Preterm birth: the ophthalmic consequences

ANNA R. O’CONNOR PhD BMedSci (Hons)

Directorate of Orthoptics and Vision Science, University of Liverpool, Liverpool

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 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 is of particular importance. Survival rates across the world are variable and are influenced by a number of factors, including geographical location, but data from the UK have shown an improvement in rates of survival to discharge over recent years. 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. 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 outcomes, 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. The types of deficits encompass cognitive abilities, behaviour, motor control and language development, all of which can affect a child’s educational needs, and persist into adulthood. 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. 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
previous study (GA <31 weeks). 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), neurological deficits, 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.

At 10 years of age most ex-preterm children have normal vision, but a small proportion have a subtle reduction without identifiable cause, including ROP or detectable neurological impairment. 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. 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 acknowledged their small sample size and potential lack of power in their analyses, but as their acuity values were similar to published normative data 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. 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) and all found an increased thickness in the central macula. However, only one 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 neurodevelopmental development, which have been utilised to evaluate areas of the visual pathway. Imaging of the optic radiations was compared with measures of visual function, using a standardised visual assessment designed for assessment in the neonatal period, to identify any relationship with white matter development. 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, but its continuing presence has resulted in further evaluation of the treatment options to optimise visual outcome. The protocol for laser treatment has been refined to maximise the response, 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), with reports of its use as a primary treatment or an adjuvant to laser therapy. One key advantage with this treatment is the ability to inject into eyes where there is poor retinal visualisation 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. 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. This child had aggressive posterior ROP and anterior segment ischa-
mia 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, 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.

**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. The location of the visual field deficit reported in this and another study 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, so although clinical assessment of visual fields is of particular importance in children with conditions such as periventricular leucomalacia, it should be restricted to this group.

Studies involving detailed measurements of the visual field outcome were undertaken in children age 7 years and older, 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 whether the child has any functional problems, which may not necessitate detailed measurements. To identify any functional deficits Dutton et al. have devised a cerebral visual impairment (CVI) inventory. 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 and visual spatial ability. However, as we have shown, 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. In addition, VEPs have been shown to be related to cognitive ability in preterm children. 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, 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, 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). 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, 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%, with more recent reports giving similar rates of 10–17.6%. 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). 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 Br Ir Orthopt J 2011; 8
motor skills,\textsuperscript{65–68} which is also known to be affected in children born preterm,\textsuperscript{69} but when reporting the findings in preterm children performing motor tasks the presence of strabismus is not always noted,\textsuperscript{73} 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.\textsuperscript{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,\textsuperscript{72} but there is evidence showing that the process of emmetropisation is affected by the presence of strabismus.\textsuperscript{73,74} One example of a specific type of strabismus affecting emmetropisation is in children with infantile esotropia.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{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 necrotising enterocolitis\textsuperscript{89} and bronchopulmonary dysplasia\textsuperscript{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.\textsuperscript{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,

\textbf{Br Ir Orthopt J 2011; 8}
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 |
|--------------------|---------------------|-----------------|-------------------|--------------------|------------|-------------------|-------------------|------------------|
| Ozdemir³⁶          | 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 |
| Yang³⁷             | 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 |
| Chen³⁸             | 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 |
| Modrzejewska³⁹     | 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%) | Correlation between AL and BW (r = 0.23) + GA (r = 0.17) in +3 to +6 range only |
| Morrison³²         | 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 |
| Varghese⁴⁰        | India               | 559             | First week of life | 35 ± 28.3 months | Admitted to nursery | Unknown | Unknown | 64.6% ≥1.0 DC in preterms (GA 24–27 weeks); MSE 22.79 (3.92) MSE ± SD = 1.5 ± 2 D; mean cylinder ≥0.3 ± 1.4 D; 31.3% myopia 0 to –4.9D, 23.9% myopia ≥5 D | None |
| Axer-Siegel⁴¹      | Israel              | 100             | Treatment for ROP | Threshold or type I ROP | Laser | Laser | SE at 3 months; stage 1 ROP, +2.1; stage 3+, +0.65 | None |
| Cook³²             | 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 | MSE ≥-4.71; 80.4% of eyes myopic, 9.8% eyes significant hypermetropia, 13% anisometropia | AL and ACD had linear growth patterns, LT little change over the study; corneal curvature correlated well with refractive state |
| Dhawan³³           | 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 |
| Cosgrave³⁴         | 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 |
| Holmstrom²⁴        | 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 at risk to emerge, 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 forROP 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.

