

Ocular changes in premature infants

Abstract

Introduction: This article aimed to review the literature on visual impairments and ocular changes in premature infants with low birth weight and gestational age.

Materials and Methods: Five electronic databases including: PubMed, Web of Science, Science direct, Ovid, and Scopus were searched. Original articles published until 2015 describing preterm infants were reviewed. Repetitive and derivative articles were excluded.

Results: Out of 100 unique, potentially relevant articles, 42 studies that addressed and met the inclusion criteria were evaluated.

Conclusion: Prematurity affects ocular structures (from anterior to posterior segment) and functions. Premature infants are at risk of myopization. Concerning the changes in premature infants a slight significant increasing in axial length, intraocular pressure, central corneal thickness, is found, Moreover, high incidence of retinal changes was reported as a result of prematurity. On the other hand, visual acuity, tear, electroretinogram, and visual evoked potential responses decrease with prematurity. The most common ophthalmic disorders in preterm infants are myopia and retinopathy of prematurity, which could affect life quality due to reduced visual acuity.

Keywords: Eye, Ocular, Prematurity, Premature infants, Preterm infants

Introduction

Preterm birth, is the birth of an infant at less than 37 weeks of gestation.(1) Preterm birth is the most common cause of mortality among infants worldwide.(2) The reported prevalence of prematurity among infants with less than 28 weeks gestational age (GA) is 33%. (3) According to Abrishami et al study, retinopathy of prematurity was reported in 26.2% of very premature infants.(4) Premature infants are at risk for cerebral palsy, developmental delays,

and vision and hearing problems. (5) Preterm infants are more likely to sustain abnormalities of visual system, which lead to reduced vision. (6) Ophthalmic complications of prematurity include refractive error, strabismus, abnormal retinal vessels or retinopathy of prematurity (ROP), visual loss due to reduced development of visual cortex, cortical visual impairments, and some rare, late-onset problems such as glaucoma, retinal detachment, and phthisis. (6) In the late 1940s, ROP was initially reported to be the most common ocular abnormality in preterm infants. (2, 7) The existing evidence presented that >50% of neonates with <1000 g birth weight (BW) show some degree of ROP. (8) The possible risk factors for ROP are as follows: oxygen, low GA and BW, hyperglycemia, low insulin-like growth factor, loss of nutrients, neonatal infections (particularly fungal), genetic factors, low blood levels of vitamin E, and light exposure (9, 10) however, low BW (LBW) and GA are the main risk factors for ROP. With respect to genetics as a predisposing factor, ROP occurs more often in white infants, as compared to black ones and in males rather than females. (2) Since premature infants have lower serum levels of vitamin E, the role of vitamin E in ROP was also considered. (7) Development of cryotherapy and laser photocoagulation in the 1980s and 1990s were considered effective modalities in preventing blindness. It has been suggested that intravitreal bevacizumab could be helpful in ROP therapy and could reduce both the myopia and astigmatism in premature infants. Blindness was significantly more common in preterm male infants, (11) which may be secondary to cicatricial ROP or intracerebral hemorrhages. (12) The first phase of ROP is initiated during the first 30–32 weeks, and the second phase, which is characterized by retinal neovascularization, begins approximately within the first 32–34 weeks of postmenstrual age. (7) Ocular changes in premature infants lead to various eye size problems and cause refractive errors in preterm infants. (13) Since most of the previous studies discussed changes in the retina and the refractive state of the eye,

this study aimed to provide an accurate and comprehensive summary of the ocular changes in preterm infants.

Methods

Data sources and searches

The data were retrieved from the following electronic databases: PubMed, Web of Science, Science direct, Ovid, and Scopus. In addition, we hand-searched the reference lists of review and original articles. The following keywords were used for our search: ‘prematurity’, ‘ocular’, ‘eye’, ‘premature infants’, and ‘preterm infants’. Using the same search parameters, all the identified journals, which were published from 1960 up to 2015, were manually searched.

Study selection

The study selection process is illustrated in Figure 1. Eligibility assessment was performed by one of the authors through reviewing the titles and abstracts. Thereafter, the full-text versions of 42 articles were reviewed independently by two authors. The inclusion criteria included studies discussing ocular changes in prematurity, all the relevant studies except for case reports, cohort studies in which follow-up was completed, studies in which participants did not have any comorbidities, and all the studies published up to 2015.

Data extraction and quality assessment

Two researchers extracted the data from the included articles. Study design and outcomes concerning refraction error, strabismus, visual acuity (VA), intraocular pressure, axial length (AXL), cornea, tear, pupil, retinae, visual evoked potential (VEP), electroretinography, and cortical visual impairments were extracted from all the included articles (Table 1). Studies were evaluated for the inclusion criteria, accurate recruitment of participants, accurate measurement to minimize exposure to bias, precise evaluation of outcomes to minimize bias, and identification of confounding factors and bias (Table 2).

