Trinity Research in Childhood Centre (TRiCC) Annual Lecture 2019

Professor Neil Marlow

“Young adult preterm: fit for the future?”

#TRiCClecture19 @TCD_TRICC

In Collaboration with Children’s Research Network
Young adult preterms: Fit for the Future?

Neil Marlow
Declaration

• Neil Marlow declares the following potential COI
  ▪ Consultancy fees from Novartis and Shire/Takeda
  ▪ Executive Board member EFCNI (unpaid)
Objectives

1. To explore the range of outcomes in early adult life following EP birth
2. To understand the relative roles of tissue injury and developmental problems in generating poor outcomes
3. To evaluate the effectiveness of early interventions
4. To discuss potential therapeutic strategies
• Saving lives

• Marginal gains

• Marginal harms

• Thinking outside the neonatal period
Survival to discharge for infants born 22–26 weeks of gestation and admitted to neonatal units in England in 1995 (EPI Cure)\textsuperscript{10}, 2006 (EPI Cure 2)\textsuperscript{2} and 2016 (MBRRACE-UK).\textsuperscript{3}
Survival rate doubles for premature babies

Kaya Burgess

The number of extremely premature babies who survive has doubled over the past decade, prompting new guidance allowing doctors to try to save babies born as early as 22 weeks into a pregnancy.

The threshold recommended by the British Association of Perinatal Medicine (BAPM) was previously 23 weeks, but experts said that intensive care had improved significantly.

In 2008 only two out of ten babies born alive at 23 weeks went on to survive. Today it is four out of ten.

Guidance previously recommended that doctors should not attempt resuscitation and “active care” for babies born before 23 weeks, as their chances of survival were too slim and those who lived were likely to suffer severe complications. It was recommended that these babies be offered palliative care to ensure their comfort.

The BAPM cited figures showing that doctors now offered intensive care to 23 per cent of babies who survived at 22 weeks. It has updated its guidance but said that each case should be assessed for chances of survival, quality of life and the wishes of parents.

The survival rate of babies born at 22 weeks is still very low. About 60 per cent have died before labour begins and of foetuses still alive when labour starts, only 63 per cent survive the birth. Only 5 per cent of babies born at 22 weeks survive to their first birthday and a third will have disabilities including blindness, deafness, severe learning difficulties or movement problems.

About 60,000 babies are born prematurely in the UK each year, of which 3,148 are considered “extremely premature” — born before 27 weeks.

Dominic Wilson, professor of medical ethics at Oxford University, said that such “complex ethical decisions” could not be reduced to simple rules.

The legal abortion limit is set at 24 weeks, allowing for the termination of foetuses at 23 and 22 weeks. Professor Wilson said that the BAPM’s guidance was “focused on the care of extremely premature babies [and] does not deal at all with questions of termination.”

Four out of ten babies born alive at 23 weeks go on to survive

ALAMY

At 22 weeks a baby in the foetal position is the size of a bell pepper

18 weeks
- Height 28cm outstretched
- Weight Less than 1lb

Source: What To Expect
Impairment

• Disability
  ▪ 1995-2006
  ▪ 15% improvement in survival
  ▪ 13% in survival with no impairment
  ▪ No change in disability

• 2019?

Moore T et al BMJ 2012
Prematurity is a continuum

<table>
<thead>
<tr>
<th>Gestational Week*</th>
<th>PAR due to gestational age*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-27</td>
<td>0.5% (0.4-0.6)</td>
</tr>
<tr>
<td>28-32</td>
<td>1.1% (1.0-1.3)</td>
</tr>
<tr>
<td>33-36</td>
<td>2.0% (1.7-2.4)</td>
</tr>
<tr>
<td>Total</td>
<td>10% (0.7-12.9)</td>
</tr>
</tbody>
</table>

MacKay et al. PLOS Medicine 2010
Prematurity is a pervasive disorder
Transition to young adult life

