Long term ophthalmic sequelae of prematurity

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Abstract

Survivors of preterm birth may present with various ocular conditions later in life. Long-term ophthalmic care in formerly preterm individuals is important as their vision may be compromised by sequelae of retinopathy of prematurity (ROP), refractive errors, strabismus, and cerebral vision impairment. They are also at risk of developing cataracts, angle closure glaucoma, and retinal detachment later in life. A protocol for follow up of preterm children with and without ROP at different ages needs to be established.

Keywords: Prematurity, arrested ocular growth, late sequelae, low vision

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Ophthalmic problems are common among children born prematurely or with low birth weight. Retinopathy of prematurity (ROP), refractive error, strabismus, and cerebral vision impairment (CVI) are some of the conditions that can lead to visual impairment in preterm children. Patients with an initial favorable outcome remain at an increased risk of ophthalmic pathologies later in life. Epidemiologic studies suggest that suboptimal nourishment of fetus and/or infants may have long-term effects resulting in increased incidence of medical problems such as hypertension, obesity, diabetes, and cardiovascular disease. This is relevant to the adult outcome of very low birth weight (VLBW, <1500 g) infants. Individually demonstrating rapid catch-up growth are considered to be at the greatest risk of medical complications. In this context, further studies are needed to establish whether prematurity causes increased structural and functional vulnerability in ocular structures during postnatal expansion reflecting in increased incidence of ocular disorders due to involutional changes over time. The potentially devastating visual effects of ROP are well known, and this article aims to highlight other conditions associated with prematurity, which can adversely affect the visual potential in preterm children. At present, the need for regular ophthalmologic follow-up in formerly preterm individuals is not adequately recognized.

Effects of Prematurity on the Eye

It is known that preterm birth affects normal retinal development and function. Optical Coherence Tomography (OCT) studies have demonstrated that the total retinal thickness at the fovea is increased, and the foveal avascular zone is smaller in children born preterm than that of children born at term, regardless of the presence of ROP. The foveal contour is abnormal with a shallow or absent foveal depression in infants born prematurely. The relevance of these changes on vision is yet to be established.

The association of refractive errors with prematurity is well-documented. During the first months of life, preterm infants demonstrate more myopia, astigmatism, and anisometropia than full-term infants. In the neonatal period, preterm infants have mainly against the rule (ATR) astigmatic axes in contrast to with the rule (WTR) in full term infants. However, preterm infants usually lose their astigmatism or become WTR by six months corrected age. In school-aged children with preterm birth, there is an increased incidence of myopia, hyperopia, and astigmatism. Refractive errors at ten years of age are four times more common in those born preterm (29.6%) than in those born at term (7.8%).

Preterm children are noted to have shallower anterior chamber depth (ACD), greater lens thickness (LT), and steeper central corneas as compared with age-matched control subjects. The presence of ROP is associated with considerably shorter ACD, thicker lens, and higher myopia and astigmatism. It has been stated that whereas hyperopia is due to short axial length (AL), myopia in a formerly preterm child is mainly attributable to anterior segment components rather than to increased AL. However, in the same study, measurements of ocular components reveal that AL is longer in myopia of prematurity as compared to eyes with other refractive errors. This implies that myopia of prematurity is mainly axial but AL appears to be relatively short as a steep cornea, shallow ACD, and a thicker lens also contribute towards the myopic error, as opposed to ordinary myopia, where these components tend to reduce the myopic error.

Emmetropia is achieved in many premature children without ROP as a steep cornea and thick lens typical of a premature eye is compensated by a shorter AL. Failure to emmetropise results in an increased incidence of not only myopia but all refractive errors.

Cerebral visual impairment (CVI) is increasingly being recognized as a more common cause of visual impairment in preterm individuals than ROP. In preterm infants, hypoxia selectively injures the periventricular deep white matter causing brain lesions known as periventricular leukomalacia (PVL). Since the optic radiations and the corticospinal motor tracts travel within the periventricular white matter, PVL is strongly associated with CVI. The reported incidence of PVL ranges from 4-15% in most studies. An Indian study found an incidence of 36.2% in a cohort of VLBW infants. The presence and severity of periventricular brain damage may be more important than consideration of birth weight alone in extremely low birth weight (<1000 g) in predicting which preterm children will be at greatest risk for experiencing visuomotor problems at 6 years of age.

