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Preterm birth: the ophthalmic consequences

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Abstract

Aim: **There is a growing body of evidence evaluating the outcomes following preterm birth. Continued evaluation is essential to determine the impact of new treatments, which can affect many areas of development. Therefore this review aims to provide an evidence-based update on the ophthalmic sequelae of preterm birth.**
Methods: **A literature search of databases was performed, focusing on publications from the last 3 years.**
Results: **New treatments are being developed to prevent severe vision loss due to retinopathy of prematurity (ROP), but as they are so new no long-term data are available. The development of new imaging techniques has allowed detailed analysis of the visual pathway, with changes in the posterior visual pathway identified and linked to visual function. Deficits of visual function in the preterm population extend beyond visual acuity, affecting functional ability in many ways, even in the presence of a normal visual acuity response. Strabismus rates continue to be increased but do not appear to have changed in recent years. Overall the literature agrees that preterm birth affects a range of ophthalmic outcomes, but there continues to be a lack of consensus as to what follow-up care is required.**
Conclusions: **Children born preterm are at continued risk of developing a range of ophthalmic sequelae but new techniques are being applied to determine their aetiology. Novel treatments for ROP have shown promise in reducing severe visual impairments, but many questions remain regarding the nature of more subtle deficits of visual functions and how they should be identified.**

Key words: Low birth weight, Preterm, Refractive error, Screening, Strabismus, Visual acuity

Introduction

Children born preterm, <37 weeks gestational age (GA), and with very low birth weight (<1501 g) account for approximately 1.5% of all live births in the United States[1] but this relatively small population require a disproportionate amount of health care resources. With increasing value being placed on health economics, a population that has a high cost in terms of both neonatal and long-term care[2] is of particular importance. Survival rates across the world are variable and are influenced by a number of factors, including geographical location,[3] but data from the UK have shown an improvement in rates of survival to discharge over recent years.[4] Initially the increase in survival rates was accompanied by an increase in disability; however, this trend appears to be declining, with a large cohort ($n = 1367$) from the UK showing an increase of 14% in survival from 1993 to 2002 but no increased rate of disability.[5] While this is encouraging, there are still a large number of children with disabilities resulting from preterm birth which encompass all areas of development, including that of the visual system.

There is a large amount of literature published on this topic: a PubMed search using the key words 'preterm birth' gave 2146 results from 2010 alone, and when combined with the word 'visual' returned 38 publications. In addition there are a number of reviews of the literature, including those evaluating the ophthalmic outcome,[6,7] but this is an ever-changing population with continuing improvements in health care, resulting in new questions and challenges for clinicians. Therefore, continued evaluation is essential, so this review will focus on publications from the last 3 years to provide an update of the latest literature.

Non-ophthalmic deficits

As a consequence of low birth weight, deficits frequently do not occur in isolation, but result in a large number of children with multiple health care issues.[8] The types of deficits encompass cognitive abilities,[9–11] behaviour,[12–14] motor control[15] and language development, all of which can affect a child's educational needs,[16,17] and persist into adulthood.[18] There is sufficient volume of work to write a separate review on each of these topics, but the focus of this review is the ophthalmic outcomes. However, there is one pertinent issue when evaluating the findings from studies of low birth weight/preterm children, which is demonstrated by studies of language development. Disorders affecting language development are common, occurring in over a third of one group of children at 3.5 years who were born before 34 weeks gestational age (GA) with an absence of major cerebral damage.[19] This rate was almost 5 times higher than the rate in full-term children. However, these findings may simply represent a delay in development, as suggested by findings in children aged 4–6 years where there was no difference between the preterms and full-term controls, in a more preterm cohort than in the

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previous study (GA <31 weeks).[20] This lack of concordance in results may be a reflection of the age at assessment, and therefore the point in development, or the different test procedures. Irrespective of the reason, these findings highlight the need to evaluate the long-term outcome to accurately evaluate the impact of preterm birth; this applies to many disorders of development, including that of the visual system.

Ophthalmic deficits

As with all types of measure of ability in preterm children, comparisons are difficult due to the variability in inclusion criteria (e.g. varying birth weight or GA), but the one common finding is an increase in all types of deficits compared with children born at term. There are three key areas of visual development of particular importance to orthoptists, which are visual acuity, strabismus and refractive errors. These will therefore be discussed in detail.

