Perinatal Research in New Zealand: Why Do We Do It? How Can We Lead? The Liggins Legacy

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Peter Gluckman
David Henderson-Smart
Anne Jaquiery
Mont Liggins
Mark Oliver

Frank Bloomfield
Stuart Dalziel
Deborah Harris
Ross Howie
David Knight
Chris McKinlay
Jeffrey Robinson
Maternal-Fetal HPA Axis

- **Maternal hypothalamus**
  - CRF
  - AVP
  - Maternal Anterior pituitary
  - ACTH
  - Maternal adrenal cortex
  - Cortisol

- **Fetal hypothalamus**
  - CRF
  - AVP
  - Fetal Anterior pituitary
  - ACTH
  - Fetal adrenal cortex
  - Cortisol

Transplacental transfer
Premature Delivery of Foetal Lambs Infused with Glucocorticoids

G.C. LIGGINS

Postgraduate School of Obstetrics & Gynaecology, University of Auckland, Auckland, New Zealand

“Partial aeration of the lungs was observed in lambs born vaginally at 117-123 days of gestation after receiving dexamethasone. It is suggested that this may be the result of accelerated appearance of surfactant activity”.

Journal of Endocrinology 45; 515-523, 1969
A Controlled Trial of Antepartum Glucocorticoid Treatment for Prevention of the Respiratory Distress Syndrome in Premature Infants


Postgraduate School of Obstetrics and Gynaecology, University of Auckland, New Zealand

Pediatrics 50; 515-525, 1972
“Original” Liggins & Howie Trial

Early neonatal mortality reduced from 15% to 3%
RDS reduced from 26% to 9%
No deaths from HMD or IVH in babies treated >24h before delivery
No increase in maternal or neonatal infection
Maximal benefit if <32 weeks and >24h after treatment
1992

“Results of several controlled trials of a simple and inexpensive treatment to reduce problems experienced by premature babies….This..shows that a treatment, which was not then in widespread use, reduced mortality in premature babies. The Cochrane Logo thus illustrates the human costs that can result from failure to perform systematic, up-to-date reviews of controlled trials”
RDS – Decade of Trial

06 in babies from trials conducted in 1970s

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liggins</td>
<td>53/542</td>
<td>89/550</td>
</tr>
<tr>
<td>Block</td>
<td>5/57</td>
<td>12/53</td>
</tr>
<tr>
<td>Taeusch</td>
<td>7/54</td>
<td>14/69</td>
</tr>
<tr>
<td>Doran</td>
<td>4/80</td>
<td>10/60</td>
</tr>
<tr>
<td>Schutte</td>
<td>11/62</td>
<td>17/58</td>
</tr>
<tr>
<td>Gamsu</td>
<td>7/130</td>
<td>16/132</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 925 922

Total events: 87 (Treatment), 158 (Control)
Test for heterogeneity: Chi² = 2.42, df = 5 (P = 0.79), I² = 0%
Test for overall effect: Z = 4.78 (P < 0.00001)

07 in babies from trials conducted in 1980s

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teramo</td>
<td>3/38</td>
<td>3/42</td>
</tr>
<tr>
<td>Collaborative Group</td>
<td>46/361</td>
<td>65/359</td>
</tr>
<tr>
<td>Nelson</td>
<td>10/22</td>
<td>11/22</td>
</tr>
<tr>
<td>Parsons</td>
<td>3/23</td>
<td>3/22</td>
</tr>
<tr>
<td>Morales</td>
<td>23/87</td>
<td>41/78</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 531 523

Total events: 85 (Treatment), 123 (Control)
Test for heterogeneity: Chi² = 3.52, df = 4 (P = 0.47), I² = 0%
Test for overall effect: Z = 3.30 (P = 0.0010)

