Prematurity, the Eye and Vision

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The Systemic and Neurologic Impact of Prematurity

- Increased risk of
  - Chronic diseases eg asthma
  - Major neurological impairment
    - moderate/severe mental retardation
    - neurosensory disorders
    - epilepsy
    - cerebral palsy

Other Developmental Deficits

- Increased risk of
  - High prevalence/low severity dysfunctions
    - learning disabilities
    - ADHD
    - borderline mental retardation
    - behavioural problems, especially social and attention problems
    - specific neuropsychological defects

Ophthalmic Manifestations of Preterm Birth

- Retinopathy of Prematurity
- Refractive Error
- Strabismus
- Cerebral Visual Impairment
- Colour Vision Defects
- Reduced Contrast Sensitivity
- Visual Field Defects
- Decreased Visual Acuity

Refractive Error

- Myopia is well known to be associated with prematurity
  - "physiological" myopia
  - Myopia of Prematurity
  - myopia associated with severe ROP
- Increased risk of all other refractive errors as well
  - overall risk of significant refractive error 29.6% in preterms, 6% in term
    - high hypermetropia
    - astigmatism and anisometropia

O'Connor AR, Stephenson TJ, Johnson A, Tobin MJ, Ratib S, Fielder AR. Change of refractive state and eye size inchildren of birth weight less than 1701 g. Br J Ophthalmol2006; 90(4): 456–460.
Larsson EK, Rydberg AC, Holmstrom GE. A population- based study of the refractive outcome in 10-year-old preterm and full-term children. Arch Ophthalmol 2003; 121(10): 1430–1436.
Huynh SC, Wang XY, Ip J, Robaei D, Kifley A, Rose KA et al. Prevalence and associations of anisometropia and aniso- astigmatism in a population based sample of 6 year old children. Br J Ophthalmol 2006; 90(5): 597–601.
O'Connor AR, Stephenson TJ, Johnson A, Tobin MJ, Ratib S, Moseley M et al. Visual function in low birthweight children. Br J Ophthalmol 2004; 88(9): 1149–1153.

Refractive Error

Table 1 Ocular dimensions in preterm population measured at 10–12 years of age[26] compared to ocular dimensions in term population measured at 10 years of age[27]

	O'Connor *et al*[26]	Zadnik *et al*[27]
Corneal power (D)	44.59 (1.71)	43.66 (1.73)
Axial length (mm)	22.47 (0.99)	23.31 (0.83)
AC depth (mm)	3.56 (0.31)	3.78 (0.23)
Lens thickness (mm)	3.50 (0.18)	3.42 (0.15)
Vitreous depth (mm)	15.41 (0.92)	16.11 (0.83)

Table 2 Refractive outcomes in preterm population compared to term population

	Larsson term controls[37]	*Larsson preterms*[37]	*O'Connor*[26]	*Holmstrom*[69]	*Fledelius*[70]	*Darlow*[48]
Age of study population (years)	10	10	10–12	2.5	7–10	7–8
Myopia % (dioptres included)	11.1 (<0)	15.2 (<0)	18.9 (<0)	10 (<0)	10.7 (<-0.25)	N/R (<0)
Hypermetropia % (dioptres included)	0.9 (>3)	4.2 (>3)	6.6 (≥3)	4 (>3)	N/R	18 (>0)
Astigmatism % (dioptre cylinder)	4.1 (≥1)	44 (≥1)	13.7 (≥1)	26 (≥1)	16 (>0)	11 (>0)
Anisometropia % (dioptre difference in MSE R&L)	0.9 (≥1)	8.9 (≥1)	9 (≥1)	8.4 (≥1)	6 (≥2)	N/R

Abbreviations: N/R, not recorded; MSE, mean spherical equivalent.

