

Visual & Perceptual Disorders
Associated with Premature Birth

David Sami MD
EyeSightMD®
Pediatric Ophthalmology & Strabismus

- The main offenders:
 - ROP (Retinopathy of Prematurity)
 - CVI (Cerebral Visual Impairment)
- & the coming of a ~~second~~ epidemic...
Third

The current problem:

- Advanced neonatology & ↑ use of assisted fertilization,
- Are promoting an ↑ population of very premature infants,
- Who are at risk for:
Learning & Movement disorders (cerebral palsy).

Ref: Hvidtjorn, Grove, Schendel, et al. CP among children born after IVF: The role of preterm delivery. Pediatrics 2006;118:475.

The problem is compounded by the frequent co-existence of Ocular & cerebral visual impairment: ROP & CVI.

Ref: 1. Pennefather PM, Tin W. Ocular abnormalities associated with cerebral palsy after preterm birth. Eye 2000; 14:78.
2. Allred EN, et al. Retinopathy of prematurity and brain damage in the very preterm newborn. JAAPOS. 2014 Jun;18(3):241-7

Children with a history of significant prematurity (BW <1500g) are at risk for morbidity at each level of the visual system.

Sensorimotor
Strabismus

Refractive:
astigmatism
& myopia

Retinal:
ROP

Cerebral:
CVI

Prematurity and Visual Impairment
Looking back:

The 1st Epidemic of Blind Babies

It is estimated 10,000 American babies were blinded in the early 1950s.

- Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. Pediatrics 2004; 113:394.

Studies directly linked the “liberal” use of oxygen to blinding retinal disease.

- Kinsey VE. Report of the Cooperative Study of Retrolental Fibroplasia. Tr Am Acad Ophth 1955;59:15-24.
- Crosse VM. Retrolental fibroplasia in the City of Birmingham. Trans Ophth Soc UK 1951;71:609-12.
- Cambell K. Intensive oxygen therapy as a cause of retrolental fibroplasia. Med J Aust 1951;2:48-50.

Oxygen for premature babies

- Routine use of oxygen in neonatal units began in the *early 1940's*.
- *Based on observations that:*
↑ FiO₂ imparts a more regular breathing pattern to premature infants.
- Thus, new incubators were designed with sleeved access ports & tight fitting gaskets, making possible maintenance of high O₂ levels for prolonged intervals.

Ref: Silverman WA. A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004; 113:394.

- *It is not clear exactly how much oxygen the babies were getting:*
 1. Trans-cutaneous & Pulse oximetry had not been developed yet.
 2. The skin color of neonates is not a reliable indicator of hypoxia.
 3. Intermittent blood gas analysis was the only option available.
- Ref: Smith CA, Kaplan E. Adjustment of blood oxygen levels in neonatal life. *Am. Dis. Child* 1942; 64:843.
- *Still, a high fraction of inspired oxygen (FiO₂) soon became part of “routine” care for premature neonates.*

- *American O₂ incubators were also adopted by the British NHS.*

Soon after the mysterious epidemic of blindness afflicting American premature babies was noted in England.

- *The same association was noted in Australia.*

- *The blind babies would develop a fibrous vascular plaque behind the lens...*
- *Termed: **Retrolental Fibroplasia***

- Crosse VM. Retrolental fibroplasia in the City of Birmingham. *Trans Ophth Soc UK* 1951;71:609-12.
- Cambell K. Intensive oxygen therapy as a cause of retrolental fibroplasia. *Med J Aust* 1951;2:48-50.

Retrolental Fibroplasia

- *Now better known as **End Stage ROP** (Retinopathy of Prematurity)*

Severe cicatricial disease that produces total retinal detachment.

- Kinsey VE. Report of the Cooperative Study of Retrolental Fibroplasia. *Tr Am Acad Ophth* 1953;59:15-24.
- Crosse VM. Retrolental fibroplasia in the City of Birmingham. *Trans Ophth Soc UK* 1951;71:609-12.
- Cambell K. Intensive oxygen therapy as a cause of retrolental fibroplasia. *Med J Aust* 1951;2:48-50.

- **1955:** NIH sponsored trial comparing “Routine” vs. “Curtailed” oxygen in babies < 1500g :
 → Rate of cicatricial disease was ↓ by 2/3.
 The “standard of care” became O2 restriction.