08 in babies from trials conducted in 1990s

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carach</td>
<td>1/12</td>
<td>0/6</td>
</tr>
<tr>
<td>Carlan</td>
<td>1/11</td>
<td>4/13</td>
</tr>
<tr>
<td>Gartie</td>
<td>21/33</td>
<td>28/40</td>
</tr>
<tr>
<td>Kari</td>
<td>34/91</td>
<td>46/90</td>
</tr>
<tr>
<td>Lewis</td>
<td>7/38</td>
<td>17/39</td>
</tr>
<tr>
<td>Silver</td>
<td>43/54</td>
<td>34/42</td>
</tr>
<tr>
<td>Amorim</td>
<td>23/100</td>
<td>43/100</td>
</tr>
<tr>
<td>Dexiprom Study Group</td>
<td>32/102</td>
<td>27/100</td>
</tr>
<tr>
<td>Guiblan</td>
<td>14/70</td>
<td>24/65</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 511 495

Total events: 176 (Treatment), 223 (Control)
Test for heterogeneity: Chi² = 18.72, df = 8 (P = 0.02), I² = 57.3%
Test for overall effect: Z = 3.67 (P = 0.0002)

09 in babies from trials conducted in 2000s

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fekih</td>
<td>3/63</td>
<td>19/68</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 63 68

Total events: 3 (Treatment), 19 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.97 (P = 0.003)
Cerebral Palsy & Developmental Delay

Relative risk = 0.60 (0.34 to 1.00)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liggins</td>
<td>3/129</td>
<td>2/107</td>
</tr>
<tr>
<td>Schutte</td>
<td>2/51</td>
<td>2/35</td>
</tr>
<tr>
<td>Collaborative Group</td>
<td>9/200</td>
<td>15/206</td>
</tr>
<tr>
<td>Kari</td>
<td>5/50</td>
<td>7/32</td>
</tr>
<tr>
<td>Amorim</td>
<td>1/60</td>
<td>2/34</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>490</td>
<td>414</td>
</tr>
<tr>
<td>Total events:</td>
<td>20 (Treat)</td>
<td>28 (Cont)</td>
</tr>
</tbody>
</table>

Relative risk = 0.60 (0.34 to 1.00)

Relative risk = 0.49 (0.24 to 1.00)

Cochrane Review
Robertson & Dalziel
“Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs. The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health.”

*NIH Consensus Conference 1994*
Lessons From the Liggins Legacy

“Can do” approach - with opportunity
Independence of thought
A “Prepared mind” - across disciplines
Role of serendipity
Perinatal Research in New Zealand: Why Do We Do It?

We have something to offer

We need the skills

We can’t afford not to
Impaired Glucose Tolerance in Men Aged 64yrs According to Birthweight

Barker, DJP. Mothers, Babies and Health in Later Life. Churchill Livingstone, 1998
Glucose Tolerance is Related to Birthweight in 5 Month Old Lambs

$r^2=0.26$, $p=0.003$, adjusted for nutrition group and current weight
The Glucocorticoid Hypothesis

Fetal exposure to excess glucocorticoid

↓

Impaired fetal growth
Cardiovascular changes
Metabolic changes
CNS changes
(Glucocorticoid receptors)

↓

Postnatal changes

Aims

To determine if antenatal exposure to betamethasone for prevention of RDS alters:

- Cardiovascular risk factors
- Hypothalamic-pituitary-adrenal axis function
- Lung function
- Reproductive function
- Bone density
- Psychological function
- Health related quality of life

