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1 **Refractive status in Nepalese preterm and full term infants early in life**

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23 **Running Head:** Refractive status in preterm infants

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27

28 **Statement of Significance**

29 This study suggests that preterm infants, even without retinopathy of prematurity, are at risk for
30 abnormal refractive development and informs the need for close monitoring of refractive error in
31 such infants, regardless of their retinopathy of prematurity status.

32 **Purpose**

33 To investigate the refractive error trend in Nepalese preterm infants without retinopathy of
34 prematurity (ROP) in the first 6 months of life and explore the association of refractive error with
35 birth weight (BW) and gestational age (GA).

36 **Methods**

37 Thirty-six preterm infants without ROP and 40 full term infants underwent cycloplegic retinoscopy at
38 birth, term (for preterm only), 3 months and 6 months chronologically. Refractive status was
39 classified into emmetropia (mean spherical equivalent refraction (SER) 0 to +3.00 D), myopia
40 (SER<0.00 D) and significant hyperopia (SER>+3.00 D). Refractive parameters at various age points
41 were compared between the preterm and full term infants using General Linear Model Repeated
42 Measures ANOVA.

43 **Results**

44 At birth, the SER in the preterm infants was $+0.84 \pm 1.72$ D, however, there was a shift towards
45 myopia at six months of age (SER= -0.33 ± 1.95 D). There was a significant difference in SER,
46 astigmatism, and anisometropia between preterm and full term infants by 6 months of age ($p < 0.01$).
47 Astigmatism and anisometropia showed an increasing trend with age in preterm infants ($p < 0.05$ at 6
48 months) in contrast to a decreasing trend in full term infants ($p < 0.05$ at three and six months). In
49 preterm infants, there was a statistically significant positive relationship between GA and SER
50 ($\beta = 0.32$, $R^2 = 17.6\%$, $p < 0.05$) but a negative relationship between BW and astigmatism ($\beta = -1.25$,
51 $R^2 = 20.6\%$, $p < 0.01$).

52 **Conclusion**

53 Preterm infants, that do not develop ROP, show a trend towards increasing myopia, and
54 demonstrate greater astigmatism and anisometropia than full term infants in their first six months of
55 life.

56 **Keywords:** Refractive error; preterm, myopia; birth weight; gestational age

57

58 With the introduction of advanced neonatal life support systems, the survival of preterm
59 neonates has significantly increased in the recent years.¹ However, the survival often comes at the
60 expense of a large number of neuro-developmental handicaps that develop secondary to the
61 complications of prematurity.^{2,3} Numerous ocular health challenges are also associated with
62 prematurity. Children who are born premature are at greater risk of having morbid ocular conditions,
63 including retinopathy of prematurity⁴⁻⁶ and refractive error^{7,8}. Moreover, eyes exhibiting retinopathy
64 of prematurity continue to present with signs of myopia, and the degree, as well as frequency of
65 myopia occurrence, is known to be related to retinopathy of prematurity status.⁹ However,
66 prematurity itself has been reported to be a precursor of refractive error development in preterm
67 infants.^{10, 11}

68 Uncorrected refractive error in infants can lead to abnormal visual development resulting in
69 amblyopia and strabismus associated with poor cognitive development and socio-economic
70 consequences.^{12,13} Longitudinal studies on full term infants indicate that refractive status varies with
71 age.^{14,15} While full term new born infants are known to be hyperopic at birth¹⁶⁻¹⁸, there has been a bias
72 towards both hyperopia and myopia in preterm infants.^{17,18} Verma et al studied the refractive status
73 of preterm infants at the age of six months and found that none of them were emmetropic.¹⁹ Further
74 studies have demonstrated a higher incidence of myopia, astigmatism, and anisometropia in preterm
75 infants than full term infants when examined at an age corresponding to term and later.²⁰⁻²³ It has
76 been previously shown that the refractive disorders, such as myopia, astigmatism, and anisometropia,
77 are common in preterm infants with or without retinopathy of prematurity.^{20,24-26} In addition, preterm
78 infants who develop retinopathy of prematurity have been found to be myopic when examined near
79 term.²⁷ These evidences, taken together, suggest that preterm infants are at risk for abnormal
80 refractive development.

