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Original Article

Refractive status and optical components in premature babies with and without retinopathy of prematurity at 5 years old

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Abstract: Objective: This study aimed to explore the influence of premature birth and mild retinopathy of prematurity (ROP) on the refractive status and the development of ocular optical components. Methods: The preterm infants who received fundus screening were divided into ROP group and non-ROP group. In addition, age matched term infants were also recruited. Results: The incidence of myopia was the highest in ROP group (13.56%), followed by non-ROP group (5.32%) and control group (1.19%). The incidence of astigmatism was the highest in ROP group (40.68%), followed by non-ROP group (18.09%) and control group (8.33%). In ROP group and non-ROP group, the corneal astigmatism and mean astigmatism were significantly higher than in control group ($P<0.05$). In ROP group, the corneal refraction was significantly higher than in non-ROP group and control group ($P<0.05$). The corneal curvature in ROP was significantly larger than that in non-ROP group and control group ($P<0.05$). The axial length in ROP group and non-ROP group was significantly shorter than that in control group ($P<0.05$). The gestational age was negatively related to corneal astigmatism and astigmatism, but positively related to axial length ($P<0.05$). The birth weight was negatively related to corneal astigmatism, astigmatism, corneal refraction and corneal curvature, but positively to axial length and spherical equivalent ($P<0.05$). Conclusion: Preterm infants with or without ROP are more likely to develop myopia and astigmatism. And low birth weight, preterm birth and ROP act simultaneously to affect the development of ocular optical components, leading to the occurrence of myopia and astigmatism.

Keywords: Preterm infants, low birth weight, retinopathy of prematurity, optical components, refractive status

Introduction

Preterm and/or low birth weight infants usually have ocular problems [1-5]. The survival rate of preterm infants is increasing with the economic development and the progression of perinatal medicine and the prevalence of retinopathy of prematurity (ROP) shows an increasing tendency. ROP has been an important cause of blindness and visual impairment in infants [6-8]. The incidences of myopia, astigmatism, strabismus, amblyopia and anisometropia in ROP infants are significantly higher than those in age-matched healthy infants [9-11]. Refractive error has been one of common complications of preterm birth and may cause visual impairment. WHO has classified myopia as one of the factors causing blindness and visual impairment [9]. To date, a large number of studies have reported that the incidence of myopia in preterm infants with or without ROP is dramatically higher than that in term infants [12]. Most term infants have the hyperopia of both eyes at birth, but preterm infants present emmetropia or myopia [13]. Some studies indicate that the incidence of myopia in preterm infants is negatively associated with birth weight and gestational age [4, 14, 15], and positively correlated with the severity of ROP [15-18]. In preterm infants, the pathogenesis of myopia is still unclear [19]. Currently, few studies analyze the ocular components in preterm infants with and without ROP, most studies investigate the refractive status in early childhood of preterm infants with and without ROP, and little is known about the refractive status after early childhood. Our study for the first time reported the results from 5-year follow up in preterm infants

with and without ROP. Currently, some investigators pay attention to the ROP children who received condensation therapy or photocoagulation therapy, and long term follow up is performed for the evaluation of refractive status [20-22], but little is known about the refractive status and visual development in ROP infants with mild ROP.

In our previous study, we investigated the refractive status and ocular components in the infants with mild ROP, low birth weight preterm infants and term infants at the age of 3-4 years. Our results showed ROP infants and preterm infants were more likely to develop myopia and astigmatism [23]. In the same population, we further investigated the refractive status and ocular components in a longer follow up, aiming to evaluate the influence of ROP and preterm birth on the development of refractive status and ocular components after early childhood.

Materials and methods

General information

The preterm infants who received fundus screening in the Affiliated Children's Hospital of Chongqing Medical University were recruited between January 2009 and February 2011, and age-matched term infants served as controls. Preterm infants were divided into ROP group and non-ROP group. There were 59 eyes from 31 subjects in ROP group (stage 1-3 prethrehold), 94 eyes from 47 subjects from non-ROP group, and 84 eyes from 42 controls. 5 years after recruitment, the corneal refraction, corneal curvature, anterior chamber depth, lens thickness, vitreous thickness and axial length were measured, and retinoscopy was performed after induction of ciliary muscle paralysis. The gestational age and birth weight were also recorded. One hundred and two met the inclusion and exclusion criteria. Of these subjects, 2 children had incomplete information, and 10 subjects were lost to follow up or refused to receive further follow up. Finally, 120 children were included for analysis.