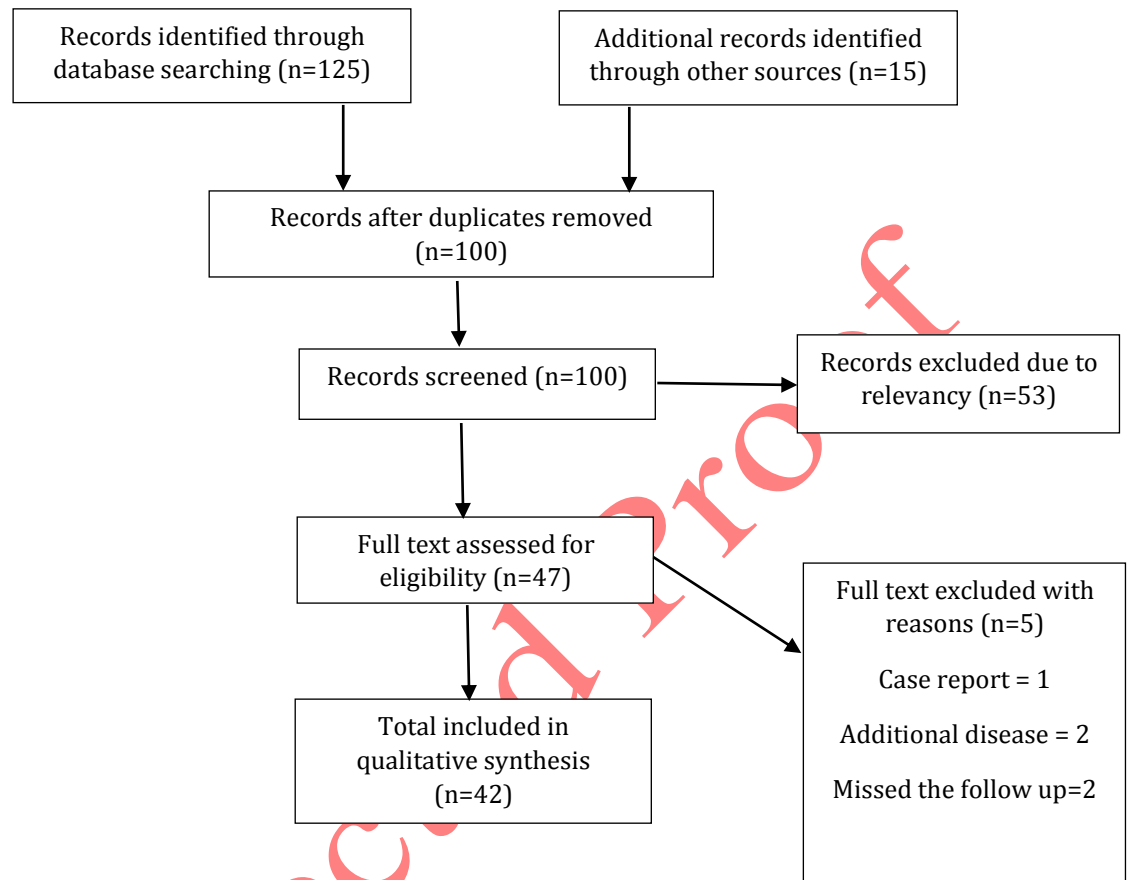


Figure 1: study selection process

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Table 1: Characteristics of included studies and extracted data

Authors	Title	Study design	Journal	Index	Extracted data
Acar D(2015)	The intraocular pressure and central corneal thickness in healthy premature infants	Cross sectional	Journal of AAPOS	Index medicus, Current contents/Clinical Medicine, ISI Alerting Services, Science citation index, Medline	IOP, Cor
Bin-Khathlan AA(2014)	Ophthalmic short- and long-term outcomes for premature infants: Results of an extended follow-up program in Saudi Arabia	Cohort	Saudi J Ophthalmol	PubMed	Str
Hsieh CJ(2012)	Refractive outcome of premature infants with or without retinopathy of prematurity at 2 years of age: a prospective controlled cohort study	Cohort	Kaohsiung J Med Sci	Index medicus, Medline, PubMed, dental literature	RE
Heravian J(2011)	Simultaneous Pattern Visual Evoked Potential and Pattern Electroretinogram in Strabismic and Anisometropic Amblyopia	Case Control	IRCMJ	PubMed	ERG
Uva M(2011)	Intraocular pressure and central corneal thickness in premature and full-term newborns	Case Control	Journal of AAPOS	Index medicus, Current contents/Clinical Medicine, ISI Alerting Services,	IOP, Cor,