References

1. Eichenwald EC, Stark AR. Management and outcomes of very low birth weight. N Engl J Med 2008; 358: 1700–1711.
2. Petrou S, Eddama O, Mangham L. A structured review of the recent literature on the economic consequences of preterm birth. Arch Dis Child Fetal Neonatal Ed 2010: Epub ahead of print. DOI: 10.1136/adc.2009.161117
3. Draper ES, Zeilin J, Fenton AC, et al. Investigating the variations in survival rates for very preterm infants in 10 European regions. the MOSAIC birth cohort. Arch Dis Child Fetal Neonatal Ed 2009; 94: F158–F163.
4. Field D, Draper ES, Fenton A, et al. Rates of very preterm birth in Europe and neonatal mortality rates. Arch Dis Child Fetal Neonatal Ed 2009; 94: F253–F256.
5. D’Amore A, Brosler S, Le Fort W, Curley A. Two-year outcomes from very low birthweight infants in a geographically defined population across 10 years, 1993–2002; comparing 1993–1997 with 1998–2002. Arch Dis Child Fetal Neonatal Ed 2010: Epub ahead of print. DOI: 10.1136/adc.2009.171876
6. O’Connor AR, Fielder AR. Long term ophthalmic sequelae of prematurity. Early Hum Dev 2008; 84: 101–106.
7. Wong V, Leung AR, Newsham D, Knox PC, Clark D. The relationship between ophthalmic deficits and functional ability in low birth weight children. Br J Ophthalmol J 2008; 5: 32–38.
8. Milligan DW. Outcomes of children born very preterm in Europe. Arch Dis Child Fetal Neonatal Ed 2010; 95: F234–F240.
9. Lohaugen GC, Gramstad A, Ensenen KA, et al. Cognitive profile in young adults born preterm at very low birthweight. Dev Med Child Neurol 2010; 52: 1133–1138.
10. Apino C, Compagnone E, Montanaro ML, et al. Preterm birth and neurodevelopmental outcome: a review. Childs Nerv Syst 2010; 26: 1139–1149.
11. Woodward LJ, Moor S, Hood KM, et al. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. Arch Dis Child Fetal Neonatal Ed 2009; 94: F339–F344.
12. van de Weijer-Bergsma EV, Wijnroks L, Jongmans MJ. Attentional development in infants and preschool children born preterm: a review. Infant Behav Dev 2008; 31: 333–351.
13. Conrad AL, Richman L, Lindgren S, Nopoulos P, Biological and environmental predictors of behavioral sequelae in children born preterm. Pediatrics 2010; 125: e83–e89.
14. Shum D, Neuling K, O’Callahan M, Mohay H. Attentional problems in children born very preterm or with extremely low birthweight at 7–9 years. Arch Clin Neuropsychol 2008; 23: 103–112.
15. Roberts G, Anderson PJ, Davis N, De Luca C, Cheong J, Doyle LW. Developmental coordination disorder in geographic cohorts of 1954-year-old children born extremely preterm or extremely low birthweight in the 1990s. Dev Med Child Neurol 2011; 53: 55–60.
16. Hornby G, Woodward LJ. Educational needs of school-aged children born very and extremely preterm: a review. Educ Psychol Rev 2009; 21: 247–270.
17. Anderson PJ, Doyle LW. Cognitive and educational deficits in children born extremely preterm. Semin Perinatol 2008; 32: 51–59.
18. Strang-Karlsson S, Andersson S, Pailey-Hyvarinen M, et al. Slower reaction times and impaired learning in young adults with birth weight <1500 g. Pediatrics 2010; 125: e74–e82.
19. Sansavini A, Guarini A, Justice LM, et al. Development of preterm birth increase a child’s risk for language impairment? Early Hum Dev 2010; 86: 765–772.
20. Aarnoudse-Moens CS, Oosterlaan J, Kuiper E, van Geullebroek JB, Weijer-Wingers Kupers N. Development of preschool and academic skills in children born very preterm. J Pediatr 2011; 158: 15–20.
21. Catoe J, Stahl A, Hellstrom A, Smith LE. Current update on retinopathy of prematurity: screening and treatment. Curr Opin Pediatr 2011; 23: 173–178.