Inclusion criteria

1) Gestational age was <37 weeks and birth weight was <2500 g [24]; 2) Their parents or legal guardians signed the informed consent to receive examinations or cooperative with clinicians; 3) There were no diseases of central nervous system or circulation system (such as cerebral palsy or congenital heart disease); 4) Refractive stroma was clear and retinoscopy was feasible; 5) There was no other organic eye diseases except for ROP.

Exclusion criteria

1) Gestational age was ≥37 weeks or birth weight was ≥2500 g; 2) Their parents or legal guardians were unavailable or refused eye examinations; 3) The subjects were unable to co-operate with examination, causing information incomplete, or cognition impairment causes the results inaccurate; 4) There was refractive media opacity of any cause, the pupils were unable to dilate after treatment, or there were other factors causing refractive difficult; 5) There was family history of high myopia.

Screening for ROP

Fundus screening was performed at 4-6 weeks after birth or at the adjusted gestational age of 32 weeks. Before examination, subjects received food and water deprivation for 2 h. Compound tropicamide eye drops (Changchun Dirui Pharmaceutical Co., Ltd) were dropped into two eyes 1 h before examination (1-2 drops; once every 10 min; 4 times). When the pupils were dilated completely, the subjects were asked to lie in a supine position, and their head was fixed. After superficial ocular anesthesia with 4 g/L oxybuprocaine, the eyelids were opened, and screening was done with the RetCam III digital retinal camera (Clarity Medical Systems Inc., USA). For subjects receiving mechanical ventilation or having poor condition, the experienced ophthalmologists used indirect ophthalmoscope and lens with refraction of 28 D to screen ROP after pupil dilation. If necessary, scleral buckling device was used to aid the observation of fundus, especially the development of peripheral retina (including the end of retinal blood vessels), and results were recorded in detail. Initial examination was done at 4-6 weeks after birth or at adjusted gestational age of 32 weeks. According to the international classification of ROP, ROP was staged and partitioned [25]: (1) Stage 1 or 2 without plus lesion in zone II and stage 1 or 2 in zone III (examination was performed once weekly); the fundus was closely monitored for

prethreshold lesions (once every 2-3 days); Laser or condensation treatment was performed within 72 h for threshold lesions; surgical intervention was performed for stage 4 or 5 lesions; (2) When ROP was not identified and there was no complete vascularization at the peripheral retina, follow up was performed once every 2 weeks until the complete vascularization at the peripheral retina.

Eye examination

The gestational age and birth weight were recorded after recruitment. 5 years after recruitment, complete eye examinations were performed, including corneal refraction, corneal curvature, anterior chamber depth, lens thickness, vitreous thickness and axial length. Retinoscopy was performed after ciliary muscle paralysis.

Corneal refraction, corneal curvature and corneal astigmatism were measured with autorefractor (RK-8100; Topcon, Tokyo, Japan). Measurement was done three times and means were calculated.

The anterior chamber depth (ACD), lens thickness (LT), thickness of vitreous body (VITR) and axial length (AL) were measured with eye ultrasound detector (KANGH CAS-2000, China). Measurement was done 8 times, and means were calculated.

Retinoscopy after ciliary muscle paralysis was as follows: 1% cyclopentolate was dropped to both eyes (1 drop per eye) three times (once every 10 min). 20 min later, the ciliary muscle paralysis was determined according to the pupillary light reflex. If pupillary light reflex was still present, additional cyclopentolate was administered, and the pupillary light reflex and pupil size were observed 15 min later. The ciliary muscle paralysis was defined as the pupil size of >6 mm and absence of pupillary light reflex (pupillary light reflex might be present in several children when the pupil size was still smaller than 6 mm). Retinoscopy was performed with ophthalmoscope (YZ24; Six Vision Corp., Suzhou, China) [26].

Data collection and processing

The degree of fraction is expressed as spherical equivalent refraction (SER) in this study: SER = spherical diopter +1/2 cylindrical diopter. Hyperopia was defined as SER of ≥+2.00 D; myopia was defined as SER of ≤-0.50 D; astigmatism was defined as absolute cylindrical diopter of ≥1.00 DC; high astigmatism was defined as absolute cylindrical diopter of ≥3.00 DC [16]. The diopter is expressed as mean ± standard deviation, and data from one eye were included for statistical analysis.