Review
- Cognitive and consequent attainment
- Social and mental health outcomes
- Lung and cardiovascular function
Spectrum of neurocognitive findings

- **Education**
  - Special needs

- **Cognition**
  - Executive function
  - Working memory

- **Socialisation**
  - Peer group
  - Affect

- **Behaviour**
  - Inattention
  - Psychiatric probs
Cognitive outcomes following EP birth

• Commonest domain of impairment
• Translates into
  ▪ Poor educational attainment
  ▪ Behavioural phenotype
• Stability over childhood poorly defined
  ▪ Bavarian Longitudinal Study (*Breeman et al Pediatrics* 2015; 136:415)
  ▪ VP/VLBW scores more stable over time
  ▪ Prediction from 20m for VPT/VLBW (r >0.50)
Cognitive trajectories

A Extremely preterm and term-born controls (observed)

E Extremely preterm and term-born by maternal education (observed)

Linsell Arch Dis Child 2018
Preterm birth: development of executive function

Effect size $d$: Difference preterm-term in SD

Selective attention

Phonemic fluency

Mulder, Marlow, Pitchford Dev Neuropsychol 2009
Key executive processes differentiating preterms

- Most δδ accounted for by Verbal processing speed and Working memory

- Including:
  - Overall FSIQ differences
  - Differences on behavioural measures (SDQ, Connors rating)
  - Academic attainment

<table>
<thead>
<tr>
<th>Predictor</th>
<th>AUC</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maths rating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal speed</td>
<td>.83</td>
<td>.73 - .93</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Working memory</td>
<td>.79</td>
<td>.68 - .90</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>English rating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal speed</td>
<td>.73</td>
<td>.61 - .85</td>
<td>.002</td>
</tr>
<tr>
<td>Working memory</td>
<td>.73</td>
<td>.61 - .85</td>
<td>.002</td>
</tr>
<tr>
<td>Teacher rating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal speed</td>
<td>.74</td>
<td>.61 - .86</td>
<td>.002</td>
</tr>
<tr>
<td>Working memory</td>
<td>.81</td>
<td>.70 - .92</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SEN provision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal speed</td>
<td>.74</td>
<td>.62 - .86</td>
<td>.001</td>
</tr>
<tr>
<td>Working memory</td>
<td>.75</td>
<td>.63 - .88</td>
<td>.001</td>
</tr>
</tbody>
</table>

Mulder, Pitchford, Marlow BJ Educ Psychol 2011, JINS 2011, ADC 2010
Spectrum

- **Education**
  - Special needs

- **Cognition**
  - Executive function
  - Working memory

- **Socialisation**
  - Peer group
  - Affect

- **Behaviour**
  - Inattention
  - Psychiatric probs
Behaviour

(a) Total Difficulties Score
(b) Emotional Symptoms Score
(c) Conduct Problems Score
(d) Hyperactivity/Inattention Score

Linsell DMCN 2018
DSM4 Outcomes

Mean difference in symptom ‘z’ scores from controls (95%CI)

O’Reilly et al PAS 2016
Database association studies

- Extremely preterm adults at risk of:
  - Increased ASD\(^1\) RR: 9.5 (1.5, 36.2)
  - Other behaviour/emotional disorders\(^1\) RR: 10.5 (5.6, 19.9)
  - ADHD\(^2\) aRR: 5.0 (2.1, 11.8)
  - Non-affective psychosis, depressive disorder, bipolar disorder\(^3\) (<32w)
  - Psychotrophic meds\(^4\)
    - Antipsychotics, antidepressants, anxiolytics
- All have “dose-dependent effect” of gestation

1. Moster et al NEJM 2008
2. Halmoy et al Biol Psychiatr 2012
3. Nosarti et al Arch Gen Psychiatr 2012
Norwegian study
Births 1967-1983 (n=867 692); 19-35y

- Schizophrenia (p=.12)
- Autism Spectrum (p=.002)
- Disorders of psych development, behaviour and emotion (p<.001)