22. Fazzi E, Bova S, Giovannanza A, Signorini S, Uggetti C, Bianchi P. Cognitive outcomes in preterm children with periventricular leukomalacia. Dev Med Child Neurol 2009; 51: 974–983.
23. Draper JR, Wyatt LM, Stager DR, Birch EE. The Teller acuity cards are effective in detecting amblyopia. Optom Vis Sci 2009; 86: 755–759.
24. Exestrom G, Larsson E. Long-term follow-up of visual functions in prematurely born children: a prospective population-based study up to 10 years of age. J AAPOS 2012; 18: 157–162.
25. O’Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. J Ophthalmol 2004; 8: 145–153.
26. Rovet J, Simic N. The role of transient hypothryoxinemia of prematurity in development of visual abilities. Semin Perinatol 2008; 32: 431–437.
27. Simic N, Westall C, Astazlos EV, Rovet J. Visual abilities at 6 months in preterm infants: impact of thyroid hormone deficiency and neonatal medical morbidity. Thyroid 2010; 20: 309–315.
28. Selvam SS, Ejenbaum F, Berezovsky A, Sacai PY, Pereira JM. Age norms for monocular grating acuity measured by sweep-VEP in the first three years of age. Arch Ophthalmol 2008; 18: 475–479.
29. Delahunt C, Falcione S, Hume R, et al. Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5 years: a millennium cohort study. J Clin Endocrinol Metab 2010; 95: 4989–4998.
30. Akerman H, Larsson E, Eriksson U, Holmstrom G. Central macular thickness is correlated with gestational age at birth in prematurely born children. Br J Ophthalmol 2010: Epub ahead of print. DOI: 10.1136/bjo.2010.184747
31. Hammer DX, Ifimia NV, Ferguson RD, et al. Foveal fine structure in retinopathy of prematurity: an adaptive optics Fourier domain optical coherence tomography study. Invest Ophthalmol Vis Sci 2008; 49: 2061–2070.
32. Tarics Y., Pia A, Li H, et al. Association of birth parameters with OCT measured macular and retinal nerve fiber layer thickness. Invest Ophthalmol Vis Sci 2011: Epub ahead of print. DOI: 10.1167/iovs.10-6365
33. Ment LR, Hirtz D, Huppi PS. Imaging biomarkers of outcome in the developing preterm brain. Lancet Neurol 2009; 8: 1042–1055.
34. Bassi L, Ricci D, Volzone A et al. Probabilistic diffusion tractography of the optic radiations and visual function in preterm infants at term equivalent age. Brain 2008; 131: 573–582.
35. Ricci D, Cesarini L, Groppo M, et al. Early assessment of visual function in full term newborns. Early Hum Dev 2008; 84: 107–113.
36. Lad EM, Hernandez-Boussard T, Morton JM, Mosheghi DM. Incidence of retinopathy of prematurity in the United States: 1997 through 2005. Am J Ophthalmol 2009; 148: 451–458.
37. Quiroz-Mercado H, Ustariz-Gonzalez O, Martinez-Castellanos MA, Covarrubias P, Dominguez F, Sanchez-Huerta V. Our experience after 1765 intravitreal injections of bevacizumab: the importance of being part of a developing story. Semin Ophthalmol 2007; 22: 109–125.
38. Mintz-Hittner HA, Best LM. Antivascular endothelial growth factor for retinopathy of prematurity. Curr Opin Pediatr 2009; 21: 182–187.
39. Dorta P, Kychenthal A. Treatment of type 1 retinopathy of prematurity with intravitreal bevacizumab (Avastin). Retina 2010; 30(Suppl 4): S24–S31.
40. Kusaka S, Shima C, Wada K, et al. Effect of intravitreal injection of bevacizumab for severe retinopathy of prematurity: a pilot study. Br J Ophthalmol 2008; 92: 1450–1455.
41. Nazari H, Modarres M, Parvash MM, Ghasemi Falavarjani K. Intravitreal bevacizumab in combination with laser therapy for the treatment of severe retinopathy of prematurity (ROP) associated with vitreous or retinal hemorrhage. Graefes Arch Clin Exp Ophthalmol 2010; 248: 1713–1718.
Preterm birth: the ophthalmic consequences