The automatic refractometer, ocular ultrasound, drug dropping, retinoscopy and data processing were operated independently by different authors, the specific examination was performed with the same person, the participants, examiners and analyzers were blind to the whole study design. Data were checked before input to assure the accuracy.

Statistical analysis

Statistical analysis was performed with SPSS version 22.0. The incidences of myopia, hyperopia and astigmatism were compared using Chi square test or Fisher exact test, followed by paired comparison. Significant difference was observed among three groups with $\alpha=0.05/3=0.0167$. The continuous data were compared using one way analysis of variance, followed by LSD test if significant difference was observed. The correlations of birth weight and gestational age with refractive status and ocular components were evaluated using Pearson correlation analysis. A value of $P<0.05$ was considered statistically significant.

Results

Of 120 subjects, there were 58 boys and 62 girls with the mean age of 5.49±0.33 years. The mean gestational age was 34.43±4.24 weeks at birth and the mean birth weight was 2216.80±798.76 g. There were 31 subjects in ROP group (19 boys and 12 girls), 47 subjects in non-ROP group (23 boys and 24 girls) and 42 subjects in control group (16 boys and 26 girls). In 31 subjects with ROP, stage 1, 2 and 3 ROP was found in 17, 4 and 1 patients, prethreshold ROP in 9 subjects, and none had threshold ROP. ROP of both eyes was observed in 28 subjects, and that of one eye in 3 subjects (right eye: n=1; left eye: n=2).

There was no significant difference in the gender among three groups ($X^2=2.533$, $P=0.282$)

Table 1. Characteristics of babies in 3 groups at baseline

	ROP group	non-ROP group	Control group
Gender (M/F)	19/12	23/24	16/26
Gestational age*	29.71±0.33[a]	32.07±2.05[b]	39.17±0.29[c]
Birth weight*	1444.36±63.98[a]	1691.83±32.32[b]	3313.43±54.96[c]

Notes: *Index means in the same line with different letters (a, b, c) were significantly different (P<0.05, ANOVA, least-significance-difference Method).

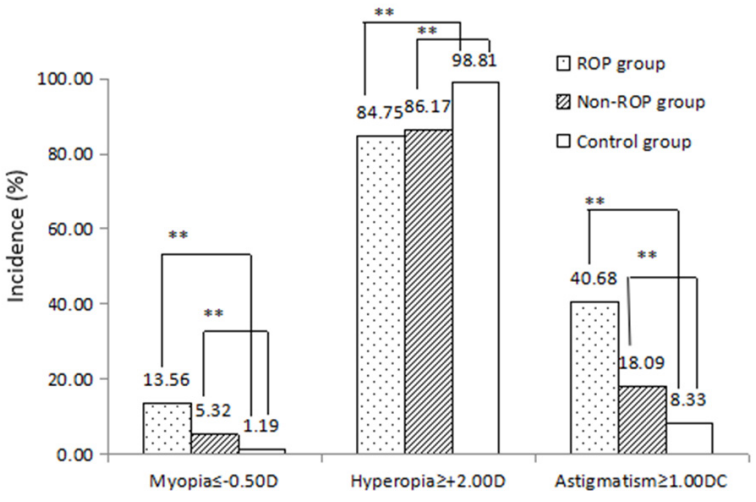

Figure 1. X-axis shows the criteria for myopia, hyperopia and astigmatism. The incidence of ametropia was calculated in ROP group, non-ROP group and control group. ***P*<0.01 among three groups (chi-square test).

(**Table 1**). In ROP group, the gestational age was the smallest and the birth weight was the lowest, followed by non-ROP group and then control group, and significant differences were observed in the birth weight and gestational age among three groups (**Table 1**). Paired comparison showed the gestational age was markedly different between ROP group and non-ROP group (F=21.924 P<0.001), between ROP group and control group (F=753.219, P< 0.001), and between non-ROP group and control group (F=587.384, P<0.001) (P<0.01) (**Table 1**). The birth weight was also significantly different between ROP group and non-ROP group (F=7.676, P=0.007), between ROP group and control group (F=1005.192, P<0.001), and between non-ROP group and control group (F= 669.94, P<0.001) (**Table 1**).