Visual perception (VP), such as proper recognition of faces and forms, orientation, depth perception, and simultaneous perception, may be impaired in lesions of visual pathways causing disabling visual problems, but visual acuity (VA) might be spared in spite of extensive lesions as fibers from the macula are widely distributed in the visual pathways, leading to the visual problems of affected children being either unrecognized or underappreciated. A population based study on Swedish schoolchildren born at less than 29 weeks gestation found an incidence of visual impairment (VA less than 6/18) in 6% but subnormal VP was detected in 42%. Children with perceptual problems caused by CVI are often considered to have learning disabilities (mental retardation) in spite of their normal intelligence. A better understanding of the child's problems by parents and teachers results in a better approach to help the affected child. Some difficulties related to prematurity may disappear with age. In a study of teenagers born preterm, periventricular white
matter lesions were found to be common, but teenagers with these lesions did not differ in neuropsychological outcomes from those without such lesions. \[16\]

Visual field defects, usually affecting the lower field, have been reported in premature children with visual impairment due to white matter damage of immaturity (WMDI) also known as periventricular leukomalacia (PVL). \[12\] Other studies did not find visual field defects in premature children as compared with control subjects, except for peripheral field defects in children who had received cryotherapy. \[13\] However, early treatment, i.e., retinal ablation administered to the avascular retina when an eye reaches high-risk prethreshold ROP, preserves peripheral vision and does not adversely affect visual field extent clinically. \[19\] Visual field studies done using static high-pass resolution perimetry reveal a tendency towards defects of the central visual fields that are unrelated to ROP and cryotherapy. \[18\]

Incidence of strabismus is increased in children born prematurely. This has been associated with retinopathy of prematurity, low birth weight, cerebral palsy, anisometropia, and refractive error. \[20\] At one year follow up of preterm Asian children, strabismus was found in 20% in the ROP group compared to 4.9% in the no ROP group. \[12\] A population-based study in preterm Nordic children born with a birth weight of 1500 g or less, found that over the first 42 months of life (corrected age), the incidence of strabismus among children without a history of ROP or neurological complications was 5.9% as compared to 22% among the children with ROP or neurological complications, with an overall incidence of 13.5%. \[21\] Amongst ten-year-old children, strabismus was noted in 16.2% premature and in 3.2% full-term children. \[22\]

It is postulated that the etiology of strabismus in preterms may differ from that of full terms as the ratio of esotropia: exotropia is 1: 1 in the low-birth weight population as compared to 3:1 in full-term children, and the incidence of near exotropia, a relatively uncommon type of strabismus, is 12%. \[1\]

Preterm birth results in major changes in the fetal milieu which may interfere with the early development of the lenses and result in cataract in both eyes, as suggested by the increased risk (10.6 times) of bilateral cataract in children with birth weight <2000 g as compared to children with a birth weight of 3000-3500 g. \[24\] Another study done on premature children within twelve months of life confirms that LBW (1500-2499 g) is strongly associated with bilateral cataracts but made the additional observation that VLBW (<1500 g) is associated with both unilateral and bilateral cataracts, \[25\] In adults with a history of preterm birth and low birth weight, cataract surgery tends to be performed at a younger age (mean 40.3 years) but improvement in vision is suboptimal. The risk of retinal tear or detachment is high (23%) following cataract surgery. \[26\]

Glaucoma is also a known complication of prematurity. The glaucoma described in ROP is usually associated with a narrow anterior angle and a shallow anterior chamber and a retrolental membrane or a swollen lens pushing the iris-lens diaphragm forward. \[22\] The Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO-ROP) study determined that in children with bilateral threshold ROP, the incidence of glaucoma at the 5.5 year examination was 2.9% in treated eyes and 6.1% in control eyes, \[28\] while the Early Treatment for Retinopathy of Prematurity (ET-ROP) study found that nearly 2% of eyes with high-risk prethreshold ROP developed glaucoma at some point during the first 6 years of life. \[22\]

In adults with regressed ROP, angle closure glaucoma may occur due to relative anterior microphthalmos consequent to arrested development of the anterior segment. Shallowing of the anterior chamber and risk of development of angle-closure glaucoma increases with age, usually manifesting during or after the third decade of life. A detailed history and consideration of the biometric data is important for diagnosis. \[29\] In some cases, a jammed anterior segment due to arrested development leads to severe glaucoma and a painful blind eye. \[2\]

It is generally believed that the occurrence of myopia in angle closure is rare; however, a recent study has revealed the presence of myopia in 22% East Asian patients with primary angle closure. These patients with angle closure have predominantly axial myopia, but the ACD is similar to those of hyperopes and emmetropes. This suggests that ACD is an important risk factor in the development of angle closure, regardless of AL or refractive status. While a multifactorial cause for angle closure in these myopes is probable, the configuration of the anterior segment may predispose them to angle closure. \[30\] This study raises the question as to whether myopia of prematurity (MOP) increases the risk of angle closure even in preterm individuals without ROP, due to arrested development of anterior segment manifesting in a shallow ACD and a thick lens, though the arrest is much less as compared to eyes with regressed ROP.