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O'Connor et al. Ophthalmological problems associated with preterm birth. Eye (2007) 21, 1254–1260

Strabismus

- Increased risk, but aetiology complex
  - 14.7% incidence during infancy, but incidence remains high through 1st decade
- ET:XT ratio is 3:1 in FT, 1:1 in LBW kids
- Independent risk factors for squint in LBW kids include
  - cicatricial ROP
  - family history, ethnic origin, maternal age
  - smoking, BW, general development quotient
  - refractive error, anisometropia

Chew E, Remsky NA, Tamboli A, Zhao J, Podgor MJ, Klebanoff M. Risk factors for esotropia and exotropia. Arch Ophthalmol 1994; 112: 1349–1354.
Brenner DL, Palmer EA, Fellows RR, Baker JD, Hardy RJ, Tung B et al. Strabismus in premature infants in the first year of life. Arch Ophthalmol 1998; 116: 329–333.
Holmstrom G, el Azzazi M, Kugelberg U. Ophthalmological follow up of preterm infants: a population based, prospective study of visual acuity and strabismus. Br J Ophthalmol 1999; 83(2): 143–150.
Penneflather PM, Clarke MP, Strong NP, Cottrell DG, Dutton J, Tin W. Risk factors for strabismus in children born before 32 weeks' gestation. Br J Ophthalmol 1999; 83: 514–518.
O'Connor AR, Stephenson TJ, Johnson A, Tobin MJ, Ratib S, Fielder AR. Strabismus in children of birth weight less than 1701 g. Arch Ophthalmol 2002; 120(6): 767–773.
Holmstrom G, Rydberg A, Larsson E. Prevalence and development of strabismus in 10-year-old premature children: a population-based study. J Pediatr Ophthalmol Strabismus 2006; 43(6): 346–352.

Cerebral Visual Impairment in Preterm Children

- Brain injury in premmies due to mild-moderate hypoxia/hypo-perfusion
  - PVL
  - periventricular haemorrhagic infarction
  - germinal matrix haemorrhage
  - cerebellar infarction

Periventricular White Matter

- most common site of hypoxia/hypo-perfusion-related injury in prem babies
  - occurs in 32% of premmies
  - occurs between W24 and W34
- as well as optic tracts and radiations, cortico-spinal tracts run here
  - spastic diplegia occurs in 5-15% of premature infants
  - visual impairment in 70% of kids with spastic diplegia
- neuro-imaging shows
  - ventriculomegaly with irregular body and trigones of lateral ventricles
  - reduced volume of PVWM
  - deep, prominent sulci that abut or nearly abut the ventricles
  - may also see delayed myelination and thinning of the corpus callosum

Patterns of Functional Deficit in CVI

- impairment in CVI is variable, from **NLP** to **normal VA** but with cognitive visual dysfunction
  - cognitive visual dysfunction is a disorder of visual processing; may have normal VA and stereo
  - occurs with cortical lesions
- visual function with cortex damage v periventricular white matter damage
  - initial VA is similar (LP & occasional fixation in 22-38% & 49-50% respectively)
  - 78% of children with damage to striate cortex improve but only 42% of those with PVL improve
  - significantly more strabismus, nystagmus & optic atrophy in PVL group
- VF defects common, especially in PVL
  - typically bilateral inferior loss (parietal optic radiations)
  - temporal lobe optic radiations less likely to be impaired in PVL

MC Brodsky et al . "Perinatal cortical and subcortical visual loss: mechanisms of injury and associated ophthalmologic signs." Ophthalmology. 2002 Jan;109(1):85-94.

CVI: associated ophthalmic and neurologic deficits

- ischemic injuries to retro-geniculate pathways causing CVI lead to different ophthalmic abnormalities if term onset v preterm onset
  - gaze disturbance
    - tonic downgaze in subcortical (preterm) visual loss
    - horizontal tonic deviation in cortical (term) loss
  - strabismus in ~80%
    - exotropia more common in cortical (term) visual loss
    - esotropia more common in subcortical (preterm) visual loss
  - nystagmus ~ 42%
    - was thought that nystagmus did not occur in retrogeniculate disease
    - now recognised that nystagmus occurs in a high frequency of children with PVL
  - optic nerves
    - normal in 56% of cortical visual loss but 24% of subcortical visual loss
    - typically optic nerve hypoplasia with pseudo-glaucomatous cupping in PVL
      - due to retrograde trans-synaptic degeneration of anterior visual pathways after scleral canals have established a normal diameter
      - occurs only in immature visual system
      - insults to mature retro-geniculate pathways do not lead to optic nerve cupping or damage