- Ref: Kinsey VE. Etiology of retrolental fibroplasia and preliminary report of the Cooperative Study of Retrolental Fibroplasia. Trans Am Acad Ophthalmol Otolaryngol 1955; 59:15.

- **1960s:** Studies suggested possible association between oxygen restriction increased neonatal:
 - mortality rate
 - cerebral palsy
 - pulmonary disease

- Gordon HH. Oxygen therapy and survival rates in prematures. Pediatrics 1957;19:967.
 - Avery ME, Oppenheimer HH. Recent increased mortality from hyaline membrane disease. J Pediatr 1960;57:533-59.
 - McDonald AD. Cerebral palsy in children of very low birth weight. Arch Dis Child 1963;38:579-88.

1970s & 80s

- Concern about possible ↑ mortality, lung dz & CP: Resulted in a liberalization of oxygen delivery.
 - At the same time technology was permitting survival of increasingly premature infants.
- ↓
- *Outcome: A second ROP epidemic*

Silverman WA. The 1953-54 Oxygen Trial and its aftermath. Control Clin Trials 1991;12:355-8.
 Schaliij-Delfos NE, Cats BP. ROP: a continuing threat in preterm infants. Dutch survey 1986-1994. Acta Ophth Scand 1997;75:72-5

What is ROP (Retinopathy of Prematurity) ?

With premature birth, vascular retinal migration arrests, producing Ischemia.

Lower gestational age and weight correlate with a larger zone of underdeveloped retina and thus Greater Ischemia.

Ref: Ng E, Connolly B, McNamara J et al. A comparison of Laser photocoagulation with Cryotherapy for Threshold ROP at 10 years. Ophthalmology 2002; 109:928

Cryotherapy / Laser Tx for ROP

Retinal vascular migration completes ~ 40 wks.

Premature birth ⇒ vascular retinal migration arrests, producing Ischemia:

- ↓ Neovascularization.
- ↓ Tractional Retinal Detachment
- ↓ Blindness

The peripheral retina is *ablated* to arrest disease progression.

Ref: Ng E, Connolly B, McNamara J et al. A comparison of Laser photocoagulation with Cryotherapy for threshold ROP at 10 years. Ophthalmology 2002; 109:928

Cryotherapy for Retinopathy of Prematurity (Cryo-ROP) Cooperative Group - 1988

Studied:

- Natural History of Dz (N = 2759)
- Randomized Trial of transcleral cryotherapy for severe (“threshold”) ROP.
- 66% of infants < 1250 g developed ROP
- 17 % Moderate ROP
- 6 % Severe (Threshold) ROP
- *Threshold defined as the stage of disease where if untreated the risk of progression to blindness is 50%.*

Ref: Archives Ophthalmology 1988; 106:471.

- Laser treatment of “Pre-threshold ROP” often does arrest the disease and prevents blindness...
- But central acuity outcomes may still be poor
- **And the peripheral visual field is sacrificed !**

Ref: Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years. Arch Ophthalmol. 2001; 119:1110.

Central acuity vs. Peripheral VF

*“A castle, on an island of vision,
in a sea of darkness”*

- Timely treatment of Near Threshold ROP often does arrest the disease and prevents blindness...

But:

- The peripheral visual field is partly sacrificed.
- Acuity outcomes are still frequently poor (~ 45%)

Ref: Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ophthalmological outcomes at 10 years. Arch Ophthalmol. 2001; 119:1110.

1990s

- Renewed interest in O2 restriction for premature babies.
- *Trans-cutaneous (tcPO2) & Pulse oximetry permitted continuous monitoring.*

- 1992: Incidence and severity of ROP related to duration of exposure to tcPO2>80mm Hg.

- Flynn JT, et al. Study of tcPO2 and incidence & severity of retinopathy of ROP. N Engl J Med 1992;326:1050-4.

- 1993: Variability of oxygen saturation in the first weeks of life is a *predictor* of ROP and its severity.

- Ramanathan R, et al. Pulse oximetry in very low birth weight infants. Pediatrics 1987;79:612-7.
 - Saito Y, et al. Progression of ROP & fluctuation in blood gas tension. Graef Arch Cl Exp Ophth 1993;231:151-6.
 - Penn J, et al. Range of PaO2 variation determines severity of ROP in rats. Invest Ophth Vis Sci 1995;36:2063-70.
 - McColm J, et al. Hypoxic O2 fluctuations produce less severe ROP than hyperoxic. Ped Res 2004;55:107-13.