Moster et al NEJM 2008
Babies born very prematurely 'more likely to be unemployed and single as adults'

The prematurely-born babies were also found to be more likely to suffer from chronic health problems as adults
Education and occupation at 19y

Fig 1. Highest school attainment

Fig 2. Occupational status
Cleveland Study

Social outcome profile as VLBW young adults

Odds Ratio (95%CI)

Substance Use
- Tobacco
- Alcohol
- Recreational

Contact with police
- Violation
- Conviction
- Incarcerated

Sexual Activity
- Intercourse
- Live birth

Hack et al NEJM 2002
Hamilton Study

Social outcome profile as ELBW adults >30 years

Income C$20,000 less
More chronic health problems
Less self esteem

Differences dependent on presence of NS impairment

Saigal et al JAMA Peds 2016
Spectrum of outcomes

**Education**
Special needs

**Cognition**
Executive function
Working memory

**Socialisation**
Peer group
Affect

**Behaviour**
Inattention
Psychiatric probs
Lung function - Spirometry

Postbronchodilator FEV₁ z scores in extremely preterm (EP) and control groups

Beckmann et al PAS 2016
Cardiovascular function

Central blood pressure values in extremely preterm (EP) and control groups

Augmentation index in extremely preterm (EP) and control groups

Beckmann et al PAS 2016
Implications for adult life

after Fletcher C, Peto R BMJ 1977
Pervasive effects of extremely preterm birth

Preterm birth

Motor disorder
Core Executive Deficits
Low IQ
Behavioural problems

Cerebral Palsy
Injury

Injury
Developmental arrest

Developmental arrest

Lung function
Vascular function
Sensory function
Other organs: e.g. Kidneys

Adult consequences
Mental Health
Education
Earning
Health
Ageing

Antenatal factors

UCL
Risk factors for preterm cognitive impairment

- Parental education
- Lower SES
- SGA
- Small OFC
- Brain injury

Doing something about it ...

- Effective early intervention?
Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants

Cochrane Database of Systematic Reviews
24 NOV 2015 DOI: 10.1002/14651858.CD005495.pub4

INFANT outcomes
Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants

Cochrane Database of Systematic Reviews
24 NOV 2015 DOI: 10.1002/14651858.CD005495.pub4

### Reviewer: Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants

#### Comparison: 1 Early developmental intervention versus standard follow-up (subgroup analysis: quality of studies)

#### Outcome: 3 Cognitive outcome at school age (WISC, Kaufman IQ)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention N</th>
<th>Mean(SE)</th>
<th>Follow-up N</th>
<th>Mean(SE)</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference IV Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-quality studies</td>
<td>124</td>
<td>99.7 (15.2)</td>
<td>62</td>
<td>101.1 (15)</td>
<td>21.2%</td>
<td>-0.09 (-0.46, 0.21)</td>
<td></td>
</tr>
<tr>
<td>Low-quality studies</td>
<td>335</td>
<td>97.8 (18.2)</td>
<td>335</td>
<td>95.0 (17.8)</td>
<td>27.8%</td>
<td>-0.01 (-0.15, 0.13)</td>
<td></td>
</tr>
<tr>
<td>Karsen 2006</td>
<td>66</td>
<td>100.0 (14.2)</td>
<td>66</td>
<td>98.2 (15.6)</td>
<td>19.2%</td>
<td>0.17 (-0.16, 0.51)</td>
<td></td>
</tr>
<tr>
<td>Kedemoney 2009</td>
<td>69</td>
<td>97.7 (15.6)</td>
<td>67</td>
<td>94.2 (15.8)</td>
<td>19.8%</td>
<td>0.02 (-0.12, 0.55)</td>
<td></td>
</tr>
<tr>
<td>Narcombe 1984</td>
<td>24</td>
<td>110.5 (11.7)</td>
<td>31</td>
<td>97.2 (13.7)</td>
<td>121.1%</td>
<td>1.02 (0.45, 1.59)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>619</td>
<td>97.0 (15.3)</td>
<td>753</td>
<td>98.0 (15.3)</td>
<td>100.0%</td>
<td>0.18 (-0.08, 0.43)</td>
<td></td>
</tr>
</tbody>
</table>