81 The magnitude of myopic refractive error in preterm infants decreases as gestational age increases.²⁸
82 Besides gestational age, low birth weight and the duration of oxygen exposure are known to be clinical

83 risk factors for ocular morbidities in preterm infants.^{29,30} It has previously been suggested that birth
84 weight instead of gestational age should be used for screening of refractive error.³⁰ However, reports
85 have also indicated a lack of relationship between birth weight and the refractive status.³¹ Therefore,
86 the association of the clinical risk factors, such as birth weight and gestational age with refractive
87 status in preterm infants is yet to be fully understood.

88 Most of the aforementioned studies have examined refractive status in preterm infants at a specific
89 age early in life or began measurements after three months of age. There is a paucity of data about
90 concurrent longitudinal changes in the refractive state early in the life of premature infants. In
91 addition, discrepancies still exist regarding the relationship of refractive error in infancy to various
92 clinical risk factors, such as birth weight and gestational age in preterm infants. To the best of our
93 knowledge, there are no published reports on the refractive error trend in Nepalese preterm infants
94 without retinopathy of prematurity. The objectives of this study were to investigate the longitudinal
95 changes in the refractive state of preterm infants in the first six months of life and to explore the
96 association of refractive parameters with birth weight and gestational age. In addition, we sought to
97 study the differences in refractive state between preterm infants and their full term counterparts.

98 **Subjects and Methods**

99 This prospective, hospital-based study included 71 preterm infants. Fifty out of the 71 preterm infants
100 completed the follow-up; however, 14 infants were diagnosed as stage 1 retinopathy of prematurity
101 either at term or later. Therefore, only 36 preterm infants without retinopathy of prematurity were
102 included in the final analyses. Forty full term healthy infants served as the control group. The cohort
103 of infants was recruited from the neonatal intensive care unit (NICU) of Tribhuvan University Teaching
104 Hospital (TUTH) in Kathmandu, Nepal. Infants with incomplete or missing records were excluded from
105 the study as were infants with retinopathy of prematurity, craniofacial or other major anomalies,
106 infants in whom the reflex was not clearly ascertainable as well as those unfit for the long examination

107 necessary for the study. The study protocol adhered to the tenets of the Declaration of Helsinki.
108 Institutional ethics committee approval and written informed parental consent were obtained.

109 The first examination was carried out at the NICU of TUTH within one week of birth for both preterm
110 and full term infants. Patient particulars were noted from the medical record file which included a
111 profile of birth history, the age of gestation, birth weight and duration of oxygen exposure. The infants
112 were then referred for follow-up examinations to the Paediatric Ophthalmology Clinic at BP Koirala
113 Lions Center for Ophthalmic Studies (BPKLCOS) where subsequent examinations were carried out at
114 term (± 1 week) (for preterm only), three months (± 1 week) and six months (± 1 week) chronologically.
115 An experienced pediatric ophthalmologist screened the infants for retinopathy of prematurity at the
116 first as well as subsequent visits. All the refractive examinations in preterm and full term infants were
117 performed by a single pediatric optometrist throughout the study duration. Because the data were
118 highly correlated between the two eyes (data not shown), only right eye (OD) data were included in
119 the study.³² However, we also investigated the difference in mean spherical equivalent refraction
120 between the two eyes to analyze for anisometropia.

121 Anterior segment evaluation was carried out with a torch light examination. For cycloplegia and
122 paralysis of accommodation, 1% tropicamide and 2.5% phenylephrine eye drops were used twice, one
123 drop in each eye at an interval of 15 minutes. Eyelids were retracted using infant wire eye speculum
124 (K 1-5350). Fundus examination was done with a binocular indirect ophthalmoscope with a 20 D
125 auxiliary lens and scleral indentation. Retinoscopy was performed by streak retinoscopy at least 30
126 minutes after the instillation of the last drop using a lens bar as well as handheld lenses. The
127 retinoscopic reflex was assessed for variability and the refraction was determined only after the reflex
128 appeared stable. The mean spherical equivalent refractive error was determined as the sum of the
129 spherical value and half of the cylindrical amount in dioptres (D).