Hello!?

What about CP, Lung Disease, & Infant Mortality ...

- The renewed interest in oxygen restriction was in fact the work of neonatologists & pulmonologists.
- Why? Studies suggest that Reducing oxygen levels improves pulmonary outcomes by ↓ free radical damage to lungs.

Saugstad OD. Oxygen for newborns: how much is too much? J Perinatol 2005; 25 Suppl 2:S45

- There does not appear to be any adverse effect on Cerebral Palsy and Mortality outcomes.

1. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks' gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106
 2. Askie LM, Henderson DJ. Restricted vs. Liberal oxygen for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database Syst Rev, 2001 (4):CD001077

- Maintaining O2 sats b/w 85-93% in infants < 1250g was associated with a ↑ mental developmental index scores at Age 18mo (as compared to saturation settings of 92-100%).

Deulofaut R, et al. Avoiding hyperoxia in infants <1250 g is associated with improved short and long term outcomes. J Perinatol 2006, 26:700.

...So, What about outcomes from studies in the 60s?...

Perhaps....

1. The conclusions were premature / based on inadequate sample sizes.
2. Neonatologists over-reacted.

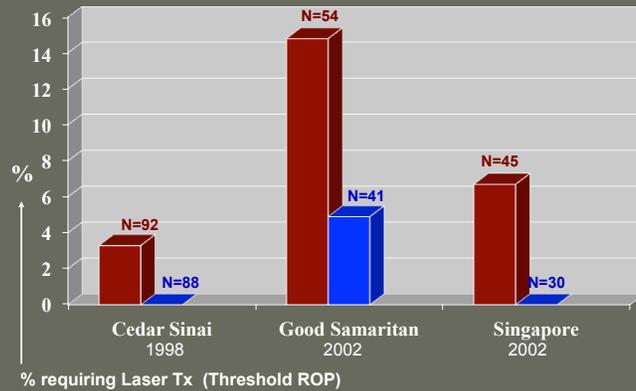
Or...

It is maintenance of more physiologic arterial oxygen saturations & better control of fluctuations in oxygen saturation (due to pulse oximetry) that have made the difference.

Studies (again !) support oxygen reduction in improving ROP outcomes...

| Study | Subjects population | SaO2 Groups | ROP |
|-----------------|-------------------------|---------------------------------------|---------------------------------------|
| Tin 2001 | < 27 wks | L 70-90% H 88-98% | 6% Tx 27% |
| Chow 2003 | 500-1500 gm | L 85-93% H 90-98% | 0% Tx 4.5% |
| Anderson 2004 | < 1500 gm > 2wks age | L <92% H >92% | 1.3% Tx 3.3% |
| VanderVeen 2005 | < 1250g or < 28 wks | L 85-93% Target 90-92% H 87-97% | 60% ↓ in prethreshold & threshold ROP |

ROP outcomes 1 year before & 1 year after implementing a reduced oxygen protocol (to keep SaO₂ between 83-92%)



So what's this business about
a possible 3rd epidemic?

The most important risk factors for prematurity related

- Retinopathy
- Cerebral Palsy
- Cerebral Visual Impairment



... Are gestational age and birth weight.

- Ref. Hvidtjorn, Grove, Schendel, et al. CP among children born after IVF: The role of preterm delivery. Pediatrics. 118:475, 2006.
Pennellfather PM, Tin W. Ocular abnormalities associated with cerebral palsy after preterm birth. Eye 14:78. 2000.

- Incidence of visual impairment among 1150 ELBW infants (400 -1000g), from 1993-1994:

401-500 g ⇒ 20% (10-15% blind)

501-800 g ⇒ 10% (1-5% blind)

801-1000 g ⇒ 5%

Reference:

Vohr BR, Wright LL, Dusick AM et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network 1993-1994.

Pediatrics. 2000 Jun;105(6):1216-26.

Highest risk group is children born
before age 25 wks...

N = 114, All ≤ 25 weeks gestation at birth.