Reduced visual acuity

Reduced acuity in preterm children may be attributable to a number of factors such as retinopathy of prematurity (ROP),[21] neurological deficits,[22] refractive errors or amblyopia; therefore assessment is of particular importance. One of the challenges of measuring vision in preterm children is that clinical assessment of visual acuity requires a certain level of cognitive ability. However, many preterm children have a developmental delay or disorder affecting their cognitive development that negates the use of optotype acuity testing. Therefore test options for quantifying vision are limited. Preferential looking (PL)-based tests are the clinical standard; these are good at detecting severe vision loss, but the sensitivity for detecting more subtle reductions in vision is reduced.[23]

At 10 years of age most ex-preterm children have normal vision,[24] but a small proportion have a subtle reduction without identifiable cause, including ROP or detectable neurological impairment.[25] It has been postulated that the lack of maternal thyroid hormone, at a time in development when the infant is not able to produce sufficient levels, resulting in transient hypothyroxinaemia of prematurity, has an impact on visual development.[26,27] Visual functions assessed at 6 months of age using a sweep visual evoked potential (VEP) found no relationship between visual acuity and thyroid levels, but a reduction in the contrast sensitivity (CS) of the children with the lower GA (<33 weeks) was associated with thyroid levels. This group of children (GA <33 weeks) were also the only ones with neurological deficits, but statistical analysis showed that this did not affect the finding of reduced CS. The authors acknowledge their small sample size and potential lack of power in their analyses, but as their acuity values were similar to published normative data[28] it is plausible that thyroid levels have little or no impact on visual acuity. However, neurodevelopmental measures at 5 years of age have been shown to be associated with neonatal hypothyroxinaemia.[29] This suggests that further investigation of CS at a later age may demonstrate a continued reduction, as CS reductions are primarily neurological rather than retinal in origin.

An alternative hypothesis for the aetiology of these subtle visual deficits is that the reduction is due to retinal damage. In the majority of children born preterm there is either an absence of retinopathy of prematurity (ROP) or only mild ROP which spontaneously regresses, but even without serious damage to the retina, the development is incomplete in all preterm children. Therefore, the disruption in retinal development due to premature exteriorisation may result in reduced acuity. A number of studies have evaluated retinal structure using optical coherence tomography (OCT)[30–32] and all found an increased thickness in the central macula. However, only one[30] analysed the relationship of the OCT findings with visual acuity (logMAR acuity test at an average age of 8 years) and this found no connection between the two measures. Based on these results the authors suggested that the identifiable differences in macular thickness may simply reflect immaturity and have no functional impact.

As no evidence has provided a link between acuity and retinal changes, the reduced acuity may be related to changes in the visual pathway posterior to the retina. Improved imaging techniques have allowed more detailed analysis of neurological development,[33] which have been utilised to evaluate areas of the visual pathway. Imaging of the optic radiations was compared with measures of visual function,[34] using a standardised visual assessment designed for assessment in the neonatal period, to identify any relationship with white matter development.[35] Analysis demonstrated that, at term-equivalent age, visual function was directly related to the development of white matter in the optic radiations. Although this assessment was undertaken at a very early age, it may provide an aetiology for previously unexplained reductions in acuity.

While normal visual acuity or mild reductions in acuity are the most common outcome, the risk of blindness from ROP is still present. The rates of ROP are low,[36] but its continuing presence has resulted in further evaluation of the treatment options to optimise visual outcome.[21] The protocol for laser treatment has been refined to maximise the response,[21] but the treatment itself has damaging effects. A new advance in the treatment for ROP has been the development of anti-VEGF drugs such as bevacizumab (Avastin),[37,38] with reports of its use as a primary treatment[39] or an adjuvant to laser therapy.[40] One key advantage with this treatment is the ability to inject into eyes where there is poor retinal visualisation[41] which may preclude the use of, or efficacy of, laser treatment. Initial results have been favourable in terms of anatomical changes; however, CRYO-ROP demonstrated that a good anatomical outcome is not always associated with a good functional outcome, with 30% having an unfavourable structural outcome at 15 years but 45% having an unfavourable acuity outcome.[42] The use of bevacizumab for ROP is a recent development, so long-term follow-up of acuity is not yet available, with only one case report found reporting acuity after the age of 3 years.[43] This child had aggressive posterior ROP and anterior segment ischaemia following laser treatment, and was given bevacizumab. A significant cataract subsequently developed in the left eye resulting in a very poor visual outcome, but the right eye, at 3 years of age, had vision of 6/9. As this treatment is still in its infancy, and reports of its use are primarily in small sample sizes with limited follow-up data, clinical trials are being undertaken to evaluate its efficacy,[44] but the early results are encouraging. However, caution is urged due to the risk of trauma or infection in the eye, or possible systemic side effects with the potential to affect multiple organs.[45]