42. Palmer EA, Hardy RJ, Dobson V, et al. Fifteen-year outcomes following threshold retinopathy of prematurity: final results from the multicentre trial of cryotherapy for retinopathy of prematurity. Arch Ophthalmol 2005; 123: 311–318.

43. Shah PK, Morris RJ, Narendran V, Kalpana N. Visual acuity and electrotetroretinography findings 3 (17) years after the first intravitreal injection of bevacizumab (Avastin) in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol 2011; 59: 73–74.

44. Fuzet-Hitterman R Jr. Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone 1 or posterior zone II. Retina 2008; 28: 831–838.

45. Darlow BA, Gilbert C, Quinn GE, et al. Promise and potential pitfalls of anti-VEGF drugs in retinopathy of prematurity. Br J Ophthalmol 2009; 93: 95.

46. SasakiSimaS, Bennett DM, Butler S, Dutton GN. Cognitive visual impairment with good visual acuity in children with posterior periventricular white matter injury: a series of 7 cases. J Paediatr Ophthalmol Strab 2009; 20–23.

47. Hellgren K, Hellstrom A, Martin L. Visual fields and optic disc morphology in very low birthweight adolescents examined with magnetic resonance imaging of the brain. Acta Ophthalmol 2009; 87: 843–848.

48. Jacobson L, Rydberg A, Eliasson AC, Kits A, Flomdmark O. Visual field function in school-aged children with spastic unilateral cerebral palsy related to different pattern of brain damage. Dev Med Child Neurol 2010; 52: e184–e187.

49. O’Reilly M, Vollmer B, Varga-Khadem F, et al. Ophthalmological, neurodevelopmental and MRI assessment of visual processing in preterm children without major neuromotor impairment. Dev Sci 2010; 13: 692–705.

50. Dutton G, Bax M Visual Impairment in Children Due to Damage to the Brain. Wiley, 2006.

51. Dutton G. Devising strategies to optimise home and school life for children with visual impairment due to damage to the brain. Available at: http://www.ssc.education.au/courses/ [accessed 11 January 2011].

52. Bohm B, Lundequist A, Smedler AC. Visual-motor and executive functions in children born preterm: The Bender Visual Motor Gestalt Test revisited. Scand J Psychol 2010: Epub ahead of print. DOI 10.1111/j.1467-9450.2010.00818.x.

53. Marlow N, Hennessy EM, Bracewell MA, Wolke D. Motor and executive brain functions at 6 years of age after extremely preterm birth. Pediatrics 2007; 120: 793–804.

54. Santos A, Duret M, Mancini J, Gire C, Deruelle C. Preterm birth affects dorsal-stream function even after age 6. Brain Cogn 2009; 69: 490–494.

55. O’Connor AR, Knox PC, Newsham D, Wong V, Clark D. Visuo-motor control in low birth weight children without major ophthalmic or neurologic sequelae. Br J Orthopt 2011; 18: in press.

56. Kubu M, Lilakova D, Hejcmanova D, Kremlacek J, Langrova J, Kuba M. Retinopathy of prematurity: a cohort study. J Pediatr Ophthalmol Strab 2009; 46: 1814–1821.

57. Feng JJ, Xu X, Wang WP, Guo SJ, Yang H. Pattern visual evoked potential performance in preterm preschoolers with average visual acuity. Acta Ophthalmol Scand 2010; 88: 591–595.

58. Stephenson T, Wright S, O’Connor A, Harries T, Wilkins R. Visual impairment with good visual acuity in children with perinatal CNS involvement. J Paediatr Ophthalmol Strab 2011; 48: 143–144.

59. Allen MC. Neurodevelopmental outcomes of preterm infants. Dev Med Child Neurol 2011; 53: 623–628.

60. Evensen KA, Lindqvist S, Indredavik MS, Skranes J, Brubakk AM, Vik T. Do visual impairments affect risk of motor problems in preterm and term low birth weight adolescents who had necrotizing enterocolitis with or without late bacteremia. J Pediatr 2010; 157: 6751–6756.

61. Haugen OH, Nepstad L, Standal OA, Elgen I, Markestad T. Visual and cognitive functions in preterm and term low birth weight children with postnatal CNS involvement. Acta Paediatr 2010; 99: 1814–1821.

62. O’Connor AR, Birch EE, Anderson S, Draper H. The functional significance of stereopsis. Invest Ophthalmol Vis Sci 2010; 51: 1909–1923.

63. Suttle CM, Melmoth DR, Finlay AL, Sloper JJ, Grant S. Eye-hand coordination skills in children with and without amblyopia. Invest Ophthalmol Vis Sci 2011; Epub ahead of print. DOI 10.1167/iovs.10-6341.