130 Based on gestational age, preterm infants were classified into extremely preterm (<28 weeks), very
131 preterm (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks).³³ Infants were further

132 classified as low birth weight (1.5 to <2.5kg), very low birth weight (1 to <1.5kg) and extremely low
133 birth weight (<1 kg).³³ Retinopathy of prematurity was classified according to the international
134 classification of retinopathy of prematurity criteria.³⁴ Infants were divided into three groups based on
135 their spherical equivalent refractive error. Emmetropia was defined as 0 to +3.00 D mean spherical
136 equivalent refraction, myopia as less than 0 D mean spherical equivalent refraction and significant
137 hyperopia as more than +3.00 D mean spherical equivalent refraction. Significant astigmatism was
138 defined as ≥ 1.00 D and significant anisometropia as ≥ 1.00 D difference in the spherical equivalent
139 between two eyes.²¹ Astigmatism was classified into with-the-rule astigmatism (WTR), positive
140 cylinder axis $90^\circ (\pm 15^\circ)$, that is, vertical meridian having greater refractive power than the horizontal
141 meridian, against-the-rule astigmatism (ATR), positive cylinder axis $180^\circ (\pm 15^\circ)$, that is, horizontal
142 meridian having greater refractive power than the vertical meridian and oblique astigmatism, all other
143 cylinder axes.²¹

144 Statistical analyses were done using SPSS v20.0 (SPSS Inc., Chicago, Illinois). Descriptive statistics
145 (mean, SD, range) were used to describe the measure and spread of continuous variables in our
146 sample. Repeated measures ANOVA was conducted for each outcome (spherical equivalent
147 refraction, astigmatism, and anisometropia) with a between subjects factor (study group with 2
148 levels), a within-subject factor (age with four levels) and one interaction term (group*age). Linear
149 regression was used to evaluate the relationship of birth weight and gestational age with mean
150 spherical equivalent refraction at birth. Fisher's exact test was used in the analysis of contingency
151 tables. A *P* value <0.05 was considered statistically significant.

152 **Results**

153 The various characteristics of 36 preterm and 40 full term infants are shown in Table 1. Gestational
154 age of preterm infants ranged from 28 to 36 weeks with a mean age of 32.9 (SD=2.23) weeks. Out of
155 36 preterm neonates, 25 (69.4%) as low birth weight and 11 (30.6%) as very low birth weight. The

156 mean weight of preterm infants at birth was 1.63 kg (SD=0.30) while that of full term infants was
157 3.49 kg (SD=0.48).

158 **Distribution of refractive error**

159 The distribution of the refractive status was determined on the basis of spherical equivalent refractive
160 error according to the pre-set criteria²¹. At birth, 69.4% of the preterm infants had emmetropia, 25.0%
161 had myopia, and 5.6% had significant hyperopic as shown in Table 2. The mean spherical equivalent
162 refractive error for these infants at birth was +0.84D (SD=1.72) (Table 4). However, there was a shift
163 towards myopia by 6 months of age with a mean spherical equivalent refractive error of -0.33D
164 (SD=1.95) (Table 4) with half of the infants (50.0%) in the myopia category. This was not true for full
165 term infants in which 95.0% of them were emmetropic at birth with a mean spherical equivalent
166 refraction of +2.19D (SD=0.66) and all of these infants were emmetropic by 6 months of age (Table 2
167 and 5). Astigmatism was equally likely to occur in preterm infants and full term infants at birth (Fisher
168 exact test, $p=0.199$) and when present, the majority of infants had ATR astigmatism (36.1% and 35.0%
169 in preterm and full term infants respectively) (Table 3).

170 **Refractive development in the first six months of life**

171 The results from the RM ANOVA with a between subjects factor (study group with 2 levels), a within-
172 subject factor (age with 4 levels), and interaction term (between group*age) with post hoc testing are
173 presented in Tables 4-6 (Table 4: within preterm; Table 5: within full term; Table 6: between group
174 comparisons at each time point). There was a significant main effect of age on spherical equivalent
175 refraction ($p<0.001$) with no significant interaction between age and study group. Multiple
176 comparisons using Bonferroni correction showed a significant difference in mean spherical equivalent
177 refraction from birth to 3 months ($p<0.001$) as well as from birth to 6 months ($p<0.001$) in preterm
178 infants. There was also a statistically significant difference in spherical equivalent refraction of full
179 term infants from birth to three months ($p<0.001$), birth to six months ($p<0.001$) as well as three
180 months to six months ($p<0.001$). Both astigmatism ($p<0.005$) and anisometropia ($p<0.05$) showed an