				Science citation index, Medline	
Chen T(2010)	Long-term Evaluation of Refractive Status and Optical Components in Eyes of Children Born Prematurely	Cohort	Invest Ophthalmol Vis Sci	Index medicus, Medline, PubMed	RE
Ng P(2008)	A Longitudinal Study to Establish the Normative Value and to Evaluate Perinatal Factors Affecting Intraocular Pressure in Preterm Infants	Cohort	Invest Ophthalmol Vis Sci	Index medicus, Medline, PubMed	IOP, Cor,
O Connor AR(2006)	Change of refractive state and eye size in children of birth weight less than 1701 g	Cohort	Br J Ophthalmol	Index medicus, Medline, PubMed	RE, AL
O'Connor A(2006)	Do infants of birth weight less than 1500 g require additional long term ophthalmic follow up?	Cohort	Br J Ophthalmol	Index medicus, Medline, PubMed	RE
Kirwan C(2005)	Central corneal thickness and corneal diameter in premature infants	Cohort	Acta Ophthalmol Scand	Index medicus, Medline, PubMed	Cor
Cook A(2003)	Ocular Growth and Refractive Error Development in Premature Infants without Retinopathy of Prematurity	Cohort	Invest Ophthalmol Vis Sci	Index medicus, Medline, PubMed	RE, AL
Rudanko S(2003)	Visual Impairment in Children Born Prematurely from 1972 through 1989	Cross Sectional	Ophthalmology	Index medicus, Medline, PubMed	Retina
Larsson E(2003)	Apopulation based study of refractive outcome in 10 year old preterm and full term children	Case control	Arch Ophthalmol	Index medicus, Medline, PubMed	RE

Saunders K(2002)	Emmetropisation following preterm birth	Cohort	Br J Ophthalmol	Index medicus, Medline, PubMed	RE
Schalij-Delfos(2000)	Long term follow up of premature infants: detection of strabismus, amblyopia, and refractive errors	Cohort	Br J Ophthalmol	Index medicus, Medline, PubMed	RE, Str,
Theng J(2000)	Refractive Errors and Strabismus in Premature Asian Infants with and without Retinopathy of Prematurity	Cohort	Singapore Med J	Index medicus, Medline, PubMed	RE, Retina, Str,
Friedman C(2000)	Relationship between serum Inositol concentration and development of retinopathy of prematurity	Cohort	J Pediatr Ophthalmol Strabismus	Index medicus, Medline, PubMed	Retina
Holmstrom G(1999)	Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus	Cohort	Br J Ophthalmol	Index medicus, Medline, PubMed	RE, Str, VA,
Holmstrom G(1998)	Ophthalmological long term follow up of preterm infants: a population based, prospective study of the refraction and its development	Cohort	Br J Ophthalmol	Index medicus, Medline, PubMed	RE, Str,
Isenberg S(1998)	Development of tearing in preterm and term neonates	Case Control	Arch of ophthalmol	Index medicus, Medline, PubMed	Tear
Fledelius HC(1996)	Pre-term delivery and subsequent ocular development	Cohort	Acta Ophthalmol Scand	Index medicus, Medline, PubMed	RE

Theo SL(1995)	Duration of oxygen therapy and exchange transfusion as risk factors associated with retinopathy of prematurity in very low birth weight infants	Cohort	Eye	Index medicus, Medline, PubMed	Retina
Laws D(1994)	Axial length biometry in infants with retinopathy of prematurity	Cross sectional	Eye	Index medicus, Medline, PubMed	AL
Lue CL(1994)	The Course of Myopia in Children with Mild Retinopathy of Prematurity	Cohort	Vision Res	Index medicus, Medline, PubMed	Retina
Spierer A(1994)	Normal intraocular pressure in premature infants	Cross sectional	Am J Ophthalmology	Medline, Scopus, Science citation index	IOP
Pike M(1994)	Patterns of visual impairment associated with lesions of the preterm brain	Cohort	Dev Med Child Neurol	Index medicus, Medline, PubMed	CVI
Gallo J(1993)	Low-grade myopia in children with regressed ROP	Case control	Acta Ophthalmol Scand	Index medicus, Medline, PubMed	Cor
Tucker SM(1992)	Corneal diameter, axial length, and IOP in premature infants	Cohort	Ophthalmology	Index medicus, Medline, PubMed	IOP
Remon L(1992)	Central and Peripheral Corneal Thickness in Full-Term Newborns by Ultrasonic Pachymetry	Cross sectional	Invest Ophthalmol Vis Sci	Index medicus, Medline, PubMed	Cor
Bich D(1992)	Retinal development in very-low-birth-weight infants fed diets differing in omega-3 fatty acids.	Cohort	Invest Ophthalmol Vis Sci	Index medicus, Medline, PubMed	ERG
Gallo	Regressed retinopathy of prematurity and its	Cohort	Br J Ophthalmol	Index medicus, Medline,	RE