Beyond visual acuity

Standardised tests of visual acuity allow comparison with normative data to determine whether it is normal for the child's stage in development. However, a response that is within normal limits on a visual acuity chart does not mean that the patient has no functional impairment to daily living. An example of this is highlighted in a report of 7 children (4 of whom were preterm) in whom the acuities were 6/9.5 or better but who had evidence of visual dysfunction, including reduced visual fields.[46] The location of the visual field deficit reported in this and another study[47] was in the inferior field in all children. In many cases the visual field deficit occurred in children with known white matter damage; however, field deficits may also occur where there is no identifiable white matter damage,[47] so although clinical assessment of visual fields is of particular importance in children with conditions such as periventricular leucomalacia, it should not be restricted to this group.

Studies involving detailed measurements of the visual field outcome were undertaken in children age 7 years and older,[47–49] as testing before this age is limited to confrontation methods with a lower degree of sensitivity, which is an important consideration in research. However, the important issue for clinicians is to detect is whether the child has any functional problems, which may not necessitate detailed measurements. To identify any functional deficits Dutton *et al.*[50] have devised a cerebral visual impairment (CVI) inventory.[51] This is given to the parents to aid in the identification of deficits of visual function and therefore allows the implementation of strategies to minimise their impact.

Other measures of visual function in which ex-preterm children have reduced scores when compared with children born at term are visuo-motor[52] and visual spatial ability.[53,54] However, as we have shown,[55] when the task is very simple it can be completed without error, but with the addition of a more cognitively demanding component, such as a memory delay, errors are seen. This highlights the discrepancy between static visual acuity testing undertaken in the clinical setting, and the use of the visual system in the real world, again reinforcing the need for other methods of identifying children with functional deficits.

Reduced response on VEP testing has been identified in preterm children, even when visual acuity was within normal limits.[56] In addition, VEPs have been shown to be related to cognitive ability in preterm children.[57] As VEP testing can be undertaken at an early age this may provide a method of predicting long-term deficits so that interventions to improve outcome can start at an early age. However, these associations were found with small selected populations and so further work is required to determine whether this approach can be applied to a larger population.

The ophthalmic sequelae of preterm birth influence many aspects of visual function, but the impact may not be limited to visual ability. Visual function and cognitive and behavioural outcomes have been shown to be related through statistical analysis,[58] but it is not possible to differentiate whether this is a causal relationship or whether they have a common aetiology. Also, a relationship between vision and the ability to perform certain tasks has been identified in children born preterm,[59,60] but again it is difficult to determine whether the relationship is causal or whether the reduction in vision and motor difficulties are both caused by a single neurological deficit. One study attempted to differentiate the possible impact of a number of factors that could be affecting the motor difficulties such as performance IQ, GA, gender, presence of cerebral haemorrhage, ROP in infancy, and the presence of strabismus (manifest or latent).[61] After these measures were factored into the analysis, visual acuity was still statistically significantly associated with performance. However, acuity accounted for only around 11% of the variability in performance, demonstrating a weak association. In a cohort of children of extremely low birth weight (<1001 g) an association was found between visual acuity and the ability to perform specific motor skill tasks,[59] with a lack of relationship between measures of illness. This again highlights the important contribution of vision to development. Ensuring the maximum visual development may therefore have a positive impact on many other aspects of a child's development, with benefits not purely restricted to the ophthalmic outcome.

Strabismus

In a previous review, the rates of strabismus in preterm children were shown to vary between 9.5% and 22%,[7] with more recent reports giving similar rates of 10–17.6%.[24,61–63] In the UK-based Millennium cohort of 14 980 children, the rates of strabismus at the age of 3 years were lower (3–4% depending on whether GA or birth weight criteria were used).[64] However, as the analysis included all low birth weight (<2500 g) or preterm (<34 weeks GA) children a lower prevalence would be expected due to the inclusion of children born at later stages in development. Despite the inclusion of the less preterm children, the risk of developing strabismus was 2.2 times higher in those with birth weight <2500 g compared with those with normal birth weight, and 3 times higher in those born before 34 weeks GA compared with those born at term.