181 increasing trend and differed significantly between age points of preterm infants. However, post hoc
182 analysis revealed differences in astigmatism and anisometropia which were significant only between
183 birth and six months ($p<0.05$). There was also a statistically significant difference in astigmatism when
184 compared between different age points in full term infants ($p<0.001$). However, a significant decrease
185 in anisometropia was noted only between birth and six months ($p<0.05$) as well as three months and
186 six months ($p<0.01$) in full term infants (Table 4 and 5).

187 **Comparison of refractive parameters between full term and preterm infants over time**

188 We also compared all the refractive parameters between preterm and full term infants at different
189 chronological age points. There was a significant effect of study groups (preterm vs full term) on
190 spherical equivalent refraction at birth ($p<0.001$), term ($p<0.001$), three months ($p<0.001$) and six
191 months ($p<0.001$) (Table 6). With an increase in age, there was also an increase in the difference in
192 astigmatism and anisometropia between preterm and full term infants (Figure 1). A statistically
193 significant difference in astigmatism was noted between preterm and full term infants at three months
194 ($p<0.01$) and six months ($p<0.001$). In contrast, a difference in anisometropia was present between
195 preterm and full term infants only at six months ($p<0.01$) (Table 6).

196 **Relationship of refractive parameters in preterm infants with birth weight and gestational age**

197 We performed linear regression analysis to evaluate the relationship of gestational age and birth
198 weight with spherical equivalent refraction, astigmatism, and anisometropia in preterm infants at
199 birth. Gestational age was significantly related to spherical equivalent refraction explaining around
200 18% of the variation ($\beta=0.32$, $R^2= 17.6\%$, $p<0.05$) whereas, there was a weak relationship between
201 spherical equivalent refraction and birth weight ($\beta= 1.45$, $R^2= 6.5\%$, $p=0.133$) (Figure 2).

202 Interestingly, there was a moderate negative statistically significant relationship between birth
203 weight and astigmatism ($\beta=-1.25$, $R^2= 20.6\%$, $p<0.01$) with approximately 20.0% of variations in
204 astigmatism being explained by birth weight. However, a poor relationship was established between

205 gestational age and astigmatism ($\beta=-0.05$, $R^2= 1.9\%$, $p=0.420$) (Figure 3). Both birth weight and
206 gestational age were poorly related to anisometropia in preterm infants at birth ($R^2= 0.7\%$, $p=0.619$
207 and $R^2= 3.3\%$, $p=0.290$ respectively).

208 **Discussion**

209 Ocular morbidities are common sequelae following premature birth. Emmetropization often fails in
210 preterm infants who develop retinopathy of prematurity, resulting in high levels of refractive error
211 and a myopic bias.^{35, 36} Due to clinical risk factors such as birth weight and gestational age,
212 prematurity might also signal abnormal refractive development independent of retinopathy of
213 prematurity status at an early stage of life. In an effort to elucidate the trend of refractive
214 development in preterm infants without retinopathy of prematurity, we measured refractive errors
215 longitudinally in a cohort of Nepalese preterm infants and their full term counterparts in the first 6
216 months of life. In addition, we explored the relationship between refractive error at birth with
217 clinical risk factors, such as birth weight and gestational age in the preterm infants. The findings of
218 this study indicate that 1) preterm infants, although without retinopathy of prematurity, are likely to
219 be at risk for abnormal refractive development early in life with a greater magnitude of myopia,
220 astigmatism, and anisometropia than the full term infants, and 2) younger infants (based on
221 gestational age) and infants with low birth weights are likely to be born with greater magnitude of
222 myopia and astigmatism, respectively.