64. O’Connor AR, Birch EE, Anderson S, Draper H. Relationship between binocular visual function, visual acuity, and fine motor skills. Optom Vis Sci 2010; 87: 942–947.

65. Allen MC. Neurodevelopmental outcomes of preterm infants. Curr Opin Neurol 2008; 21: 123–128.

66. Thorns A, Noonan CP, Marsh IB. The psychosocial effects of adult strabismus: a review. Br J Ophthalmol 2011; 95: 450–453.

67. Granet DB. Strabismus: aligning the doctor’s vision with the patient’s need. Br J Ophthalmol 2011; 95: 443–444.

68. Morrison DG, Emanuel M, Donahue SP. Risk of refractive pathology after spontaneously regressed ROP in emmetropic patients. J Pediatr Ophthalmol Strab 2010; 47: 141–144.

69. Vroom AM, Riddell PM. Hypo-accommodation responses in hypermetropic infants and children. Br J Ophthalmol 2011; 95: 231–235.

70. Ingram RM, Lambert TW, Gill LE. Visual outcome in 879 children treated for strabismus: insufficient accommodation and vision deprivation, deficient emmetropisation and anisometropia. Strabismus 2009; 17: 148–157.

71. Darlow BA, Stager DW, Wang J, O’Connor A. Longitudinal changes in refractive error of children with infantile esotropia. Eye 2010; 24: 1814–1821.

72. Oderm M, Koylu S. Occular growth and morbidity in preterm children without retinopathy of prematurity. Jpn J Ophthalmol 2009; 53: 623–628.

73. Yang CS, Wang AG, Sung CS, Hsu WM, Lee FL, Lee SM. Long-term visual outcomes of laser-treated threshold retinopathy of prematurity: a study of refractive status at 7 years. Eye 2010; 24: 17–20.

74. Cohan TC, Tsai TH, Shih YF, et al. Long-term evaluation of refractive status and optical components in eyes of children born preterm. Invest Ophthalmol Vis Sci 2010; 51: 6140–6148.

75. Modrzewiska M, Grzesiak W, Karczewicz D, Zahorski D. Refractive status and ocular axial length in preterm infants without retinopathy of prematurity with regard to birth weight and gestational age. J Perinat Med 2010; 38: 327–331.

76. Varghese RM, Sreenivas V, Puliyel JM, Varughese S. Refractive status at birth: its relation to newborn physical parameters at birth and gestational age. PLoS One 2009; 4: e4469.

77. Axer-Siegel R, Maharashak I, Snir M, et al. Diode laser treatment of retinopathy of prematurity: anatomical and refractive outcomes. Retina 2008; 28: 839–846.

78. Cook A, White S, Battembury M, Clark D. Ocular growth and refractive error development in premature infants with or without retinopathy of prematurity. Invest Ophthalmol Vis Sci 2008; 49: 1999–2007.

79. Davidson S, Quinn GE. The impact of pediatric vision disorders in adulthood. Pediatrics 2011; 127: 334–339.

80. Cosgrove E, Scott C, Goble C. Ocular findings in low birthweight and premature babies in the first years: do we need to screen? Eur J Ophthalmol 2008; 18: 104–111.

81. White AL, Hellstrom A, Strabismus follow-up at 2 years of age of all children previously screened for retinopathy of prematurity: is it worthwhile? Acta Ophthalmol Scand 2006; 84: 631–635.

82. O’Connor AR, Stewart CE, Singh J, Fielder AR. Do infants of birth weight less than 1500 g require additional long term ophthalmic follow up? Br J Ophthalmol 2006; 90: 451–455.

83. Royal College of Ophthalmologists, Royal College of Paediatrics and Child Health. Guideline for the Screening and Treatment of Retinopathy of Prematurity. London: RCO, May 2008.

84. Davidson S, Quinn GE. The impact of pediatric vision disorders in adulthood. Pediatrics 2011; 127: 334–339.

85. Martin CR, Dammann O, Allred EN, Ishak AM, Vik T. Retinopathy of Prematurity. London: RCO, May 2008.

86. Pathai S, Cumberland PM, Rahi JS. Prevalence of and early life influences on childhood strabismus: findings from the Millennium Cohort Study. Arch Pediatr Adolesc Med 2010; 164: 250–257.

87. Grant S, Melmoth DR, Morgan MJ, Finlay AL. Prehexision deficits in amblyopia. Invest Ophthalmol Vis Sci 2007; 48: 1139–1148.