BV-02  Ocular and Neural Complications of Premature Birth
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School of Optometry

Disclosure Statement
• Nothing to disclose

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Normal gestation and birth-weight

- **Normal gestation**
  - 40 Wks

- **Normal Birth weight**
  - 7.5 lbs (boys)
  - 7 lbs (girls)

- **Premature birth**
  - < 38 wks Gestation Age (GA)
Birthweight (BW)

- **LBW (Low)**
  - 2500 gm / 5.5 lbs
- **VLBW (Very Low)**
  - 1500 gms / 3.3 lbs
- **ELBW (Extremely Low)**
  - 1000 gms / 2.2 lbs
- Infant is 26 wks / 842 grams
Respiratory complications (in NICU)

- Respiratory distress syndrome (RDS)
  - Needing assisted ventilation or CPAP (continuous positive airway pressure)
- CLD, Chronic Lung Disease
  - Respiratory support at 36 wks corrected gestational age
Respiratory complications cause most morbidity and mortality

- **RDS**
  - “Baby” alveoli limit gas exchange
  - Difficult to inflate lungs
  - Must re-inflate completely each breath
  - Surfactant not produced until 32-35 weeks

Alveoli at 28 wks
Respiratory problems after discharge

- Increased number of hospitalizations
- Increased severity of colds or URI
- Pneumonia
- Asthma
- Sensitivity to lung irritants like smoke, pollution
### Respiratory Complications by GA Preterm Outcome Table (POT)

<table>
<thead>
<tr>
<th>Gestational Age (Wk)</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
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<tbody>
<tr>
<td># Births</td>
<td>190</td>
<td>223</td>
<td>268</td>
<td>300</td>
<td>377</td>
<td>487</td>
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<tr>
<td>% Still births</td>
<td>25</td>
<td>20</td>
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<td>10</td>
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<td>&lt;5</td>
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<tr>
<td>BW</td>
<td>900</td>
<td>1000</td>
<td>1100</td>
<td>1300</td>
<td>1500</td>
<td>1600</td>
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<tr>
<td>% RDS</td>
<td>90</td>
<td>85</td>
<td>80</td>
<td>70</td>
<td>50</td>
<td>40</td>
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<tr>
<td>% CLD</td>
<td>40</td>
<td>35</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Home O2</td>
<td>20</td>
<td>15</td>
<td>5</td>
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Acute complications con’t..

- IVH: Intraventricular Hemorrhage
- PVL: Periventricular Leukomalacia
- ROP: Retinopathy of Prematurity
- PDA: Patent Ductus Arteriosus
- NEC: Necrotizing Enterocolitis
- Sepsis
Intraventricular hemorrhage

- Source of Hr is a fragile capillary network which supplies the germinal matrix surrounding the lateral ventricles
  - Involutes by term
- GM vessels can’t autoregulate
- Rapid changes in BP rupture GM vessels, which bleed around (peri) and into (intra) the ventricles
IVH Graded I - IV

- I germinal matrix Hx
- II blood within but not distending ventricle
- III blood filling and distending ventricular system
- IV blood spilling out to surrounding brain tissue
IVH: complications

- **Acute sequelae**
  - Neonatal stroke
  - Ischemic damage / Periventricular Leukomalacia

- **Chronic sequelae**
  - Hydrocephalus
  - MR/DD
  - CP
  - Eye signs: CVI, Low Vision
Periventricular leukomalacia

- Hypoxic / ischemic injury of the developing white matter around the ventricles
  - IVH causes further injury
- Evidenced by:
  - Atrophic dilation of lateral ventricles
  - Reduced amount of PV white matter
    - Often around occipital horns
  - Thinned corpus collosum
  - Cerebellar atrophy
PVL imaged by MRI

A
Normal white matter

B
Reduced white matter

PVL
PVL Complications

- Death in ~50% (14x risk of death compared to grade III or IV IVH)
- CP (spastic diplegia)
- MR (verbal > performance IQ)
- Vision and optic nerve problems (more later)
Immature retinal vasculature

Retinal vessels grow outwards from the disc, but peripheral retina is not vascularized until 32 (nasal) or 40 (temp) wks
Retinopathy of prematurity: Stage 3
### Additional Complications by wks