J(1991)	sequelae in children aged 5-10 years			PubMed	
Autzen	Central corneal thickness in premature babies	Cohort	Acta Ophthalmol	Index medicus, Medline,	Cor
T(1991)			Scand	PubMed	
Isenberg	The fixed and dilated pupils of premature neonates	Cohort	Am J	Medline, Scopus, Science	Pupil
S(1990)			Ophthalmology	citation index	
Heravian	Binocular summation in visually evoked response	Cross	OPO	Index medicus, Medline,	VEP
J(1990)	and visual acuity	Sectional		PubMed	
Autzen	Central corneal thickness in full-term newborns	Cross	Acta Ophthalmol	Index medicus, Medline,	Cor
T(1989)		Sectional	Scand	PubMed	
Talyor	VEP's in normal full-term and premature neonates:	Cross	Electroencephalogr	Index medicus, Medline,	VEP
M(1987)	Longitudinal versus cross-sectional data	Sectional	Clin Neurophysiol	PubMed	
Brown	Visual acuity in newborn and preterm infants	Case	Am J	Medline, Scopus, Science	VA
A(1986)	measured with grating acuity cards	Control	Ophthalmology	citation index	
Norcia	Spatial frequency sweep VEP: Visual acuity during	Cross	Vis Res	Medline, Scopus, Science	VEP
A(1985)	the first year of life	sectional		citation index	
Nissenkorn	Myopia in premature babies with and without	Cohort	Br J Ophthalmol	Index medicus, Medline,	RE
(1983)	retinopathy of prematurity			PubMed	
Fledelius	Ophthalmic changes from age of 10 to 18 years.	Case	Acta Ophthalmol	Index medicus, Medline,	Cor
H(1982)	Part III ultrasound ophthalmometry and keratometry of anterior eye segment	control	Scand	PubMed	
Fledelius	Ophthalmic changes from age of 10 to 18 years. A	Case	Acta Ophthalmol	Index medicus, Medline,	RE, VA

H(1981)	longitudinal study of sequels to low birth weight. II. Visual acuity	control		PubMed	
Hittner	Anterior segment abnormalities in cicatricial	Cross	Annual meeting	PubMed, Scopus	Cor
H(1979)	retinopathy of prematurity	sectional	american academy of ophthalmology		

IOP: Intra ocular pressure, Cor: Cornea, Str: Strabismus, RE: Refractive error, AL: Axial length, VA: Visual acuity, CVI: Cortical visual impairment, ERG: Electroretinography, VEP: Visual evoked potential.

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Table 2: Quality assessment of included studies

Cross sectional study	Describe the setting, locations, and relevant dates	Given the eligibility criteria	Clearly define all outcomes, exposures and predictors	Clearly define all potential confounders, and effect modifiers	Bias
Acar D (2015)	Yes	Yes	Yes	Yes	Yes
Rudanko S(2003)	Yes	Yes	Yes	No	Yes
Laws D(1994)	Yes	Yes	Yes	Yes	No
Spierrer A(1994)	Yes	Yes	Yes	No	No
Remon L(1992)	Yes	No	Yes	Yes	No
Heravian J(1990)	Yes	Yes	Yes	Yes	No
Autzen T(1989)	Yes	Yes	Yes	Yes	Yes
Talylor M(1987)	Yes	Yes	No	Yes	Yes
Norcia A(1985)	No	Yes	Yes	Yes	No
Hittner H(1979)	Yes	Yes	Yes	Yes	No
Cohort study	Accurate Recruitment of study participants	Accurate Measurement of exposure to minimum bias	Accurate Measurement of outcome to minimum bias	Identification of confounding factors	Completed follow up
Bin-Khathlan AA(2014)	Yes	Yes	Yes	No	Yes
Hsieh CJ(2012)	Yes	Yes	Yes	Yes	Yes

Chen T(2010)	Yes	Yes	Yes	No	Yes
Ng P(2008)	Yes	Yes	Yes	No	Yes
O'Connor A(2006)	Yes	Yes	Yes	No	Yes
O Connor A(2006)	Yes	Yes	Yes	No	Yes
Kirwan C(2005)	Yes	Yes	Yes	No	Yes
Cook A(2003)	Yes	Yes	Yes	Yes	Yes
Saunders K(2002)	Yes	Yes	Yes	Yes	Yes
Schalij-Delfos(2000)	Yes	Yes	Yes	No	Yes
Theng J(2000)	Yes	Yes	Yes	No	Yes
Friedman C(2000)	Yes	Yes	Yes	No	No
Holmstrom G(1999)	Yes	Yes	Yes	Yes	Yes
Holmstrom G(1998)	Yes	Yes	Yes	Yes	Yes
Fledelius HC(1996)	Yes	Yes	Yes	No	Yes
Theo SL(1995)	Yes	Yes	Yes	No	Yes
Lue CL(1994)	Yes	Yes	Yes	No	Yes
Pike M(1994)	Yes	Yes	Yes	Yes	No
Tucker SM(1992)	Yes	Yes	Yes	Yes	Yes
Bich D(1992)	Yes	Yes	Yes	Yes	No
Gallo J(1991)	Yes	Yes	Yes	No	No
Autzen T(1991)	Yes	Yes	Yes	No	Yes
Isenberg S(1990)	Yes	Yes	Yes	No	Yes
Nissenkorn (1983)	Yes	Yes	Yes	No	Yes
Case-control study	Focusing a clearly question	Accurate Recruitment of cases	Accurate Selection of controls	Accurate Measurement of exposure to minimum bias	Considering confounding factors
Uva M(2011)	Yes	Yes	Yes	Yes	Yes

Heravian J(2011)	Yes	Yes	Yes	Yes	No
Larsson E(2003)	Yes	Yes	Yes	Yes	No
Isenberg S(1998)	Yes	Yes	Yes	Yes	Yes
Gallo J(1993)	Yes	Yes	Yes	Yes	No
Brown A(1986)	Yes	Yes	Yes	Yes	No
Fledelius H(1982)	Yes	Yes	Yes	Yes	No
Fledelius H(1981)	Yes	Yes	Yes	Yes	No

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Results

Most studies reported that ROP could have diverse effects on ocular structure and function through refractive error, AXL, retinae, strabismus, intraocular pressure, cornea, and vision. The findings of the relevant studies are discussed below and were summarized in table 3.