223 **Distribution of refractive error**

224 In our study, the prevalence of myopia in preterm infants increased from birth to six months with
225 50.0% having myopia (mean spherical equivalent refraction <0 D) at 6 months compared to 25.0% at
226 birth. In contrast, nearly all of the full term infants had emmetropia (mean spherical equivalent
227 refraction 0 to 3.00 D) throughout the six-month study period (At birth: 95.0%, At six months: 100%).
228 We found a much lower prevalence of hyperopia in preterm infants than has been reported

229 previously (76.8%⁸, 66.6-70%¹⁹). This difference in refractive error prevalence in preterm infants
230 might be due to several reasons. Firstly, our study set a criterion for refractive error classification
231 regarding significant hyperopia as $>+3.00$ D in accordance with previously used limits. Although it is
232 not explicitly clear what criteria were used in the previous studies, it is likely that the conventional
233 way of classifying refractive error (hyperopia >1.00 D) might have resulted in a greater prevalence of
234 hyperopic refractive error in previous studies. Secondly, cyclopentolate was used to achieve
235 cycloplegia in the aforementioned studies. While it is difficult to attribute the lower prevalence of
236 hyperopia found in our study solely to the use of a different cycloplegic drug (tropicamide) as both
237 of these agents have been reported to yield similar results in healthy infants⁴³, we are not able to
238 completely rule out this possibility. Thirdly, there are ethnic differences between the infants across
239 these studies (Nepalese, Indian and Israeli cohorts) and refractive outcomes are known to vary with
240 ethnicity.^{37, 38} In a multicenter, longitudinal observational study of refractive error prevalence in four
241 ethnic groups, Kleinstei et al noted a significant difference in refractive error prevalence as a
242 function of ethnicity (Chi-square test, $p<.001$) even after controlling for age and sex.³⁷ Although we
243 are not aware of any studies involving Nepalese infants that allow direct comparisons to our
244 findings, the ethnic variations in prevalence of refractive error globally suggest that the differences
245 across the various studies might well be attributed to ethnicity.

246 The cohorts of preterm and full term infants in our study were equally likely to have astigmatism at
247 birth. These results corroborate the findings of previous works reported in the literature.^{23, 30}
248 Interestingly, we found that ATR astigmatism was more prevalent among astigmatic preterm infants,
249 which is in agreement with a previous study of 59 preterm infants.²³ However, a large proportion of
250 both preterm and full term infants were reported to have WTR astigmatism in a different study.³⁰
251 While the exact reasons for such discrepancy remain unclear, we speculate that the ethnic
252 differences in study population, as mentioned earlier, might be a contributing factor.

253 **Refractive development in the first six months of life**

254 Prior studies that have evaluated refractive status in preterm infants report a wide range of values in
255 the literature (+0.87 to -1.54 D).^{46,47,48} We found a mean spherical equivalent refraction of +0.82 D in
256 our cohort of preterm infants at term, which compares favorably with values reported by Cook et al
257 (+0.74 D)⁴⁶ at 40 weeks of postmenstrual age and Saunders et al (+0.87D)²³ at term. Interestingly,
258 our finding differs from Gordon et al's report of -1.00 D⁴⁷ at between 35 and 40 weeks
259 postmenstrual age and Fledelius report of -1.54 D⁴⁸ at term. However, it should be noted that there
260 was a preponderance of younger infants (based on gestational age) in Gordon et al's study which
261 might have resulted in a more myopic refractive error. Also, the refractive error data in Fledelius'
262 study was a mathematical adjustment from a wider range of postmenstrual ages. Infants in
263 Fledelius' study were examined between 36 and 54 weeks postmenstrual age and some of them had
264 regressed stage 1 or 2 retinopathy of prematurity.

265 The analysis of refractive error as a function of age indicated a trend towards relative myopia as well
266 as an increase in astigmatism and anisometropia in preterm infants. Although spherical equivalent
267 refraction continued to show a relatively myopic trend in full term infants, astigmatism and
268 anisometropia decreased in magnitude as the infants grew older. Our findings for full term infants
269 are consistent with those of Saunders et al²³; however, preterm infants showed a contrasting trend,
270 as Saunders and colleagues, in their study, noted a decrease in all refractive parameters (spherical
271 equivalent refraction, astigmatism, and anisometropia) from birth to six months.

