Adolescent and Youth Outcomes after Very Preterm Birth

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Darling, you must know... I was premature. But I'm past that now...
Very low birthweight - <1500g

Very preterm - <32 weeks

VLBW/VP are 1%-2% live births

Survival - 90% to discharge

1986  413 VLBW infants. 82% survival – 338 survivors
2008  c.800 VLBW infants. 90% survival – 720 survivors
**VLBW / VP childhood outcomes**

- Neurosensory impairments – CP 10%
- Behavioural problems
- Cognitive delay
- Educational underachievement 40%

White matter abnormalities on brain MRI at term equivalent predictive of later problems 49%

Woodward *NEJM* 2006;355:685

Reduced WM volume, ventriculomegaly, thinning of corpus callosum, delayed myelination
In 1986 all 413 VLBW NZ infants admitted to NICU were included in prospective study of ROP
- prospective data on 173 perinatal variables
- 58% received antenatal steroids
- 23% Maori
- 25% small for gestational age
- 33% were <1000g
- Survival to discharge 82% (338)

The cohort were followed-up at 7-8 years
A further 12 children had died
298 children assessed (96% those in NZ, 91% all survivors)

Severe disability – 5% (CP unable to walk; blind; IQ>3sd below Mean on WISC)
Moderate disability – 5% (CP but ambulant; deaf; IQ 2-3sd below Mean)
Mild disability – 15% (mild CP; IQ 1-2sd below Mean)
Overall CP 6%

Also had comprehensive visual assessment at this time
Outcome at school age - VLBW

IQ distribution for Term and VLBW infants
## Outcome at school age - VLBW

*Arch Dis Child 1998; 79: F12-20 and other data*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Term</th>
<th>VLBW Multiplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural Problems</td>
<td>7%</td>
<td>2-3x</td>
</tr>
<tr>
<td>Cognitive Impairment</td>
<td>11%</td>
<td>2.5x</td>
</tr>
<tr>
<td>Below ave School Perf.</td>
<td>15-20%</td>
<td>2x</td>
</tr>
<tr>
<td>Enrolled special class</td>
<td>1%</td>
<td>6x</td>
</tr>
</tbody>
</table>
Outcome after VLBW

Best evidence from population based studies over time is that:

With increasing survival rates, overall disability is either not increased or less

For the most premature infants, eg 23 weeks or below, overall outcome remains very poor

VLBW/VP “tip of iceberg”. Are many more moderate and late preterm infants. Indications are that they have a similar range of problems but with a lower incidence.
**VLBW Adolescents and Young Adults**

Evidence from:

- National registry data (eg Scandinavia)
- National (Dutch POPS study born 1983), or regional Hospital based cohorts

Date from 1970’s or early 1980’s

Few received antenatal steroids

          Doyle *Pediatrics* 2010;126:342
**VLBW Adolescents and Young Adults**

Pioneering work of Saroj Saigal – Hamilton, Ontario

*JAMA* 1996; 276: 453

**ELBW adolescents born 1977-82, aged 12-16 years**

- 27% had neurosensory impairments
- Had more limitations in self-care, pain, sensation and cognitive attributes on direct measures

**BUT** 71% ELBW vs 73% controls gave utility rating >0.95 for health status

Dinesen *Arch Dis Child* 2002  
exVLBW, LBW, Term at 18-20yrs

Objective QoL, less in VLBW (Societal standards)  
Subjective QoL, no different (Life experiences and preferences)
VLBW NZ 1986 Young Adult Study

At 22 years, 230 (71% survivors)

- 56% had ANS
- 25% <1000g
- 25% <28 weeks gestation
- 26% Maori
- 47% male

vs. 69 controls, born at term in 1986.
Reasonably well matched – NS differences

Traced and assessed by face-to-face interview
Evidence is some catch-up growth continues to adolescence

NZ VLBW 1986 cohort at 22 yrs

<table>
<thead>
<tr>
<th></th>
<th>VLBW cohort (N=230)</th>
<th>Controls (N=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt (Kg) Mean (SD)</td>
<td>72.1 (17.0)</td>
<td>77.7 (16.4)</td>
<td>&lt;.016</td>
</tr>
<tr>
<td>Ht (cm) Mean (SD)</td>
<td>167 (9.7)</td>
<td>171 (10.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circ. Mean (SD)</td>
<td>88.7 (14.1)</td>
<td>89.9 (12.9)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI Mean (SD)</td>
<td>25.9 (5.7)</td>
<td>26.5 (4.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Most other studies also show Ht reduced by 4-8 cm
VLBW Adolescents and Young Adults – Growth