Discussion

Refractive error: Preterm birth affects the process of emmetropisation through arrested development of the anterior segment, (14, 15) or mechanical restriction as a result of biological stress secondary to retinopathy. (15) Mohammadzadeh et al stated that refractive error is the most common ophthalmic disease in low birth weight children and myopia is the most refractive error. (16) High incidence of myopia in premature infants could be related to preterm birth, ROP, or disease treatment. (13) In a cohort study performed on LBW infants, the mean sphere equivalent was $+0.67D \pm 1.62$ with 19% being myopic and 6.6% with high hypermetropia. (13) On average, there was one diopter sphere shift in the mean sphere equivalent towards myopia. (13) The mean J0 and J45 (power vector) was -0.04 and -0.03, respectively, and the cylinder power and its axis showed a little change. (13) ROP increases the risk of anisometropia; although, ROP did not have an effect on presence of refractive errors in this cohort study. (13) Prematurity and ROP can imperil emmetropisation in infants. (8) Steeper corneas and thicker lenses promote the focusing power of the eye leading to myopia. This myopia, which is not due to ROP, is of low degree and is referred to as 'myopia of prematurity'. (17) Studies have shown that premature infants are more susceptible to all refractive errors including astigmatism, hypermetropia, and anisometropia than their term counterparts. (17) Myopia associated with severe ROP, progresses during the first six-nine months of life and to a lesser extent thereafter, becoming relatively stable by around three years of age. However, mild myopia associated with prematurity, has a later onset and

progresses in severity until the teen age. (8) At the age of five years, children with ROP were found to be bespectacled and have amblyopia and myopia more than non-ROP ones. (18) Duration of oxygen supplementation and hospital stay were considered as important predictive factors for the development of amblyopia and refractive errors. (18) Holström et al. (19, 20) followed 248 infants for three and half years, and observed increased incidence of myopia, astigmatism, and anisometropia in premature infants. Different studies showed that the incidence of myopia was inversely associated with BW and GA, but positively with increased severity of ROP. (5, 13, 21, 22) Nearly all the premature infants with ROP of stage three or above were myopic, on the other hand, children with no ROP or stage one ROP showed similar prevalence of myopia, emmetropia, and hyperopia. (5) Chen et al. reported that almost 70% of children had with-the-rule astigmatism, whereas oblique astigmatism was found in 25% of children, and less than 5% of children showed the against-the-rule astigmatism. (5) Myopia group demonstrated the highest amount of astigmatism (-1.56 D), and emmetropia group showed the lowest amount of astigmatism (-0.80 D). (5) The probability of developing myopia or hypermetropia in preterm infants is higher than in term ones. (23) Nissenkorn indicated that premature infants are generally hyperopic, and subsequently become myopic. (24) The incidence of myopia is significantly higher in infants with ROP, as compared to the ones without ROP. (25) According to Fielder and Quinn study myopia in premature infants divided in to three groups: 1) physiologic myopia; 2) myopia with preterm birth; and 3) ROP related myopia. The prevalence of myopia differs and depends on following factors: preterm birth, low BW and GA, the severity of ROP, and emmetropization in early infancy. (26) ROP was the main predictive factor for both astigmatism and anisometropia. (27) O'Connor et al. proposed two kinds of emmetropisation in premature infants: 1) a gradual increase in refractive errors in those children with ROP treated by in early childhood; and 2) the permanent refractive status in those with regressed

ROP or without ROP. (13) It was stated that myopia of prematurity, tends to regress during the first year of life, resulting in emmetropic or hyperopic status; however, this shift does not occur with severe ROP. Arrested development of the anterior segment is the main cause of occurrence of myopia of prematurity. Low AXL to power ratio, shallow anterior chamber, and thick lenses are three basic characteristics of myopia of prematurity. (28) Most premature infants become myopic as they grow, and ROP is the main cause of anisometropia. Amblyopia and with-the-rule astigmatism are more prevalent in premature infants, as compared to full term ones.

