22%, LT by 2% and vitreal length by 10% from week 33 to 41. This suggests that the anterior segment of the eye is changing the most during the weeks following birth – a finding also observed by Fledelius.[15] Tucker *et al.*[7] found an increase of 45% in corneal diameter between week 25 (6.2 mm) and week 37 (9.0 mm) in 70 pre-term infants. The proportions of each of the measurement parameters relative to AL at 33, 40 and 52 weeks is given in Table VI, and the results compared with data given by Larsen[19] for 40 emmetropic adult males. It appears that the relative ratio of ACD to AL in adulthood is almost achieved at 3 months post-term in the infants in this study whose mean gestational age was 29 weeks (therefore their approximate post-natal age is 6 months). The relative size of LT decreases by 5.1% and the vitreal length increases by 4.2% between 52 weeks and adulthood. LT is approximately one quarter of the total AL at 33 weeks; by 52 weeks it is one fifth, and by adulthood one sixth of AL.

The results of the present study highlight the rapid growth in ocular axial length and particularly in anterior chamber depth during the weeks after birth in pre-term infants. The data are specific to a subset of premature babies deemed to be at risk of developing ROP but who, in fact, did not have any of the clinical features of ROP during repeated fundal examinations. The relative growth rates of the various ocular compartments are also presented, as is the relationship between axial length and birth weight, biparietal diameter and occipito-frontal diameter. This information is necessary before a study of the role of ROP in the development of ocular growth can be undertaken.

Key words: Ocular biometry, Pre-term infants, Retinopathy of prematurity, ultrasound.

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