Other Brain Injuries in Prematurity

- after profound hypotensive event or cardiopulmonary arrest
- deep gray matter and brainstem nuclei affected
- survival poor, but survivors often have
  - athetosis
  - quadriparesis
  - severe seizure disorders
  - mental retardation

Retinopathy of Prematurity

- a vaso-proliferative disorder affecting low birth weight premature infants
- still a leading (preventable) cause of blindness throughout the world
- standardised international classification (ICROP) and robust evidence-based treatment guidelines (CRYO-ROP and ET-ROP) have led to improved outcomes in the developed world

Risk Factors for ROP: Historical Perspective

		"First epidemic" (1940–1950s)	"Second epidemic" (1970–1980s), and "third epidemic" in middle-income countries	ROP in NICU of 21st century
Risk factors				
Prematurity		+	++	++++
Low birth weight		+	++	++++
High oxygen supplementation		++++	+++	+
Illness		+	+	+/–
Babies at risk				
<1,000 g	Survival rate	+	++	++++
	Risk of ROP	+	++	+++
1,000–1,500 g	Survival rate	+++	++++	++++
	Risk of ROP	+++	+	+/–
Ocular outcomes		Poor	Moderate	Good

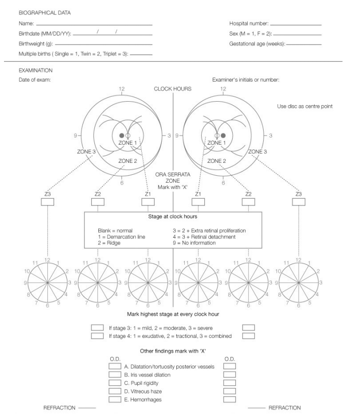
Adapted from Gilbert et al.,[10] p. 275, Table 16.11, used with permission.

Source: C Gilbert et al. Visual Impairment and Blindness in Children. In GJ Johnsson et al (eds). Epidemiology of Eye Disease. London. 2004. Quoted in AR Fielder & GE Quinn. Retinopathy of Prematurity. In D Taylor & C Hoyt. Pediatric Ophthalmology and Strabismus. 2005.

Stage 1	Demarcation line
Stage 2	Ridge
Stage 3	Ridge with extraretinal fibrovascular proliferation
Stage 4	Subtotal retinal detachment
	Extrafoveal
	Retinal detachment including fovea
Stage 5	Total retinal detachment

Funnel	
Anterior	**Posterior**
Open	Open
Narrow	Narrow
Open	Narrow
Narrow	Open

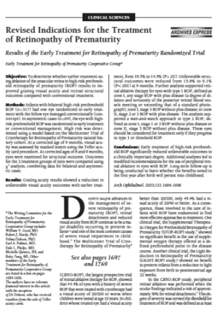
From Committee for Classification of Retinopathy of Prematurity.[116]



Cicatricial Changes in ROP

- Peripheral
  - vascular
    - avascular peripheral retina
    - abnormal non-dichotomous branching
    - circumferential connections between arcades
    - telangiectasias
  - retinal
    - pigmentary changes
    - VR interface changes
    - thin retina
    - peripheral folds
    - vitreous membranes
    - lattice-like degeneration
    - retinal breaks
    - TRD, RRD
- Posterior

Early Treatment for Retinopathy of Prematurity



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Revised Indications for the Treatment of Retinopathy of Prematurity

Results of the Early Treatment for Retinopathy of Prematurity Randomized Trial

*Early Treatment for Retinopathy of Prematurity Cooperative Group**

Objective: To determine whether earlier treatment using ablation of the avascular retina in high-risk prethreshold retinopathy of prematurity (ROP) results in improved grating visual acuity and retinal structural outcomes compared with conventional treatment.