AXL: Although short AXL was reported by some studies, but AXL is expected to be larger in premature infants than term ones. The results of O' Conner study showed that there was no statistically significant relationship between ROP and AXL. Nonetheless, those with severe ROP had the largest eyes. Axial lengths were as follows: in preterm infant without ROP=22.51 mm, stage 1=22.41 mm, stage 2=22.39 mm, and stage 3/4=22.63 mm. In addition, there was no significant association between BW and AXL.(13) Laws et al. (29) stated that severe ROP associated with shorter AXL. AXL increase in a linear model, s at a rate of 0.16 mm per week, accordingly in four weeks, an infant's eyes grew by 0.64 mm. (15)

Retina: Studies of retina in premature infants showed that topography of photoreceptors is affected by ROP, which consequently affects VA. Optic disc also gets involved in premature infants, and ROP is the main change in the retina. Law et al.(29) proposed two postulations:, the retina in ROP in premature infants has dysfunctional abnormalities and affects eye growth; in addition ROP could cease or delay the normal migration of the photoreceptors from the fovea, which causes a change in the microscopic topography of the central retina and consequently affect VA. This could change emmetropisation mechanism. Macula is pigmented but undistinguishable on ophthalmoscopy up to 34 weeks postconceptional age (PCA). Macular annular reflex is differentiable by 36 weeks PCA, although the foveal light

reflex is not clinically clear until 42 weeks PCA. The incidence of ROP is mostly seen in infants with lower GA and BW. (25) Evidence showed that the highest incidence of ROP occurs at the 24 weeks of gestation, and the lowest ROP is found in the >32 weeks of gestation. (30) Retinopathy of prematurity was significantly more common when mechanical ventilation continued for more than two weeks. (11) Friedman et al.(31) in the United States have reported that oxygen therapy for more than 30 days was associated with ROP. Teoh et al. (32) in Malaysia demonstrated that infants receiving oxygen every day were at risk of ROP 1.156 times more than other neonates, and that oxygen therapy for more than 30 days resulted in a more than 90% chance of ROP. Sabzehi et al also stated that oxygen therapy for more than five days is a risk factor in progressing the ROP. (33)

Strabismus: Studies regarding strabismus indicate that ROP is the principal cause for high incidence of ocular misalignment; in addition, esotropia and pseudo-strabismus are the most common among others. ROP has widespread effects on ocular structure and function, including refractive errors, and also increase the risk of abnormalities of ocular alignment (strabismus).(8) At the age of five years, infants with ROP were found to have strabismus more than infants without ROP. (18) Holström et al. followed 248 infants for three and half years and found increased incidence of strabismus in premature neonates, as compared to full-term ones. (19, 20) Bin-khaltan et al. diagnosed squint in 36 infants with a cumulative incidence of 14% and mean GA of 27 weeks (GA range: 23–34 weeks). Esotropia was diagnosed in 20% of the ROP group and 5.5% of the non-ROP group. Exotropia diagnosis was made in 4% of infants, with an incidence of 11% and 2% in the ROP and non-ROP groups, respectively. (30) Ocular misalignment is more prevalent in premature infants (BW< 1500 g or GA<34 weeks) compared with normal infants. The prevalence of strabismus was 25% and 9.8% in the ROP and non-ROP groups, respectively in three years of follow-up.

(25)

Intraocular pressure: Several studies have demonstrated higher intraocular pressure values in premature infants. (34, 35) however, lower intraocular pressure measures have also been reported. (36) On the other hand, some studies reported that intraocular pressure appears to be normal in premature infants. (37)

Cornea: Most studies found higher central corneal thickness (CCT) values in premature infants. (34, 35) Uva et al. observed a strong negative correlation between PCA and CCT. (35) Researchers determined that the corneal thickness of premature newborns at three months of age decreased significantly (to the same level as full-term newborns). (38, 39) A significant decrease in CCT has been found up to 40th week, with no significant decline in CCT after that point. Corneal hydration, corneal evaporation, and corneal remodeling were considered as possible factors for decrease in CCT during the first weeks of life. (35, 39-41) Keratometry demonstrated steeper corneal curvature in LBW populations, as compared to term newborns. (42-44)

Visual acuity (VA): It has been stated that both VA and contrast sensitivity reduced in premature infants due to ROP, retinal changes, and neurological factors. A correlation between reduced VA and low GA was found. There was a significant difference between the mean VA of eyes with ROP and the eyes without ROP. Poor vision (<0.5 logMAR) was common in eyes with severe ROP, while good vision (>0.2 logMAR), was mostly observed in eyes without ROP. Effective factors for reduced VA including: GA, BW, intraventricular hemorrhage, degree of ROP, cryotherapy, and spherical equivalent. Intraventricular hemorrhage, obvious neurological sequelae, and degree of ROP, particularly cryotreated ROP, were proved to be important factors affecting VA of the better eyes. ROP may not be the only cause of impaired VA in prematurely born children; but neurological complications may have a considerable effect on this problem. (20) The very low BW children had significantly poorer contrast sensitivity than normal BW ones. Measured preferential looking

(PL) acuity as early as 32 weeks PCA was about 20/2000, which improved to about 20/400 at 42 weeks PCA, 20/150 at 57 weeks PCA, and 20/60 by 92 weeks PCA. Mature acuity (20/20) is achieved after three years of age. (45)

Tear: Premature infants showed reduced tear secretion in both basal and reflex tears, in compared with full-term infants.(46)

Pupil: Pupils of preterm infants (less than 31 weeks PCA) are only about 4 mm in diameter, and do not respond to light. (47)