Formerly preterm children also have reduced distance and near visual acuity as compared with full-term children, even when children with ROP and neurological disorders are excluded. \[31\] It has been speculated that cone damage may occur following prolonged exposure to illumination such as during treatment for jaundice. Intrauterine infections are a common cause of preterm labor and prenatal endotoxin exposure may be harmful to the developing retina and optic nerve. \[1\]

Prematurely born children have significantly lower contrast sensitivity (CS) in the low- and mid-range spatial frequencies. Contrast sensitivity estimates the ability to detect daily life objects, which may explain visual problems in preterm children despite a normal VA. \[32\] Deficits in CS vision in low birth weight children persists even in the absence of ROP or known neurological abnormalities. \[33\]
Children with regressed ROP are more vulnerable to vitreoretinal complications such as retinal tears, retinal detachment (RD), and vitreous hemorrhage in the long term. It is postulated that some preterm eyes with a poorly vascularized retina may be unable to tolerate trauma, disease, or the changes associated with aging. Retinal tears may be due to the failure of a scarred retina to expand along with the postnatal expansion of the eyeball.\[2\] The retinal holes are characteristically multiple with a prevalence of equator and posterior types.\[24\] Late RD is the main vision-threatening condition in patients with regressed ROP during childhood.\[35\] Lifelong follow up of high risk patients is probably necessary so that early diagnosis and treatment can be instituted.\[34\]

The CRYO-ROP study found that in preterm children with birth weights less than 1251 g and severe (threshold) retinopathy of prematurity (ROP) in one or both eyes, there was a gradual increase in unfavorable structural outcomes between the 1-year and 15-year outcome assessments. Between 10 and 15 years of age, new retinal folds, detachments, or obscuring of the view of the posterior pole occurred in 4.5% of treated and 7.7% of control eyes. In treated eyes, unfavorable outcomes averaged 0.35% per year, while control eyes averaged 0.51% per year.\[36\]

A recent population-based cohort study has found that, between 1987 and 2008, individuals born at <28 weeks gestation have a nine-fold increase in the risk of RD while those born at 28-31 weeks gestation have a 3 times higher increase in risk as compared to peers born at term. Preterm birth at 32-36 weeks of gestation was not found to be associated with an increased risk of RD.\[37\]

As is evident from above discussion, there is a greatly increased risk of ophthalmic deficits in preterm children with severe ROP or severe neurological disorders and in those with mild or no ROP. Children in the latter group are not routinely followed up. There is no standardized approach for the ophthalmic care follow up of children screened for retinopathy of prematurity (ROP).\[38\] At present, even in developed countries, follow up of preterm infants is haphazard.\[39\] A survey of existing ophthalmic follow up protocols in the United Kingdom (UK) for VLBW children found a large variation in criteria used for follow up; 21% of respondents using birth weight (BW) and gestational age (GA), 22% using stage 3 or treated ROP, the remainder considering a combination of these factors. There was no consensus regarding when follow up should commence (from 3 months to 3 years) or cease (1-8 years).\[38\]

In countries where preventive child healthcare is well organized, such as Sweden, ophthalmological screening of children is done mainly to detect refractive errors and strabismus.\[40\] However, apart from these conditions, preterm children, especially with regressed ROP, are at increased risk for glaucoma, retinal detachment, and defects in visual perception. These conditions require detailed examination and are likely to be missed at routine screenings under preventive child healthcare programs.

Long-term effects of prematurity in individuals who have reached early adulthood without any diagnosed ophthalmic problem remains largely unknown. More studies are needed on preterm children to determine the schedule, method of assessment, and duration of follow up examinations. Multiple protocols will probably be needed, which will vary based upon the presence or absence of ROP, severity of ROP, birth weight, gestational age, and presence of CVI. The CRYO-ROP study recommends that it is of value to have long-term, regular follow up of eyes with threshold ROP.\[35\] The question as to whether ophthalmologic follow up should be continued well into adulthood needs to be clarified by future studies.

### Conclusion

Adverse ophthalmic sequelae of prematurity may manifest later in life. It is recommended that all preterm infants with a gestational age less than 32 weeks should be screened at the age of one year, in the third year of life, and just before school age for the detection of refractive errors, amblyopia, and strabismus.\[41\] A comprehensive follow-up, which includes fundus examination and tests of visual perception, is also necessary and a protocol needs to be formulated for it. Parents should be counseled that even preterm infants with a favorable primary outcome should have regular ocular examinations throughout childhood and beyond.

### References