<table>
<thead>
<tr>
<th>Wks</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
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<tr>
<td>BW</td>
<td>900</td>
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<td>% IVH</td>
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<td>10</td>
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<td>1</td>
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<tr>
<td>% PVL</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>% ROP</td>
<td>15</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>% Sepsis</td>
<td>40</td>
<td>40</td>
<td>25</td>
<td>20</td>
<td>10</td>
<td>5</td>
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<tr>
<td>% PDA Tx’d</td>
<td>45</td>
<td>40</td>
<td>25</td>
<td>15</td>
<td>10</td>
<td>5</td>
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“Threshold of Viability” POT at ~21-25 wks

<table>
<thead>
<tr>
<th>Wks</th>
<th>23*</th>
<th>24*</th>
<th>25*</th>
<th>26</th>
<th>27</th>
<th>28</th>
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<tbody>
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<td>138</td>
<td>182</td>
<td>150</td>
<td>190</td>
<td>223</td>
<td>268</td>
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<tr>
<td>% Still births</td>
<td>55</td>
<td>35</td>
<td>25</td>
<td>25</td>
<td>20</td>
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</tr>
<tr>
<td>BW</td>
<td>600</td>
<td>650</td>
<td>750</td>
<td>900</td>
<td>1000</td>
<td>1100</td>
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<tr>
<td>D/Ch. alive</td>
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<td>50</td>
<td>60</td>
<td>80</td>
<td>90</td>
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<tr>
<td>% ROP</td>
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<td>Mod-Sev. Disability**</td>
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<td>40</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>10</td>
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</tbody>
</table>

** Disability (POT)

- Cerebral palsy
  - (unlikely to ever walk; walk with assistance)
- Vision (acuity <20/100 better eye)
- Deaf (Requiring bilateral hearing aids or cochlear implant)
- Developmental delay ≥ 2 SD from mean
Impairment by decade


Pop. = all babies 500- to 999-g born at one hospital; graph shows status at 20 mos. CA
Changes in impairment linked to Tx for RDS

- Assisted ventilation
  - Intubation, CPAP
  - Exogenous surfactants
- Prenatal steroids
- Postnatal steroids
  - frequently prescribed during the 1990s to facilitate extubation and reduce BPD by controlling lung inflammation
Changes in Tx for RDS per decade

<table>
<thead>
<tr>
<th></th>
<th>82–'89; N=496)</th>
<th>90–'99; N = 749)</th>
<th>00–'02; N = 233)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>762 141</td>
<td>755 143</td>
<td>750 144</td>
<td>0.52</td>
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<tr>
<td>Gestational age, wk</td>
<td>25.8 2.1</td>
<td>25.5 2.1</td>
<td>25.5 2.2</td>
<td>0.04</td>
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<tr>
<td>Range</td>
<td>20–32</td>
<td>20–35</td>
<td>17–34</td>
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<tr>
<td>Antenatal steroid</td>
<td>0 (0)</td>
<td>309 (41)</td>
<td>180 (78)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surfactant therapy</td>
<td>4 (1)</td>
<td>464 (62)</td>
<td>191 (82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Oxy at 36 wk</td>
<td>77 (32)</td>
<td>234 (46)</td>
<td>84 (51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postnatal steroids</td>
<td>14 (6)</td>
<td>269 (53)</td>
<td>38 (23)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Postnatal Steroids to Tx RDS?

- N=2358 ELBW babies
- 84% examined at age 18-22 mos
- 16% Tx’d (smaller, sicker with low, med or high dose dexamethasone)
- With higher dose:
  - Increased OR death, CP, sensory impairment, cognitive impairment
- No safe age for postnatal steroids

Deaths from NEC increase after limiting postnatal steroids

- **NEC**: necrotizing enterocolitis
  - Necrosis and perforations of the intestinal wall
- **Surgical removal of dead bowel tissue**
  - Colostomy (temporary)
- **Cyclomydrl**
  - 0.2% cyclopentolate and 1.0% phenylephrine
Eye signs in ELBW

- Reduced VA
  - On average, 20/30 would be expected
  - 16% 20/40 – 20/60
  - 10% > 20/60

- Myopia

- Steeper cornea, smaller eye

- ROP
Classic ROP

- CRYO-ROP Study Group
  - International Classification of ROP
  - Randomized clinical trial (cryo Tx. Vs. no Tx)
    - Tx advised for eyes reaching “threshold” disease
    - 5 contiguous or 8 cumulative clock hours of stage 3 ROP in zones 1 or 2 in the presence of plus disease
  - Cryo Sx decreased retinal detachments by 50%
  - After 10 years, acuity < 20/100 in 45.4% of treated eyes
Staging active disease

Immature retina
Stage 1 ROP
Stage 2
Stage 3
Stage 4
Plus disease
Location

- Temporal ora serrata
- Nasal ora serrata
- Zone I
- Zone II
- Zone III
- Macular center
- Optic nerve
Update on STOP-ROP

- 649 Premies with Pre-T ROP randomized to supplemental (SP) (N=324) vs. standard (Std) Oxy (N=325)
- Progression to threshold
  - 48% (Sp) vs. 41% (Std).
- Similar rates in Sp Vs. Std groups of retinal detachments, folds and macular ectopia.