Electroretinography: Heravian et al. reported that retinal neurotransmitters have a major role in generating retinal responses. They also demonstrated that electroretinography (ERG) can be applied to detect retinal anomaly and any disturbances in photoreceptors. (48) The result of ERG shows significant immaturity in amplitude and implicit time at 36 weeks PCA. The response develops fast in healthy preterm infants, as by 57 weeks PCA, amplitude and implicit time reach the adult values. Cone responses improved in the perinatal period. Cone response and 30 Hz flicker cone response approach the adult responses at 57 weeks PCA; however, rod responses mature at a slower rate., Rod response shows a reduction in amplitude at 34–36 weeks PCA. . Even at 57 weeks PCA, substantial immaturity of the rod response is also present. (49)

VEP: Studies showed that latency and VEP acuity decrease in premature infants. Flash VEPs have been incorporated from premature infants at 24 weeks PCA and only a long latency negative peak is declared. (50) The latency of the positive peak reduces from about 220 msec at 34 weeks PCA to 190 msec at 40 weeks PCA, and to 120 msec by 52 weeks PCA. Transient pattern reversal VEPs have been recorded from premature infants at 30 weeks PCA and the results showed that the pattern reversal response comprises a single positive peak with a latency of about 330 msec. Latency declines to 240 msec by 40 weeks PCA and 125

msec by 53 weeks PCA. VEP as an objective method could be useful in prediction of VA. (51) The earliest VEP acuity reports were from infants at 36 weeks PCA; at this age, VEP acuity is about 20/200. VEP acuity matures rapidly to about 20/60 at 57 weeks PCA and to 20/30 by 66 weeks PCA. (52)

Cortical visual impairment: Cortical visual impairment is more prevalent among preterm infants, which might be associated with congenital infections or malformations and neurological disorders. Severe intraventricular hemorrhage is strongly associated with poor acuity. In cases with normal acuity outcomes, other visual problems such as strabismus or nystagmus, may be present. Premature infants with cortical visual impairment have abnormal flash VEPs, pattern VEPs, or both. (53)

Table 3: Findings of included articles

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Study	Study design	Region	Sample	Age	Findings
Acar D(2015)	Cross sectional	Turkey	470	35.94±4.00 W	Both IOP and CCT values were found to be significantly higher in premature infants.
Bin-Khathlan AA(2014)	Cohort	Saudi Arabia	360	27±2.50 W	Esotropia and exotropia were diagnosed in 20% and 11% in premature infants, respectively.
Hsieh CJ(2012)	Cohort	Taiwan	109	30.40±2.04 W	The incidence and magnitude of significant refractive errors increased with severe ROP and with age.
Heravian J(2011)	Case Control	Iran	40	unavailable	Electroretinography can be applied to detect retinal anomaly and any disturbances in photoreceptors.
Uva M(2011)	Case Control	Italy	33	31±3.00 W	IOP measurements were slightly greater than in full-term newborns because of an increased CCT.
Chen T(2010)	Cohort	Taiwan	108	29.32±2.86	Comparison of refraction and optical components showed that the degree of myopia and astigmatism was higher in the ROP group. The degrees of myopia and astigmatism were higher in the ROP group than in the non-ROP group.
Ng P(2008)	Cohort	China	104	29.8 W	The IOP was significantly and negatively associated with postconceptional age.
O Connor AR(2006)	Cohort	United Kingdom	293	10-12 Y	There was a 1 diopter sphere shift in the MSE towards myopia over the 10–12 year period. Although those with severe ROP had the largest eyes, there was no significant association between birth weight and axial length.
O'Connor A(2006)	Cohort	United Kingdom	Unavailable	Unavailable	Premature infants, who are not routinely followed up, have a high risk of developing treatable refractive errors and strabismus.
Kirwan C(2005)	Cohort	Ireland	35	31W	Premature infants have thick corneas and small corneal diameters.
Cook A(2003)	Cohort	United Kingdom	68	29.4±1.87 W	Premature were myopes and became hyperopes towards the age. Premature infants has shorter AXLs, shallower anterior chambers, and more highly curved corneas.

Rudanko S(2003)	Cross Sectional	Finland	125	23-36 W	Retinopathy of prematurity, optic atrophy, and cerebral amblyopia were the main diagnoses associated with visual impairment.
Larsson E(2003)	Case control	Sweden	217	10 Y	Significant refractive errors were 4 times more common in 10-year-old prematurely born children than in full-term controls.
Saunders K(2002)	Cohort	Ireland	59	31.6 W	Myopia and anisometropia were associated with prematurity. The early emmetropisation process differed from that of the full term group.
Schalij-Delfos(2000)	Cohort	Netherland	130	Less than 37 W	Premature infants were known to have strabismus, amblyopia and refractive error in 5 years follow up.
Theng J(2000)	Cohort	Singapore	113	30.2 W	Premature babies with ROP had higher rates of myopia and strabismus than those without ROP.
Friedman C(2000)	Cohort	United state	93	27.2±1.8 W	Premature infants with ROP have lower mean serum inositol compared with those without ROP.
Holmstrom G(1999)	Cohort	Sweden	260	29 W	The overall incidence of subnormal vision and strabismus in children born prematurely was higher than in a full term population of the same age.
Holmstrom G(1998)	Cohort	Sweden	248	29 W	The risk of refractive errors is higher in preterm infants than in infants born at term, and also prematurely born infants without ROP do run an increased risk of having myopia and anisometropia.
Isenberg S(1998)	Case Control	United state	36	30-37 W	Reflex and basal tear secretion reduce in premature infants.
Fledelius HC(1996)	Cohort	Unavailable	88	31 W	There was a more curved cornea and a shorter axial length than expected from refractive value.
Theo SL(1995)	Cohort	Malaysia	113	32.1±2.5	Duration of oxygen therapy is significantly associated with development of ROP.