Although there have been numerous reports of the increased rate of strabismus in children born preterm, there is a paucity of evidence evaluating the impact and whether it differs from that in children born at term. Strabismus, amblyopia and a lack of binocular functions have all been shown to affect the ability to perform fine motor skills,[65–68] which is also known to be affected in children born preterm,[69] but when reporting the findings in preterm children performing motor tasks the presence of strabismus is not always noted,[53] which limits the interpretation of the data. Strabismus can also affect quality of life in a number of ways, including self-image, job prospects and relationships.[70,71] However, evaluating the impact on some of these aspects, such as job prospects, necessitates very long term studies. Therefore it is currently unknown what the impact is, or whether the presence of strabismus has a bigger impact in people who have additional health problems which occur more frequently in the preterm population.

Refractive errors

There are a number of reports from 2008–2010 of increased rates of refractive error in the preterm population; the findings are summarised in Table 1. Inclusion in the table was not selective, all studies found being included. However, it is recognised that the quality of the studies is variable, which is exemplified by the small sample sizes of some of them.

The results shown in Table 1 differ in many respects, which can be related to inclusion criteria, country of origin and age at assessment; but they do show increasing rates of all types of refractive errors with an increase in myopia in the older children, or those treated for ROP. The measures of eye size showed that low birth weight had an impact on eye growth, but the correlation coefficients demonstrated only partial correlation between the factors, highlighting the multifactorial nature of eye growth.

Of the studies included in Table 1, only one excluded cases of strabismus,[72] but there is evidence showing that the process of emmetropisation is affected by the presence of strabismus.[73,74] One example of a specific type of strabismus affecting emmetropisation is in children with infantile esotropia.[75] The typical reduction in hypermetropia seen in early childhood in children without strabismus did not occur; however, the result was not a permanent refractive error but a delay in emmetropisation, which began after the age of 8 years. Therefore when evaluating the refractive outcomes in a population with known increased rates of strabismus, anything which could potentially affect emmetropisation should be factored into the analysis.

Targeted vision screening: Is it necessary?

Despite advances in knowledge into the mechanisms of the ophthalmic deficits there continues to be a lack of consensus regarding clinical care. Vision screening is advocated for all children at the age of 4.5 years but, due to the increased risk of ophthalmic deficits in low birth weight children, it could be argued that these children require additional assessments. Previous evidence identified a large variation in the eye care provision for this population, in particular for those with no or regressed ROP detected in the neonatal period.[85,86] This varies from regular, often annual assessments for a number of years, to some infants being discharged after the neonatal period. Subsequently the Royal College of Ophthalmologists updated their guidelines on screening for ROP in 2008,[87] with the following recommendations for long-term care:

> The outcome of preterm babies without ROP and those who developed stages 1 or 2 are similar and the guideline development group do not recommend, unless there is specific concern, follow-up other than the routine national screening that is undertaken between 4½ and 5 years of age.
>
> The guideline development group agreed that all babies with stage 3 ROP in which ROP resolved spontaneously and those babies requiring treatment require ophthalmic review at least until 5 years of age.

These recommendations assume that any deficits developing after the neonatal period will be detected by the routine screening procedures in place for all children. However, it is not known whether the deficits detected at 4.5 years respond to treatment in the same way as in children born at term or whether earlier identification would improve outcomes. Regular visits to an ophthalmologist have been recommended,[88] due to the long-term risk of retinal detachment associated with preterm birth, even in the absence of ROP, but if additional examinations are unnecessary then this could be a drain on limited resources. Nevertheless if the children do require additional assessments but are not receiving them, this would be detrimental to their visual development. Follow-up studies have focused on assessment towards the end of the visual development period, when it would be possible to undertake detailed assessments at a time when the deficits would have developed. Therefore, there is a lack of information regarding the natural history of the ophthalmic sequelae, and without identifying the time of onset or the development course it is not possible to determine the optimum approach for the long-term care.

Is there a high-risk group?

As the number of low birth weight children has risen, any additional assessments would have a significant impact on clinical provision. Therefore, identifying a subgroup who have the greatest risk of developing ophthalmic sequelae would minimise the impact on limited finances: the numbers of unnecessary examinations would be low but all cases of ophthalmic sequelae would be identified. However, the risk for the development of long-term deficits varies for each child. For example it is dependent on what happens in the neonatal period, where illnesses such as nectrotising enterocolitis[89] and bronchopulmonary dysplasia[90] increase the risk of a poorer neurodevelopmental outcome. However, factors not related to the prematurity also have an impact on outcome. This is demonstrated by the association between ethnicity and the development of ROP.[91] This makes the identification of all high-risk children a challenging proposition.