63 % required retinal ablation for proliferative ROP

Visual impairment affected a significant number:

Boys (32.6%) Male > Female

Girls (9.2%) p = 0.004

Ref: Jacobson et al. Visual impairment is common in children born before 25 wks gestation. Acta Paediatr. 2008. Sept

The forecast:

- Current technology is allowing micro-premies to survive in the absence of clear ethical guidelines.
-
- 23 to 26 week old, 500-750 gram babies:
 - Immature lungs and retina:
Often not sustained at steady O2 saturation levels,
& require ↑ FiO2 ...
⇒ Develop **Threshold ROP**.

Surviving ROP is just the beginning...

↑ risk for :

1. Refractive errors
↑↑ Myopia & Astigmatism
 2. Retinal Detachment
 3. Strabismus
 4. Poor acuity despite good anatomic outcome
- Ocular disorder is often complicated by coexistent cerebral visual impairment.

- Ref: Cryo-ROP Cooperative Group Archives Ophthalmology 2005; 123:311.

CRYO-ROP: 15 year outcomes

- Unfavorable visual acuity outcomes in 45% of treated (threshold) eyes, vs. 65 % of control (untreated threshold) eyes.
- Progressive increase in the rate of retinal detachment,
↑ by 0.35% / yr in treated group (cumulative)
↑ by 0.51% / yr in control eyes.
- Conclusion: Need for continued follow-up.

- Ref: Cryo-ROP Cooperative Group. 15 year outcomes. Archives Ophthalmology 2005; 123:311.

“Threshold” ROP and ETROP

- *Due to significant risk for unfavorable outcome with ROP that is moderately severe but less severe than “threshold”:*
- *ETROP (Early Treatment of ROP) Guidelines were developed*

Good WV. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Early Treatment for Retinopathy of Prematurity Cooperative Group. Trans Am Ophthalmol Soc. 2004;102:233-48

Wheeler et al. Retinopathy of prematurity in infants weighing less than 500 grams at birth enrolled in the early treatment for retinopathy of prematurity study. Ophthalmology. 2011 Jun;118(6):1145-51

*Looking ahead...
IGF Supplementation for VLBW
premature infants*

Premature birth cuts off the maternal source of Insulin-like Growth Factor (IGF-I)
And the ability of premature babies to make adequate IGF is deficient.

IGF deficiency correlates with poor post-natal growth and the development of ROP.

The combination of IGF supplementation & O2 restriction may significantly reduce ROP.

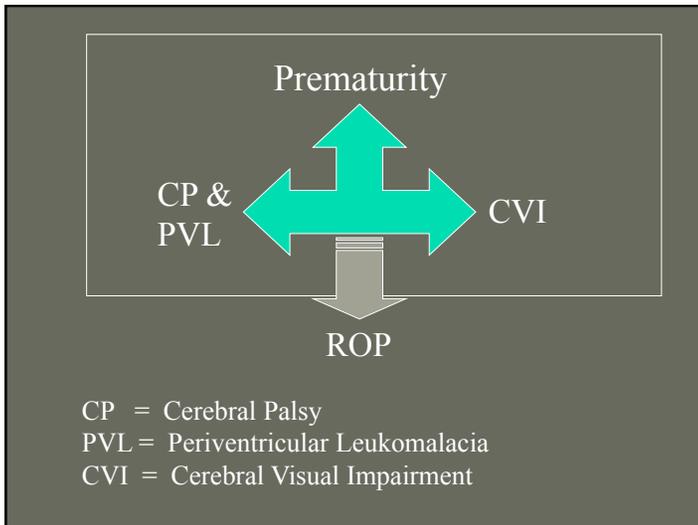
Ref:
1. Smith LE. Pathogenesis of ROP. Growth Horm IGF Res 2004;14 Suppl A:S140-S144.
2. Stahl A, Hellstrom A, Smith LE. Insulin-like growth factor-1 and anti-vascular endothelial growth factor in ROP: has the time come? Neonatology 2014;106(3):254-60

*Looking ahead...
Intravitreal Anti-VEGF injections*

*Appear to be quite effective in arresting neovascular disease.
Can create persistent large avascular zones of the retinal periphery
May produce peripheral corneal ulceration*

*Absorb across the blood ocular barrier...
- ROP regression seen in the contralateral eye
- ? Effect on developing brain...*

Hwang CK, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after Intravitreal Bevacizumab versus Laser Photocoagulation for Retinopathy of Prematurity: A 5-Year Retrospective Analysis. Ophthalmology. 2015 May;122(5):1008-15
Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond). 2013 Jul;27(7):787-94



Neonatal brain injury & CVI

- *In the past*, most cases were related to
 - Meningitis (H. influenzae)
 - Encephalitis (Herpes)
- *Currently*, In developed countries, the majority of cases are related to perinatal hypoxia-ischemia.
- Perinatal hypoxia often correlates with prematurity.
- CVI is now the single greatest cause of visual impairment in children in the United States.