### School Age

#### Subtotal (95% CI)

| Heterogeneity: Test (Chi-squared) = 0.05, df = 4, p = 0.91; I² = 0% |
|--------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Test for overall effect | z = 1.32 (p = 0.18) |
| Not estimable |

### Test for subgroup differences

Not applicable

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Cochrane Database of Systematic Reviews
24 NOV 2015 DOI: 10.1002/14651858.CD005495.pub4
Infant Health and Development Program

Heavier BW group – IQ

Lower BW group – IQ

<1250-2500g or <37w

<1251g

1250-2500g or <37w

<1251g

McCormick Pediatrics 2006
Doing something about it ...

- Effective early intervention?
  - Too early?
- Working memory training?
- Processing speed?
- Inattention?
- Educational support?
  - Too late?
Cognitive outcomes

• Measurement challenging
• Development not cognition
• IQ is a global summary score
• IQ comprises a series of processes
  ▪ Basic functions – processing speed
  ▪ Executive functions – higher order
• Functions differentiate over time
• Intervene when differentiating?
The fate of British Cycling changed one day in 2003

• ..the performance of British riders had been so underwhelming that one of the top bike manufacturers in Europe refused to sell bikes to the team because they were afraid that it would hurt sales if other professionals saw the Brits using their gear.
  
  James Clear

• Dave Brailsford –

  “the aggregation of marginal gains”
Cerebral Palsy rates

Figure 1  Birthweight specific trends in cerebral palsy.

Pharoah et al Arch Dis Child. 1990
Potentially better practices

VON Qi initiative e.g.:
• Neurodevelopment – 16 practice changes
• BPD – 13 PBP identified
• Sepsis bundle reduced infection rates
  ▪ Antibiotic stewardship
• Staffing – reduced staffing turnover
• Neonatal abstinence
• ALL need local leadership for QI team
Can we improve outcomes further?

- Antenatal Steroid
- No RCT data
- Key positive influence in many studies (confounded)

Morgan et al. BMC Pregnancy & Childbirth 2016
Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate

- No RCT data <24 weeks
- Accuracy of dating?
- Should this stop its use?
- PReCePT Study
Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route

- No RCT data
Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route
- Physiological cord clamping

Tarnow Mordi et al AmJOG 2017
Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route
- Physiological cord clamping
- Senior person at delivery
  - Obstetric
  - Neonatal
Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route
- Physiological cord clamping
- Senior person at delivery
- Care in the right place

Marlow et al ADC F&N 2014
Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route
- Physiological cord clamping
- Senior person at delivery
- Care in the right place
- Neonatal care

Stabilisation
- Respiratory support
- Gentile care
- Quiet
- Skin to skin?
- Delay intubation
- Immediate CPAP
- Less invasive surfactant
- INSURE
- Avoid catecholamines?
- Early steroids?
- Early caffeine?

Early Care
- Gentle care
- Quiet
- Skin to skin?
- Early colostrum
- Avoid catecholamines
- Avoid ventilation/NIV
- Institute preventive strategies
- LISA
- Prevent nosocomial infection
- Avoid long antibiotic courses

Et cetera
- Engage parents/improve confidence
- Facilitate attachment
- Etc
- Etc

Et cetera
- Engage parents/improve confidence
- Facilitate attachment
- Etc
- Etc
Summary

1. Prematurity produces a range of adverse outcomes through into early adult life
2. The origin of long term outcomes is a subtle mix between sociodemographics, specific developmental changes and tissue injuries
3. Current developmental and neonatal interventions are of uncertain efficacy in changing these long term outcomes
4. Potential therapeutic strategies include marginal improvements in a range of neonatal care issues and developing better informed post discharge interventions