Incidences of ametropia and distribution of astigmatism diopter

The incidence of myopia was the highest in ROP group (8/59, 13.56%), followed by non-ROP group (5/94, 5.32%) and control group (1/84, 1.19%), and significant difference was observed among three groups (X^2=6.114, P<0.05). Paired comparison showed no significant difference between ROP group and non-ROP group, but there was marked difference between ROP group/non-ROP group and control group (P<0.05). The incidence of hyperopia was the highest in control group (83/84, 98.81%), followed by non-ROP group (81/94, 86.17%) and then ROP group (50/59, 84.75%), and significant difference was observed among three groups (X^2=7.123, P<0.05). Paired comparison showed significant difference between control group and non-ROP group (X^2=6.130, P<0.05) and between control group and ROP group (X^2=6.933, P<0.05), and there was no marked difference between non-ROP group and ROP group (X^2= 0.053, P=0.818). The incidence of astigmatism was the highest in ROP group (24/59, 40.68%), followed by non-ROP group (17/94, 18.09%) and control group (7/84, 8.33%), and there was significant difference among three groups (X^2=17.549, P<0.05). Further paired comparison showed marked difference in the incidence of astigmatis between ROP group and control group (X^2=14.714, P<0.05) and between non-ROP group and control group (X^2=5.794, P< 0.05), but there was no significant difference between ROP group and non-ROP group (X^2= 3.133, P=0.077) (**Figures 1** and **2**).

Refractive status and ocular components

Table 2 showed the refractive status and ocular components in three groups. The corneal astigmatism was the highest in ROP group, followed by non-ROP group and then control group, and there was significant difference among three groups (F=4.612, P=0.011; F=6.287, P=0.002). Further paired comparison showed there was dramatic difference in corneal astigmatism be-

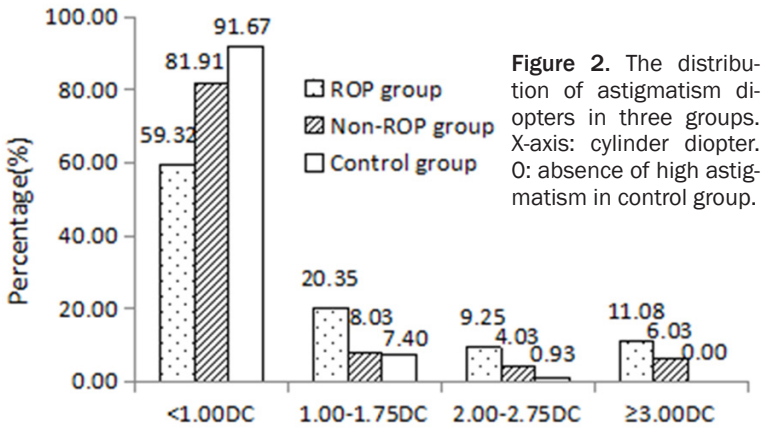

Figure 2. The distribution of astigmatism diopters in three groups. X-axis: cylinder diopter. 0: absence of high astigmatism in control group.

tween ROP group and control group and between ROP group and non-ROP group (P< 0.05), but significant difference was not observed between control group and non-ROP group (P>0.05). SER was similar among three groups (F=0.224, P=0.800). Significant differences were noted in the corneal refraction (F=7.845, P<0.05), corneal curvature (F=7.385, P<0.05) and axial length (F=5.635, P<0.05) among three groups. Further paired comparison indicated significant differences in corneal refraction and corneal curvature between ROP group and non-ROP group as well as between ROP group and control group (P<0.05), but there were no significant differences between non-ROP group and control group (P>0.05). The axial length was the longest in control group, followed by non-ROP group and then ROP group. Significant difference was observed between ROP group and control group as well as between non-ROP group and control group (P<0.05), but no significant difference was noted between ROP group and non-ROP group (P>0.05). The lens thickness (F=0.004, P=0.996), anterior chamber depth (F=0.634, P=0.532) and thickness of vitreous body (F=2.043, P=0.133) were comparable among three groups.

Correlations of gestational age and birth weight with refractive status and optical components

Table 3 showed the correlations of gestational age and birth weight with refractive status and optical components. Results showed gestational age was negatively related to corneal astigmatism (r=-0.184, P=0.016) and astigmatism (r=-0.231, P=0.003), but negatively to axial length (r=0.228, P= 0.003). Birth weight was negatively associated with corneal astigmatism (r=-0.254, P=0.001), astigmatism (r=-0.279, P<0.001), corneal refraction (r=-0.258, P=0.001), lens thickness (r=-0.245, P= 0.001), and corneal curvature (r=-0.243, P=0.001), but positively with axial (r=0.248, P=0.001) and SER (r=0.155, P=0.044). Gestational age and birth weight had no relationships with lens thickness, thickness of vitreous body and anterior chamber depth.