Ref: Dutton et al. Cortical visual impairment. Eye 1996; 10:291

*Cerebral Visual Impairment (CVI)**

- Most commonly related to neonatal hypoxic-ischemic brain injury in premature infants.
- Often apparent on MRI and post-mortem as *Periventricular Leukomalacia (PVL)*

PVL: Necrotic calcifications around the ventricles.

Ref: Pediatric Ophthalmology and Strabismus, 3rd Ed, Ed: Taylor & Hoyt, 2005. Chapter 63, Hoyt S.

What is the connection between Prematurity, CVI & CP?

A common site of injury from neonatal hypoxic injury is the periventricular white matter:

Periventricular leukomalacia

Both *Optic & Corticospinal tracts* pass through this region:

Thus PVL & CP often co-exist.

1. Whitaker et al. Neonatal cranial UTZ abnormalities in LBW infants: relation to cognitive outcomes at six yrs of age. *Pediatrics*. 1996; 98:719.
2. Giovanni et al. CVI in Preterm Infants with PVL. *Dev Neurology* 1997; 17:331

Up to 70% of premature children with Spastic diplegia also have CVI.

1. Huo et al. Chronic CVI in children. *BJO* 1999; 83:670.

Visual Behaviors of Infants with CVI

- *Light gazing (up to 60%)*
- *Flickering fingers in front of eyes against a light source*
- *Photophobia (decreases over time)*

Ref: Jan et al. Light gazing by visually impaired children. *Dev Med Child Neurol*. 1990; 32:755.
Jan et al. Photophobia and CVI. *Dev Med Child Neurol*. 1990; 35:473.

Behavioral Characteristics of Children with CVI

The majority have some residual visual function.

Have problems with both:
visual discrimination (acuity) &
visual perception (interpretation)

See better when:
in familiar environments, &
directed where and what to look for.

Often use touch to interpret what is seen.

Poor depth perception.

Typically identify color better than form.

Ref: Jan et al. Behavioural characteristics of children with CVI. *Dev Med Child Neurol*. 1987; 29:571

Behavioral Characteristics Cont...

Blunted or avoidant social gaze

Brief fixations, intermittent following

Peripheral vision dominates when reaching

Visual attention for moving stimuli may be better than for static stimuli

Vision for navigation may be unexpectedly good

Potential for improvement over time

Parents are often much disturbed by the child's lack of social gaze and direct eye contact.

Ref: Jan et al. Behavioural characteristics of children with CVI. Dev Med Child Neurol. 1987; 29:571

Inferior VF Defects in CVI

- Inferior VF defects are associated with impaired ability to make accurate visually guided movement of the lower limbs.
- Particularly problematic when combined with movement disorders (cerebral palsy).

Ref: Dutton GN, Saeed A, Farhad B et al. 2004
Association of inferior visual field impairment in children with cerebral visual dysfunction. Eye 2004 18:27.

Clinical Research in CVI:

Low Light Learning Environment

There is increasing evidence that there is a subset of children with CVI who actually see better in dim lighting.

This is contrary to the traditional teachings of "good illumination / high contrast."

Much of this work is still in the research arena...

Ref: Good WV. Development of a quant. method to measure vision in children with CVI Trans Am Ophth Soc. 2001;99:253-69.
Good WV, Hou C. Sweep visual evoked potential grating acuity thresholds paradoxically improve in low-luminance conditions in children with cortical visual impairment. Invest Ophthalmol Vis Sci. 2006 Jul;47(7):3220-4.

Cerebral Palsy & Prematurity

Periventricular Leukomalacia (PVL) is strongly associated with cerebral palsy (CP) & mental delay.

Ref: Whitaker, Feldman, Van Rossem et al. Neonatal cranial ultrasound abnormalities in low birth weight infants: relation to cognitive outcomes at six years of age. Pediatrics. 1996; 98:719.