Methods: Infants with bilateral high-risk prethreshold ROP (n=317) had one eye randomized to early treatment with the fellow eye managed conventionally (control eye). In asymmetric cases (n=84), the eye with high-risk prethreshold ROP was randomized to early treatment or conventional management. High risk was determined using a model based on the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity natural history cohort. At a corrected age of 9 months, visual acuity was assessed by masked testers using the Teller acuity card procedure. At corrected ages of 6 and 9 months, eyes were examined for structural outcome. Outcomes for the 2 treatment groups of eyes were compared using χ^2 analysis, combining data for bilateral and asymmetric cases.

... ment, from 19.5% to 14.5% (P=.01). Unfavorable structural outcomes were reduced from 15.6% to 9.1% (P<.001) at 9 months. Further analysis supported retinal ablative therapy for eyes with type 1 ROP, defined as zone I, any stage ROP with plus disease (a degree of dilation and tortuosity of the posterior retinal blood vessels meeting or exceeding that of a standard photograph); zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. The analysis supported a wait-and-watch approach to type 2 ROP, defined as zone I, stage 1 or 2 ROP without plus disease or zone II, stage 3 ROP without plus disease. These eyes should be considered for treatment only if they progress to type 1 or threshold ROP.

Conclusions: Early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. Additional analyses led to modified recommendations for the use of peripheral retinal ablation in eyes with ROP. Long-term follow-up is being conducted to learn whether the benefits noted in ...

ET-ROP Treatment Algorithm

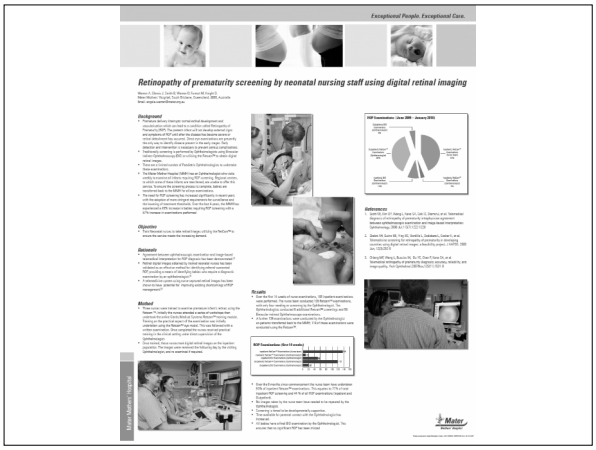
			Treatment considerations
Zone 1	Plus disease	Any stage ROP	Consider treatment
	No plus disease	Stage 1 or 2	Observe very closely for progression or presence of plus
		Stage 3	Consider treatment
Zone 2	Plus disease	Stage 1	Observe for progression
		Stage 2 or 3	Consider treatment
	No plus disease	Stage 1	Observe for progression or presence of plus
		Stage 2	Observe for progression or presence of plus
		Stage 3	Observe very closely for progression or presence of plus
Zone 3[b]	Plus disease	Any stage ROP	Observe closely for progression
	No plus disease	Any stage ROP	Observe for progression or presence of plus

[a] The ET-ROP study defined type 1 ROP as ROP of sufficient severity to warrant treatment and type 2 as ROP that should be very closely monitored for progression or development of plus disease. For the purpose of this study, plus disease was defined as sufficient dilation and tortuosity of the posterior poles vessels in two or more quadrants. No recommendations based on the results of the ET-ROP study were made for ROP less severe or ROP in zone 3 and the recommendations in this instance are the authors' own.
[b] ROP in zone 3 cannot by definition reach threshold severity and treatment must be tailored to the individual patient.

Table reproduced from: D Taylor & C Hoyt. Pediatric Ophthalmology and Strabismus. 2005.

What are the challenges that ROP poses?

- examination / interpretation of findings require specialised training
- infants need multiple examinations, requiring co-ordination between NICUs and ophthalmology screening programs
- shortage of physicians available to treat ROP



Exceptional People. Exceptional Care.

Retinopathy of prematurity screening by neonatal nursing staff using digital retinal imaging

Mater Mothers' Hospital

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