272 Previous studies investigating refractive error distribution in full term infants have consistently
273 reported moderate hyperopia using either atropine (Gernet: +2.75 D)⁴⁹ or cyclopentolate (Luyckz:
274 +2.40 D⁵⁰; Saunders et al: +3.47 D²³ and Blomdahl: +3.60 D⁵¹) as cycloplegic agents. Consistent with
275 these reports, we found moderate hyperopia (mean spherical equivalent refraction = +2.19 D) in full
276 term infants at birth. The hyperopic error reduced with age and subsequently decreased to +1.06 D
277 at six months— a trend similar to that reported previously by Saunders et al (+3.47 D at birth to
278 +2.36 D at 6 months). Because infants' eyes are known to emmetropize with age and gradually
279 develop towards a state of no refractive error, it is not surprising to see a decreasing trend in

280 hyperopia. However, we observed relatively low hyperopia in full term infants at all examination age
281 points in compared to previous reports. As discussed previously, different ethnicities in the study
282 cohorts (Asians in the present study vs Caucasians in Saunders et al's study) and to a lesser extent,
283 the choice of cycloplegic drug might have contributed to the inconsistencies in the findings across
284 studies. Further studies comparing full term and preterm infants for refractive differences in older
285 populations might aid in our understanding of the mechanisms behind such differing trends.

286

287 **Comparison of refractive parameters between full term and preterm infants over time**

288 Preterm infants were relatively myopic when compared to their full term counterparts at all
289 examination age points. At birth, preterm infants were more likely to have anisometropia and a
290 greater astigmatism than their full term peers. These findings of the current study are similar to that
291 reported by Saunders and colleagues in a Caucasian cohort.²³ However, in contrast to Saunders et
292 al's study, the differences in refractive parameters (spherical equivalent refraction, astigmatism, and
293 anisometropia) between preterm and full term infants also persisted at six months of age.

294 Furthermore, there was a contrasting trend of refractive development with age between these two
295 cohorts— Preterm infants showed a trend for increasing astigmatism and anisometropia, whereas
296 full term infants showed the opposite trend with decreasing astigmatism and anisometropia.

297 However, in both cohorts, there was an increase in relative myopia with age. Saunders et al, in their
298 study, did not identify such differing trends of refractive development between preterm and full
299 term infants throughout the six-month study period.²³ The authors, however, highlighted the
300 differences in refractive parameters early (i.e. at birth and at term) and indicated that preterm and
301 full term infants might differ in relation to their refractive development.²³

302 **Relationship of refractive parameters in preterm infants with birth weight and gestational age**

303 In our study, younger preterm infants (in terms of gestational age) showed a higher degree of myopia
304 suggesting that the degree of relative myopia at birth might be directly related to gestational age. This
305 is in line with a previous study by Dobson et al³⁵, who reported an inverse relation between gestational

306 age and spherical equivalent refraction, with the youngest infants being more myopic. Because eye
307 size in preterm infants tends to be smaller with lower gestational age, one might expect a hyperopic
308 refractive error in younger preterm infants. However, it may well be that the reduced radius of
309 curvature of refractive structures, such as cornea and lens might be the contributing factor for myopia
310 in preterm infants early in life. Previous studies have suggested an increase in corneal curvature as a
311 precursor to myopia associated with prematurity and a poor relation between axial length and
312 refractive status at birth in premature infants.^{39,40} It should, however, be noted that such relationship
313 between gestational age and myopia has not always been observed.²³ This was speculated to be due
314 to the close association between birth weight and age, which might make it extremely difficult to
315 discriminate between the effect of early birth and small size on refractive components.²³ Although,
316 gestational age and astigmatism at birth were not associated in our study, there was a negative
317 association between birth weight and astigmatism in preterm infants. This is in contrast to the
318 previous report that gestational age correlates better with astigmatism than birth weight in preterm
319 infants.²³ Furthermore, at birth, we did not see any association between either gestational age or birth
320 weight with anisometropia. Because there are considerable differences in study cohorts across these
321 studies and variations are likely to occur accordingly, these findings need to be interpreted with care.
322 Moreover, there was a large variability in the data as evident from the scatterplots (Figure 2 and 3).