There is a high incidence of CVI among premature children with Cerebral Palsy & PVL

Ref: Giovanni C, Fazzi B, Coluccini P, et al. CVI in Preterm Infants with PVL. Pediatric Neurology 1997; 17:331

Severity of CVI is the strongest independent predictor of neuro-developmental scores in prematures with PVL and abnormal neurological exam (CP).

Ref: Cioni, Bertuccelli, Boldrini et al. Correlation between visual function, neurodevelopmental outcome, and MRI findings in infants with PVL. Arch Dis Child Fetal Neonatal Ed. 2000; 82:F134.

Neurological Outcomes of Prematurity

There is overwhelming evidence that the risk of major neurological disability is ↑ among LBW (<1500g) infants as compared to full term infants.

- Cole, Hagadorn, Kim et al. Criteria for Determining Disability in Infants and Children: Low Birth Weight. Evidence Report/Technology Assessment No. 70. AHRQ Publication No. 03-E010. Dec 2002.

Pennefather & Tin 2000:

Children with CP & a Hx of Prematurity < 32wks gestation:

| N = 558 | CP (54) | No CP |
|-----------------|---------|-------|
| Nystagmus | 16.7% | 0.6% |
| Cicatricial ROP | 14.8% | 1.6% |
| CVI | 11.1% | 0.2% |
| Strabismus | 51.9% | 8.4% |

Ref: Ocular Abnormalities associated with cerebral palsy and preterm birth, Eye 2000; 14:78.

Strabismus:

A marker for Neurological Outcomes of Prematurity

10-12 year F/U of babies <1700g - born in the Mid 1980's compared to 11 yo full term controls. N= 293 of 572.

⇒ **19.3 % incidence of Strabismus as compared to 3% in full term children.**

Ref: O'Connor, Stephenson, Johnson et al. Strabismus in children of birth weight less than 1701 g. Arch Ophthalmol. 2002 Jun;120:767.

68 preterm infants with IVH. Mean gestational age was 28.1 weeks (range 24-35).

Strabismus developed in 30 infants (44.1%).

Ref: O'Keefe M, Kafli-Hussain N, Fliteroff I, Lanigan B. Ocular significance of intraventricular haemorrhage in premature infants. Br J Ophthalmol. 2001 Mar;85(3):357-9

Finnish Registry of Visual Impairment

During the 18 years covered by study, the increasing incidence of survival of infants born < 1500g (3 lbs) was associated with increasing incidence of severe visual impairment .

Visual Impairment often was accompanied by cerebral palsy, epilepsy, and mental handicap.

Ref:
Randanko et al. Visual impairment in children born prematurely 1972-2989. Ophthalmology. 2003 Aug 110:1639.

- European studies show that almost 50% of all children with cerebral palsy (CP) have a hx of preterm delivery.
- Twins have 4x higher risk for CP than do singletons.

Ref: Hvidtjorn, Grove, Schendel, et al. CP among children born after IVF. Role of preterm delivery. Pediatrics. 2006; 118:475.

- In the USA there are approx 55,000 live births per year with BW < 1500 g.

90% survive: 10% develop CP, 50% cognitive deficits.

Translates to nearly 5000 new cases of CP / year and 10-20,000 with learning disabilities...

Ref: Kinney H. The near term human brain and risk for PVL: A review. Semin Perinatol. 2006; 30:81.

Some final thoughts...

Current technology is allowing micro-premies to survive in the absence of clear ethical guidelines.

23 to 25 week old, 500 gram babies who develop the complications of hypoxic-ischemic brain injury:

Comorbid conditions of ROP, CVI, & CP

Problem List:

1. Poor acuity and depth perception
2. Poor gait and balance - may be compounded by inferior VF defect
3. Sequelae of Intraventricular hemorrhage:
Hydrocephalus, Seizure disorder

Ref:

Hvidtjorn, Grove, Schendel, et al. CP among children born after IVF: The role of preterm delivery. *Pediatrics*. 2006; 118:475.
Pennefather PM, Tin W. Ocular abnormalities associated with cerebral palsy after preterm birth. *Eye* 2000; 14:78.
Oshen TM, Dx, Tx and prevention of Cerebral Palsy. *Clinic Obst Gyn*. 2008; 51:816

Thank you for your attention