Discussion

Since 1940s, preterm infants have been cared in closed incubators with a high concentration of oxygen, which significantly increases the incidence of ROP in preterm infants [27]. Currently, the medical care of preterm infants is significantly improved, but ROP is still a major problem in preterm infants due to its close relationship with small gestational age and low birth weight [28, 29]. A large number of studies show preterm birth and ROP may impair the vision, which might be explained as follows: First, the departing from intrauterine environment ahead of time may affect the eye development and the emmetropization after birth [11, 30, 31]. Secondly, studies have shown that preterm birth can affect the development of optical components in the eyes, further impacting the optical refraction. Preterm infants are more likely to develop myopia of prematurity (MOP) [30, 32, 33], which is opposite to the common myopia in school age [34]. MOP is characterized by short axial length [31, 32], increased corneal curvature [31, 32, 35], shallow anterior chamber [31], lens thickening and increased lens refraction [36]. Thirdly, mild ROP or ROP in degenerative phase may also affect the development of retina [37]. Thus, it is estimated that ROP may affect the maturation and differentiation of rod cells to affect the eye growth and visual development.

Our results showed the incidence of myopia was 12.77% in ROP preterm infants and 5.00% in non-ROP preterm infants, which were signifi-

Table 2. Refractive status and optical components in 3 groups

		ROP group	Non-ROP group	Control group
Refractive status	Corneal astigmatism (D)*	-1.47±0.92[a]	-1.10±0.83[b]	-1.05±0.46[b]
	Astigmatism (D)*	1.08±1.16[a]	1.08±0.992[a]	0.56±0.45[b]
	Spherical equivalent fraction (D)	1.44±1.09	1.44±0.94	1.48±0.88
	Corneal refraction (D)*	43.86±2.02[a]	42.86±1.73[b]	42.91±1.12[b]
Optical components	Corneal curvature (mm)*	7.89±0.37[a]	7.69±0.30[b]	7.68±0.20[b]
	Anterior chamber depth (mm)	3.07±0.24	3.01±0.21	3.04±0.23
	Lens thickness (mm)	4.41±0.26	4.41±0.22	4.41±0.23
	Vitreous thickness (mm)	15.08±0.95	14.74±0.67	14.99±0.58
	Axial length (mm)*	22.15±1.06[a]	22.16±0.75[a]	22.47±0.56[b]

Notes: *Index means in the same line with different letters (a, b) were significantly different (P<0.05, ANOVA, least-significance-difference Method).

Table 3. Correlations of gestational age and birth-weight with refractive status and optical components

		Gestational age	Birth-weight
Refraction	Corneal astigmatism (D)	r=-0.184*	r=-0.254**
	Astigmatism (D)	r=-0.231**	r=-0.279***
	SER (D)	r=-0.042	r=0.155*
	Corneal refractive power (D)	r=-0.076	r=-0.258**
	Corneal curvature (mm)	r=0.065	r=-0.243**
Optical components	Anterior chamber depth (mm)	r=0.015	r=-0.019
	Lens thickness (mm)	r=-0.028	r=-0.089
	Vitreous thickness (mm)	r=0.043	r=0.117
	Axial length (mm)	r=0.228**	r=0.248**

Notes: *P<0.05 vs. refraction or optical component; **P<0.01 vs. refraction or optical component; ***P<0.001 vs. refraction or optical component.