323 **Limitations of the study**

324 All 76 subjects participating in the study were Nepalese. Since refractive errors are known to vary
325 with ethnicity, we are unable to generalize the results of this study to similar cohorts from ethnic
326 groups other than of Nepalese origin. Furthermore, the cohort of infants recruited for the study was
327 also limited by its sample size; hence, caution must be applied in extrapolating these findings.
328 Additional studies with larger samples and diverse populations need to be undertaken to lend
329 weight to these results. In order to ensure meaningful comparison of findings across studies, we
330 implemented refractive error classification criteria previously used in studies investigating refractive
331 development in preterm infants over a long period after birth (2- 3.5 years)^{21,23}. However, it is

332 important to bear in mind these unconventional criteria when drawing inferences from the present
333 study. Although, the refractive status of all infants at various age points was evaluated under
334 cycloplegia, the combination of tropicamide and phenylephrine was used to achieve the cycloplegic
335 effect instead of cyclopentolate— a cycloplegic drug of choice in children. The measurement of
336 various biometric parameters, such as axial length and corneal curvatures would have potentially
337 provided further insights on differences in refractive error outcomes between preterm and full term
338 infants. However, these parameters were not measured as a part of this study. Although, both
339 preterm and full term infants in our study were followed up for six months to observe the
340 longitudinal changes, we are unable to determine how the refractive parameters would have
341 continued to develop over the course of a longer critical period of development. Further studies
342 need to be undertaken to determine whether the differences in refractive parameters between
343 preterm infants and their full term counterparts in the first six months of life as observed in our
344 study continues further progression as the infants grow older.

345 **Conclusion**

346 In summary, our study demonstrated that Nepalese preterm infants are at risk for abnormal
347 refractive development with a trend towards increasing magnitude of ametropia (i.e. myopia,
348 astigmatism and anisometropia). Such refractive trend is likely to occur in preterm infants even
349 when they do not develop retinopathy of prematurity, and could present a major challenge to the
350 developing visual system. It is, therefore, essential to monitor the preterm infants for refractive
351 outcomes regardless of their retinopathy of prematurity state.

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357

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468 **Figure legends**

469 **Figure 1.** (a) Astigmatism (right eye) and (b) anisometropia in preterm and full term infants at
470 different age points. Error bars represent standard error of mean. The open circles (o) and dotted
471 lines (---) indicate values for full term infants whereas the filled circles (●) and continuous line (—)
472 indicate corresponding values for preterm infants. D represents dioptres.

473 **Figure 2.** Association between spherical equivalent refraction (SER) in right eye (OD) at birth and (a)
474 gestational age (in weeks) as well as (b) birth weight (in kg) in preterm infants. D represents
475 dioptres.

476 **Figure 3.** Association between astigmatism in right eye (OD) at birth and (a) gestational age (in weeks)
477 as well as (b) birth weight (in kg) in preterm infants. D represents dioptres.

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480 Table 1. Baseline statistics of the study population

	Preterm	Full term
N	36	40
M/F	14(38.9%)/22(61.1%)	16(40.0%)/24(60.0%)
Gestational age (weeks)		
28 to <32	10 (27.8%)	----
32 to <37	26 (72.2%)	----
37 or more	----	40 (100%)
Mean \pm SD	32.89 \pm 2.22	39.45 \pm 1.38
Range	28.00 - 36.00	37.00 - 42.00
Birth weight (kg)		
<1.0	----	----
1.0 to <1.5	11 (30.6%)	----
1.5 to <2.5	25 (69.4%)	----
\geq 2.5	----	40 (100%)
Mean \pm SD	1.63 \pm 0.30	3.49 \pm 0.48
Range	1.20 - 2.40	2.50 - 4.30

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489 Table 2. Classification of refractive error (right eye) in 36 preterm and 40 full term infants at birth,
 490 term (preterm only), 3 months and 6 months.

	Preterm n (%)				Full term n (%)		
	Birth	Term	3 months	6 months	Birth	3 months	6 months
Emmetropia (SER 0-3 D)	25 (69.4)	25 (69.4)	20 (55.6)	18 (50.0)	38 (95.0)	40 (100.0)	40 (100.0)
Myopia (SER <0 D)	9 (25.0)	9 (25.0)	16 (44.4)	18 (50.0)	----	----	----
Significant Hyperopia (SER >3 D)	2 (5.6)	2 (5.6)	----	----	2 (5.0)	----	----

491 Values are expressed as N (%); SER, spherical equivalent refraction

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495 Table 3. Type of astigmatism (right eye) in preterm and full term infants.