Update on STOP-ROP

- Higher rates of pneumonia and/or exacerbations of CLD in SP (13.2%) vs. Std (8.5%)
- At 50 wks, more babies in SP group:
  - remained in hospital (12.7% vs. 6.8%), on oxygen (46.8 vs 37%) and on diuretics (35.8 vs. 24.4%)

Update on ETROP

- Premies with “Pre-threshold Dz” defined below were randomized to early laser vs. conventional Tx.
- Pre-threshold defined by natural history study as:
  - Zone 1, any stage, (sub-Th)
  - Zone 2, stage 2 with plus Dz
  - Zone 2, stage 3, with or without plus Dz (sub-Th)

Update on ETROP

- Early Tx reduced unfavorable acuity (19.8% to 14.3% (P < .005) and structural (15.6% to 9.0% (P < .001) outcomes at 9 months.

- Early Tx advised for “Type 1 ROP”
  - Zone 1, any stage, plus Dz
  - Zone 1, stage 3 without plus Dz
  - Zone 2, stage 2 or 3, with plus Dz

Outcome after implementing ETROP guidelines

- After the ETROP guidelines were implemented, there was a decrease from 10.3% to 1.9% of eyes developing Stage 5 retinal detachment, despite this group having a lower average EGA and lower average birth weight.

CNS related eye signs in ELBW

- Strabismus
- CONH
- Optic atrophy
- Nystagmus
- Ocular motor apraxia
- Defective smooth pursuit and saccades
- Cortical vision impairment
- Visual field deficits
- Vision perception deficits
- Visual attention deficits
IVH: eye and vision sequelae

- Grade IV: 44% in case series had small disc by RetCAM compared to control, full term babies
  - BJO 2006; 90(4):465
Fig. 1. Grade of MRI findings
A: Mild, localized white matter damage without enlarged lateral ventricle. B: moderate, white matter somewhat reduced with mildly enlarged lateral ventricle (arrows show irregular ventricular dilation that was most obvious posteriorly). C: severe, diffuse white matter is damaged with extreme enlargement of lateral ventricle (white matter adjacent to lesions from anterior horns [open arrows] to trigones [solid arrows] is lost).
PVL ➔ extensive cupping

- Other eye findings
  - Reduced VA
  - VF defects
  - Exaggerated crowding
  - Poor spatial ability
  - Poor visual perceptual skills
  - CONH
New information suggests a much higher incidence of vision problems in babies who also had sudden hypotension and oliguria (63% vision problems) compared to babies with PVL alone (9%). Incidence of CP was 88% vs. 43% respectively.

Cortical Vision Impairment (CVI)

- Bilaterally reduced vision
- Normal retina and ERG
- Absence of prominent nystagmus
- History*
  - Perinatal hypoxia, prematurity, hydrocephalus, CNS abnormalities, seizures
  - 69% had multiple risk factors

CVI: eye / vision signs

- Esotropia (19%)
- Exotropia (40%)
- Nystagmus (21%)
- Optic atrophy (42%)
- Significant refractive error (> +3.0; < -2.0) (20%)
- Limited prognosis to recover vision
VP deficits in ex-premature children

recognition, orientation, depth perception, motion perception, and/or simultaneous perception by questionnaire
Dutch Project on Preterm and SGA Infants at 19 years

- Infants born < 32 wks and/or BW < 1500 gm
- 74% of 959 survivors completed survey
  - 12.6% had cognitive or sensory impairment
- Compared to controls:
  - 2x as many needed special ed (24%)
  - 3X as many were neither employed or in school at age 19 (7.6%)
Summary: Ocular and Neural complications of Premature Birth

**Ocular**
- Myopia
- Retinal
  - Acute ROP, usually transient
  - Scarring and retinal detachment in a few
- Strabismus
- Optic atrophy and cortical vision impairment
- Cupping from periventricular leukomalacia

**Neural (additional)**
- Intraventricular hemorrhage
  - Cerebral palsy, mental retardation, hearing and vision impairment
  - CVI... Visual perceptual impairment
- Periventricular leukomalacia
  - Same, more marked
  - Deep cupping from retrograde nerve cell death