cantly higher than in term infants. The incidence of myopia in ROP infants was similar to the findings reported by Wang et al [8] in preschool children (5-7 years) with mild ROP (11%), but higher than that reported by Tuupurainen *et al* (8.6%). Myopia was defined as corneal fraction of ≤-0.50 D in our study, but ≤-1.00 D in the study of Tuupurainen, which may be a factor causing difference between two studies. In addition, the incidence of myopia in ROP infants was higher than that reported by Nissenkorn *et al* [17] (50%) and by Cryo-ROP Study Group [38] (16.2%). This discrepancy might be ascribed to the difference in the aged of children studied (5 years old in our study and 2-8 years old in the study of Nissenkorn et al) because the incidence of myopia is increasing in school age. In addition, the birth weight in the study of Cryo-ROP Study Group was lower than 1251 g, but the mean birth weight was 2165.74±808.88 g in our study, while low birth weight is one of important factors causing myopia. The incidence of myopia in preterm infants without ROP was similar to that reported by Muna al Oum [39] (6.9%), but lower than that reported by Nissenkorn (16%), which might be attributed to the younger age in our study. In the present study, the incidence of hyperopia was the lowest in ROP group (85.11%), followed by non-ROP group (86.67%) and the highest in control group (98.39%). The incidence of hyperopia in ROP subjects was higher than that reported by Ta-Ching Chen et al [40] (23%) and by Muna al Oum et al [39] (48.3%). This discrepancy might be ascribed to the younger age in our study because hyperopia will be improved over age. It is widely accepted that preterm birth may increase the risk for myopia, which was consistent with our finding.

In the present study, the incidence of astigmatism was the highest in ROP group (40.43%), followed by non-ROP group (18.33%), and the lowest in control group (8.06%), and there was marked difference among groups (P<0.05). In addition, the astigmatism was negatively related to gestational age and birth weight. The incidence of astigmatism in our study was similar to that reported by Davitt BV *et al* [41] (42%) and by Muna al Oum *et al* [39] (40.9%). Holmstrom *et al* [42] speculated that both low birth weight and ROP could increase the inci-

dence of astigmatism. They reported that 52% of preterm infants with birth weight of <1500 g developed astigmatism of ≥1.00 D and 18% presented astigmatism of ≥2.00 D at gestational age of 6 months. Correlation analysis showed the lower the birth weight was, the smaller the gestational age was, the higher the degree of astigmatism was, which was consistent with our findings in the same population at 3-4 years. This further confirms that small gestational age, low birth weight and ROP may increase the risk for astigmatism.

Preterm birth has significantly influence on the development of optical component and refractive status, but the mechanisms are very complex. The reduction in anterior chamber depth, the increases in corneal curvature and the lens thickness and elevation of refraction may cause refractive error in preterm infants. Our results showed ROP infants at 5 years old showed high corneal curvature and short axial length, which were similar to the characteristics of MOP. MOP belongs to a special type of MOP and may be caused by the reduction in axial length, subsequent increase in corneal curvature and the increase in lens refraction in the emmetropization. Any condition causing decompensation in the emmetropization may result in the occurrence of myopia. However, our study failed to identify the reduction in anterior chamber and lens thickening. This implies the pathogenesis of MOP is not accompanied by these characteristics. Chen *et al* [40] reported that ROP infants often had shallow anterior chamber, lens thickening and increase in corneal curvature, but shortening of axial length was not found, which further confirms our findings.

Preterm birth may alter the corneal curvature, and the change in corneal curvature is parallel to those in axial length, anterior chamber depth and lens thickness, which is a prerequisite in the emmetropization. In term infants, the corneal curvature reduces rapidly soon after birth, and the axial length increases simultaneously. These changes assure the smooth emmetropization of the eyes. Inagaki *et al* [43] found the corneal curvature was 49.5 (1.82) D in preterm infants at 2 weeks after births, which was significantly higher than that in term infants 47.0 (1.19) D. Yamamoto *et al* [44] also found the mean corneal curvature was 50.75 D at early stage of preterm infants, but it was 48.06 D in term infants. These findings suggest the corneal curvature is larger in preterm infants, which is consistent with our finding.

There were limitations in this study: (1) More accurate adjusted gestational age should be used in future studies; (2) Several subjects were lost to follow up in this study. The influence of gestational age and birth weight on the refractive status and optical components should be further investigated in future longitudinal studies with larger sample size; (3) In studies on the incidence of refractive error and preterm infants, the definition of preterm birth regarding the gestational age and birth weight is different, which causes the differences in the incidences of myopia, hyperopia and astigmatism.

Taken together, our results show the incidences of myopia and astigmatism increase significantly in preterm infants with and without ROP at 5 years old, the corneal curvature increases, but the axial length reduces. These indicate that low birth weight, preterm birth and ROP act together to affect the development of optical components of the eyes, finally resulting in refractive error. Thus, we should pay attention to preterm birth and ROP in infants, and visual examination and follow up should be performed timely in preterm infants. Once refractive error is observed, early intervention and treatment can be administered, aiming to improve the long term visual quality and quality of life.

Disclosure of conflict of interest

None.

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