Rather than relying on findings from the neonatal period, assessment of the neurodevelopmental outcome within the first year may be beneficial in identifying a high-risk group, as the aetiology of many visual problems in preterm children is neurological in origin,

Table 1. Summary of the findings from studies in 2008–2010 evaluating the refractive outcome of low birth weight/ex-preterm children

Authors	Country of research	No. of children	Age at assessment	Inclusion criteria	ROP status	Treatment for ROP	Refractive errors	Biometry results
Ozdemir[76]	Turkey	26	5–7 years	≤34 weeks GA	None	N/A	21% ⩾ +2.0DS; 5.7% ⩾+1.0DC; myopia nil, 11.5% anisometropia ⩾1.0D	AL correlated with BW ($r = 0.57$) and GA ($r = 0.82$) but not ACD or LT
Yang[77]	Taiwan	30	7–9 years	<34 weeks GA or <2000 g BW	All had threshold ROP	Laser	77% <0.0DS; 16.7% myopia >6D; 35% astigmatism >3D; 46.7% anisometropia ⩾1.5D	None
Chen[78]	Taiwan	108	7–9 years	<35 weeks GA or <1500 g BW	44% had ROP, 27% ⩾ stage 3	Laser or surgical repair	MSE = 1.02 ± 3.53 (SD); 47% <−0.5D; 23% >+0.5D	Higher ACD, lower LT, lower corneal astigmatism in non-ROP vs ROP group + in mild ROP vs advanced ROP group
Modrzejewska[79]	Poland	180	6 months	≤36 weeks GA or <2500 g BW + no astigmatism	None	N/A	82.9% hypermetropic (18% >+3 to +6); 17.1% myopic (2.6% <−6D)	Correlation between AL and BW ($r^2 = 0.23$) + GA ($r^2 = 0.17$) in +3 to +6 range only
Morrison[72]	USA	226	First visit <18 months, second <89 months	No strabismus or ocular abnormalities	Spontaneously regressed	N/A	24% mild myopia <1.5 D; 3 cases with significant refractive error	None
Varghese[80]	India	559	First week of life	Admitted to nursery	Unknown	Unknown	64.6% ⩾1.0 DC in preterms (GA 24–27 weeks); MSE 22.79 (3.92)	None
Axer-Siegel[81]	Israel	100	35 ± 28.3 months	Treatment for ROP	Threshold or type I ROP	Laser	MSE ± SD −1.5 ± 4.2 D; mean cylinder +0.3 ± 1.4 D; 31.3% myopia 0 to −4.9D, 23.9% myopia >−5D	None
Cook[82]	UK	136	32–52 weeks PMA	<32 weeks GA or <1500 g BW	14% stage 1, 19% stage 2, 9% stage 3, 9% threshold	Laser	SE at 3 months: stage 1 ROP, +2.12; stage 3+, +0.65	AL and ACD had linear growth patterns, LT little change over the study; corneal curvature correlated well with refractive state
Dhawan[83]	India	93	1+ year after laser treatment	Laser treatment for ROP	Requiring treatment	Laser	MSE −4.71; 80.4% of eyes myopic, 9.8% eyes significant hypermetropia, 13% anisometropia	None
Cosgrave[84]	UK	211	1 year	<1501 g and ≤31 weeks GA	15.2% ROP; 1% required treatment	Laser	3.75% without ROP had refractive error (myopia<0.0 D, hypermetropia >4 D, astigmatism ⩾1 D, anisometropia >1 D), 6.7% with ROP had refractive error	None
Holmstrom[24]	Sweden	199	2.5 years	<1501 g BW	40% had ROP; 11% treated	Cryotherapy	16.6% MSE <0 or >+3; 29.6% astigmatism ⩾1 D; 7.5% anisometropia ⩾1 D	None

ACD, anterior chamber depth; AL, axial length; LT, lens thickness; MSE, mean spherical equivalent; N/A, not applicable; PMA, post-menstrual age.

and deficits of vision occur in conjunction with other neurodevelopmental deficits. There are no current guidelines for standardised follow-up of neurodevelopmental impairment in preterm children, but it has been reported that they are about to emerge,[92] which may help identify the children at high risk of developing ophthalmic sequelae. However, if this is not a routine assessment, any benefit of a reduced number of assessments for the ophthalmic team, would be at the expense of an increase in workload for the paediatrics team.

Summary

Although the disability rates in ex-preterm children appear to have reached a plateau, the profile of these children is still one of increased risk of a range of ophthalmic and developmental deficits. The question remains as to whether additional screening is warranted for these children, and what form that should take. Novel treatments for ROP will potentially result in lower rates of severe vision loss; however, challenges remain for those with milder degrees of vision loss, and in particular identifying functional impairments in the presence of normal high-contrast visual acuity.

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