The growth velocity dilemma

Smaller size at birth plus poor growth linked with poorer neurodevelopment and increased risk of health problems

Neonatologists strive to achieve improved growth in VLBW infants

Animal and epidemiological data show upward crossing of percentiles has increased risk of CVS disease, impaired insulin tolerance, etc

Some evidence that for ELBW group BMI Z-scores increase from 3 years to adulthood
VLBW Adolescents/Young Adults – Metabolic

<32 weeks (AGA and SGA) vs controls at age 4 - 10 years
had reduced insulin sensitivity \((P=0.002)\)

Hofman *NEJM* 2004;351:2179

VLBW vs controls at age 18 - 27 years
had increased insulin resistance and impaired GTT

Hovi *NEJM* 2007;356:2053

Decreased bone mineral density in VLBW young adults
both M and F in lower lumbar spine, femoral neck

Hovi *PLoS Med* 2009 Aug
Changes in lung capacity with age, contrasted between those born very preterm with those born at term, illustrating the effects of smoking, started at different ages, on both groups (dashed lines)

*Courtesy Lex Doyle*
**FEV<sub>1</sub>** ( % predicted for age, height and sex)

<table>
<thead>
<tr>
<th>Study (year published)</th>
<th>Age studied (years)</th>
<th>Preterm groups</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BPD</td>
<td>No BPD</td>
</tr>
<tr>
<td>Halvorsen (2004)</td>
<td>19.7</td>
<td>87.8 (13.8)</td>
<td>97.7 (12.9)</td>
</tr>
<tr>
<td></td>
<td>n=12†</td>
<td>n=34</td>
<td>n=46</td>
</tr>
<tr>
<td>Doyle (2006)</td>
<td>18.9</td>
<td>81.6 (18.7)</td>
<td>92.9 (12.8)</td>
</tr>
<tr>
<td></td>
<td>n=33*</td>
<td>n=114</td>
<td>n=37</td>
</tr>
<tr>
<td>Vrijlandt (2006)</td>
<td>19</td>
<td>90.1 (19.8)</td>
<td>99.2 (17.9)</td>
</tr>
<tr>
<td></td>
<td>n=8‡</td>
<td>n=12‡</td>
<td>n=48</td>
</tr>
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</table>

**FEV<sub>1</sub>** < 80% is abnormal  
**FEV<sub>1</sub> / FVC** < 75% is abnormal

VLBW / VP young adults may exercise less and have reduced aerobic and exercise capacity

*Courtesy Lex Doyle*
VLBW Young Adults – Respiratory outcomes

NZ 1986 VLBW cohort at 7-8 years

52% had been diagnosed with asthma at some time, compared to 27% of contemporary NZ children in ISAAC study.

At 22 years

32% cohort vs 12% controls (P<0.01) had wheeze in past year.

But just as likely to be daily smoker: 28% vs 26%
VLBW Young Adults – cardiovascular disease

CVS disease accounts for 40% all deaths in gen. population
IHD is commonest cause of death – 23%

BP in VLBW/VP young adults

  Systolic BP consistently elevated in studies
  Diastolic BP elevated in some but not all

Other areas to investigate

  Endothelial function
  LV function
VLBW Young Adults – renal disease

Major part of nephrogenesis occurs in third trimester

Acute renal failure in up to 18% VP infants

Jetton *Curr Opin Pediatr* 2012;24: 191

Dutch POPS study suggests:
- reduced renal growth
- higher serum creatinine
- higher microalbumin excretion at 19 years
VLBW Young Adults – vision

VLBW/VP associated with increased risks of impaired acuity, myopia, squint – 2-3x general population

ROP may double the risk; if treated ROP risk still greater

Adverse visual outcomes may affect neurological development

UK Midlands <1701g cohort. Age 10-14 years
50% adverse visual outcomes

Ontario ELBW adolescents
36% prescription glasses vs 10% controls
by young adulthood 64% vs 37%
VLBW Young Adults – cognitive function

VLBW/VP - in childhood impairments in:
  behaviour, cognitive function, school performance
and problems in:
  use/understanding of language
  visuo-spatial abilities
  executive functioning

Largely unknown whether these persist to adolescence and beyond. Is degree of neural WM plasticity that may modify adverse effects