	WTR n (%)	ATR n (%)	Oblique n (%)	No astigmatism n (%)
Preterm	10 (27.8)	13(36.1)	6 (16.7)	7 (19.4)
Full term	8 (20.0)	14 (35.0)	4 (10.0)	14 (35.0)

496 Fisher's exact test, $p < 0.05$ (study groups vs presence of astigmatism)

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501 Table 4. Refractive error in preterm infants at different chronological age points

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	Birth	Term	3 months	6 months	P^1	P^2	P^3
SER (OD)	+0.84 ± 1.72 (-3.50 to +4.50)	+0.82 ± 1.72 (-3.50 to +4.50)	+0.21 ± 1.78 (-4.00 to +3.00)	-0.33 ± 1.95 (-5.00 to +2.50)	1.000	<0.001	<0.001
Astigmatism (OD)	1.11 ± 0.84 (0 to 3.00)	1.12 ± 0.85 (0 to 3.00)	1.25 ± 0.92 (0 to 3.25)	1.34 ± 0.98 (0 to 3.25)	1.000	0.117	<0.05
Anisometropia*	0.44 ± 0.64 (0 to 2.00)	0.45 ± 0.63 (0 to 2.00)	0.57 ± 0.71 (0 to 2.25)	0.68 ± 0.84 (0 to 3.00)	1.000	0.339	<0.05

503 Values are expressed as Mean ±SD (Range) in Dioptres; SER, spherical equivalent refraction; OD,
504 right eye

505 P^1 , birth vs term; P^2 , birth vs 3 months; P^3 , birth vs 6 months

506 *Relative difference in refractive error between the two eyes

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511 Table 5. Refractive error in full term infants at different chronological age points.

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	Birth	3 months	6 months	P^1	P^2	P^3
SER (OD)	+2.19 ± 0.66 (+1.00 to +3.50)	+1.70 ± 0.63 (+0.75 to +3.00)	+1.06 ± 0.68 (0 to +3.00)	<0.001	<0.001	<0.001
Astigmatism (OD)	0.79 ± 0.71 (0 to 2.00)	0.63 ± .57 (0 to 2.00)	0.51 ± 0.50 (0 to 2.00)	<0.001	<0.001	<0.01
Anisometropia*	0.40 ± 0.46 (0 to 1.75)	0.34 ± .33 (0 to 1.00)	0.26 ± 0.30 (0 to 1.00)	0.769	0.049	<0.01

513 Values are expressed as Mean ± SD (Range) in Dioptres; SER, spherical equivalent refraction; OD,
514 right eye

515 P^1 , birth vs 3 months; P^2 , birth vs 6 months; P^3 , 3 months vs 6 months

516 *Relative difference in refractive error between the two eyes

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522 Table 6. Refractive error in preterm vs full term infants

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		Preterm	Full term	<i>P</i>
SER (OD)	Birth	+0.84 ± 1.72	+2.19 ± 0.66	<0.001
	Term	+0.82 ± 1.72	----	----
	3 months	+0.21 ± 1.78	+1.70 ± 0.63	<0.001
	6 months	-0.33 ± 1.95	+1.06 ± 0.68	<0.001
Astigmatism (OD)	Birth	1.11 ± 0.84	0.79 ± 0.71	0.072
	Term	1.12 ± 0.85	----	----
	3 months	1.25 ± 0.92	0.63 ± 0.57	<0.01
	6 months	1.34 ± 0.98	0.51 ± 0.50	<0.001
Anisometropia	Birth	0.44 ± 0.64	0.40 ± 0.46	0.726
	Term	0.45 ± 0.63	----	----
	3 months	0.65 ± 0.69	0.34 ± 0.33	0.069
	6 months	0.68 ± 0.84	0.26 ± 0.30	<0.01

524 Values are expressed as Mean ± SD in Dioptres; SER, spherical equivalent refraction; OD, right eye

525 Since the measures of refractive error are same for both birth and term age points for full term

526 infants, the corresponding data are presented for birth only, leaving empty cells for term

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