Laws D(1994)	Cross sectional	United kingdom	134	27±2.1 W	There is linear growth in axial length during the neonatal period in premature infants although axial length decreased with increasing stage of ROP.
Lue CL(1994)	Cohort	United state	87	Less than 30 W	Most of the premature infants with ROP have myopia and visual acuity is significantly poor in these patients.
Spierer A(1994)	Cross sectional	Israel	Unavailable	Unavailable	Intra ocular pressure is lower in premature infants.
Pike M(1994)	Cohort	Unavailable	42	35 W	Preterm cerebral insults may produce a variety of visual difficulties.
Gallo J(1993)	Case control	Unavailable	10	Unavailable	Higher keratometric diopter values were found in myopic premature children than in emmetropic full term children and myopic full term children.
Tucker SM(1992)	Cohort	Canada	70	25-37 W	Corneal diameter and total axial length showed parallel linear increases although no significant correlation were found between intra ocular pressure and gestational age.
Remon L(1992)	Cross sectional	Spain	152	Unavailable	The differences of central corneal thickness and peripheral corneal thickness between male and female babies and between right and left eyes were not statistically significant.
Bich D(1992)	Cohort	United state	81	30.4±1.5 W	Retinal function varies with dietary supply of omega 3 fatty acid in very low birth weight infants.
Gallo J(1991)	Cohort	Sweden	134	Less than 33 W	Children with a birth weight below 1000 g and a gestational age less than 30 weeks present the highest rate of regressed ROP.
Autzen T(1991)	Cohort	Denmark	13	Less than 33 W	There was no correlation between gestational age, birth length and weight and central corneal thickness.
Isenberg S(1990)	Cohort	United state	30	26 W	Mydriasis should not be considered indicative of a central nervous system disorder, and a pupil unresponsive to light should not be considered suggestive of blindness until a preterm infant reaches at least 32 weeks' postconceptional age.
Heravian J(1990)	Cross Sectional	Iran	50	Unavailable	VEP as an objective method can predict VA.

Autzen T(1989)	Cross Sectional	Denmark	30	Unavailable	There was no correlation between gestational age, birth weight, and CCT.
Taylor M(1987)	Cross Sectional	Canada	75	22-42 W	The 22-23 week GA neonates had no identifiable waves. In all infants > 24 weeks a large negative wave is seen with a latency around 300 msec (N300). After 27 weeks GA a late positive wave was present (P400), but with more variable latency and morphology. Between 30 and 35 weeks GA a small positive wave (P200) was seen in over one-third of the neonates; this component was present in all infants > 36 weeks GA.
Brown A(1986)	Case Control	United state	Unavailable	Unavailable	Visual acuity of infants at 39 to 40 weeks of gestational age was about 0.023 stripes per minute of arc, or 0.69 cycles per degree (20/866). Between 34 and 44 weeks of gestational age, visual acuity improved at the rate of 0.46 octaves per month.
Norcia A(1985)	Cross sectional	United state	197	1-53 W	This visual acuity estimate change from a mean of 4.5 c/deg during the first month to about 20 c/deg at 8- 13 months of age.
Nissenkorn (1983)	Cohort	Israel	155	Unavailable	Myopia were found in 50% of the premature infants with ROP, while only 16% myopic premature infants were found among those who did not have ROP.
Fledelius H(1982)	Case control	Denmark	70	Unavailable	Premature infants represent significantly lower value of corneal curvature radius.
Fledelius H(1981)	Case control	Denmark	137	Unavailable	As compared with low-birth-weight, full-terms show a significantly higher cumulated visual acuity score.
Hittner H(1979)	Cross sectional	United state	36	Unavailable	Keratometry demonstrated steeper corneal curvature in LBW populations, as compared to term newborns.

Uncorrected Proof

Conclusion

In conclusion, the prevalence of visual impairment is more in preterm infants because of ROP and perinatal brain lesions. Myopia is a prevalent refractive error in premature infants due to large AXL. VA, VEP acuity, and contrast sensitivity decrease due to ROP. Esotropia is the most common form of strabismus in premature infants. Corneal assessment illustrated that corneal curvature is steeper, and central corneal thickness is less in premature infants, as compared those born at term. There was no statistically significant difference between male and female infants in any of the measured variables at any point of time. Careful evaluation of infants with GA of 32 weeks or less for any prematurity-induced ocular changes is recommended.

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