MRI scans in VLBW young adults from 1966-77 show increased ventricular volume, reductions in corpus callosum and alterations in grey and white matter
Figure 1  Differences in mean IQ for gestational age and birth weight SDS and environmental and personal factors in multiple regression analyses.
VLBW Young Adults – Methods at 22yrs

Participants given comprehensive questionnaire at a face-to-face interview, covering

- socio-demographic factors
- health
- education
- social roles

Supplemented by information from medical records

Parents also administered a postal questionnaire
Methods

Behaviour, physical and mental health measures
- BRIEF (behavioural rating of executive function)
- ADHD symptoms self-report
- ODD symptoms self-report
- SF-36 (short form health and functioning survey)
- SCL-90 (psychometric check list)

Statistical comparisons – chi square, t-test or Poisson regression as appropriate
## Educational qualifications

<table>
<thead>
<tr>
<th>Measure</th>
<th>VLBW cohort (N=230)</th>
<th>Controls (N=69)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% no formal qualifications</td>
<td>14</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>% high school qualifications only</td>
<td>30</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>% tertiary technical qualifications</td>
<td>41</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>% university degree</td>
<td>15</td>
<td>30</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Trend to lower educational attainment most marked in those with prior disability at age 7-8 (30% no quals, 21% high school, 41% tertiary, 3% degree). No effect of B Wt.
## Current living arrangements

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<thead>
<tr>
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<th>VLBW cohort (N=230)</th>
<th>Controls (N=69)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>% living with parents</td>
<td>38</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>% cohabiting partner</td>
<td>29</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>% living with flatmates</td>
<td>16</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>% living alone</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>% other</td>
<td>11</td>
<td>4</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Trend more exaggerated for ELBW and those with mod/severe disability at 7-8 years
**Selected other outcomes at 22 years**

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<th>VLBW (N=230)</th>
<th>Controls (N=69)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>% Welfare dependent (ever)</td>
<td>51%</td>
<td>30%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>% With romantic partner</td>
<td>58%</td>
<td>75%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>% Has few or no friends</td>
<td>53%</td>
<td>32%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>% Weekly alcohol use</td>
<td>37%</td>
<td>38%</td>
<td>NS</td>
</tr>
<tr>
<td>% Cannabis use (past 12m)</td>
<td>30%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>% Arrested (ever)</td>
<td>17%</td>
<td>25%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Trend for less risk taking for those with moderate/severe disability at 7-8 years
SF-36 is Short Form Health Survey that allows quality of life scores to be derived.
Norm based SF-36 scale for 18-24 years

<table>
<thead>
<tr>
<th>% &gt;1SD below mean</th>
<th>VLBW cohort (N=230)</th>
<th>Controls (N=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical component summary</td>
<td>15.7</td>
<td>13.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>6.6</td>
<td>4.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Overall functioning

<table>
<thead>
<tr>
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<th>VLBW cohort (N=230)</th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self esteem score Mean (SD)</td>
<td>31.7 (5.1)</td>
<td>31.8 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Life satisfaction Mean (SD)</td>
<td>41.6 (5.2)</td>
<td>42.1 (5.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Consistent message from literature.
Although objective measures of health status and QoL are lower than controls – self-rating shows no difference from their peers
VLBW Adolescents/Young Adults – Summary

Most VLBW/VP adolescents are doing well and rate their health and QoL similar to their peers.

May have declared (eg CP) or undeclared health problems - (eg raised Ct, lower aerobic capacity)

Often more socially isolated than their peers

It is possible VLBW/VP graduates may be at risk of early ageing – current research trying to identify biomarkers for this

Mod/late preterm may have similar issues, lower incidence but higher overall prevalence
VLBW Young Adults – Current Study

Current HRC grant

250 (77%) VLBW cohort and 100 controls come to Christchurch for two days of investigations:

- Ht, Wt, Waist circumference, BMI, Body fat
- Blood tests - fasting insulin, glucose, HbA1C, cotinine, plasma hormones, biochemistry
- BP, Echocardiogram, ECG, peripheral artery tonometry
- Respiratory function tests
- Visual function, retinal photographs
- Dental examination
- Cognitive and Neuropsychological Functioning assessments
- Questionnaire
- Cranial MRI (100 cohort, 50 controls)
Snow and adolescence are the only problems that disappear if you ignore them long enough.

Thank you