at 30 years of age.
<table>
<thead>
<tr>
<th></th>
<th>8 Treatment course</th>
<th>24 Stage of labour at entry</th>
<th>32 Place of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 First</td>
<td>0 Before labour</td>
<td>0 Normal</td>
</tr>
<tr>
<td></td>
<td>2 Second</td>
<td>In labour: dilatation</td>
<td>5 Elsewhere (specify)</td>
</tr>
<tr>
<td></td>
<td>3 Third</td>
<td>&lt; 2cm.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-3 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug given</td>
<td>3 3-4 cm</td>
<td>33-34 Single or multiple</td>
</tr>
<tr>
<td></td>
<td>1 Betamethasone</td>
<td>4 &gt; 4 cm</td>
<td>31 1 Single</td>
</tr>
<tr>
<td></td>
<td>5 Control</td>
<td></td>
<td>3 Twin</td>
</tr>
<tr>
<td></td>
<td>No. of doses given</td>
<td>25-26 Ethanol infusion</td>
<td>3 3 Triplet</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Total duration:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-13</td>
<td>Maturity at entry. weeks days</td>
<td>0 None</td>
<td>34 Order</td>
</tr>
<tr>
<td></td>
<td>25 1</td>
<td>1 &lt; 12 hr</td>
<td>0 Single</td>
</tr>
<tr>
<td></td>
<td>(if uncertain estimate weeks, 9 in Col. 9)</td>
<td>2 12-24 hr</td>
<td>1 First</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 24-36 hr</td>
<td>2 Second</td>
</tr>
<tr>
<td>14-16</td>
<td>Maturity at delivery (as above)</td>
<td>4 36-48 hr</td>
<td>3 Third</td>
</tr>
<tr>
<td></td>
<td>35 6</td>
<td>5 &gt; 48 hr +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 Not known</td>
<td></td>
</tr>
<tr>
<td>17-19</td>
<td>Entry-delivery interval (days and completed</td>
<td>26 Interval start-delivery</td>
<td>35 Presentation</td>
</tr>
<tr>
<td></td>
<td>eighths of a day)</td>
<td>N.A.</td>
<td>0 Vertex</td>
</tr>
<tr>
<td></td>
<td>044</td>
<td>1 &lt; 24 hr</td>
<td>1 Breech</td>
</tr>
<tr>
<td></td>
<td>(Days and completed eighths of a day)</td>
<td>2 24-48 hr</td>
<td>2 Other(specify)</td>
</tr>
<tr>
<td>20-21</td>
<td>Final urinary oestriol 99 = not done or NK</td>
<td>2-7 days</td>
<td>9 Not known</td>
</tr>
<tr>
<td></td>
<td>15 mg</td>
<td>4 1-3 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 3 weeks +</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 Not known</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Liquor lecithin analysis</td>
<td>27-28 Salbutamol infusion</td>
<td>36 Method of delivery</td>
</tr>
<tr>
<td></td>
<td>0 No</td>
<td>(Codes as for cols 25-26)</td>
<td>0 Spontaneous</td>
</tr>
<tr>
<td></td>
<td>5 Yes</td>
<td></td>
<td>1 Forceps vertex</td>
</tr>
<tr>
<td>23</td>
<td>Delivery planned?</td>
<td>27 Duration 28 interval</td>
<td>2 Operative breech</td>
</tr>
<tr>
<td></td>
<td>0 No</td>
<td>1</td>
<td>3 Caesarean elective</td>
</tr>
<tr>
<td></td>
<td>If yes, indication:</td>
<td>2</td>
<td>4 Caesarean non-elective</td>
</tr>
<tr>
<td></td>
<td>1 H.O.P. Syndromes</td>
<td>3</td>
<td>9 Not known</td>
</tr>
<tr>
<td></td>
<td>2 Isoimmunisation</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Placenta praevia</td>
<td>5</td>
<td>Indication(s) for</td>
</tr>
<tr>
<td></td>
<td>4 Diabetes</td>
<td>9</td>
<td>operative delivery:</td>
</tr>
<tr>
<td></td>
<td>9 Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Date of delivery: 04 19 0
Methods - Tracing

Participant

Mother

Siblings

NWH archived records

Birth register

NHI computer database

Electoral role

Telephone directory

Internet directories

If lost to follow-up

Death register

Steroid Follow-up Study
Residing overseas
(total = 80)

- USA 8
- Canada 1
- England 25
- Wales 2
- Ireland 1
- Spain 1
- Italy 1
- Israel 1
- Hong Kong 1
- Australia 36
- Cook Islands 1
- Peru 1
- Bermuda 1
Antenatal exposure to betamethasone for the prevention of neonatal RDS does not alter:

- Body size
- Blood pressure
- Fasting lipids
- Fasting cortisol
- Lung function
- Reproductive function
- Prevalence of diabetes & cardiovascular disease
- Bone density at 30 years of age

Dalziel et al, Lancet 365, 1856, 2005
Antenatal exposure to betamethasone for the prevention of neonatal RDS does not alter:

• Cognitive functioning
• Attention
• Psychiatric morbidity
• Handedness
• Health related quality of life

at thirty-one years of age

Dalziel et al, BMJ 331: 665, 2005
75g Oral Glucose Tolerance Test

- **Insulin (mIU/L)**
  - Betamethasone
  - Placebo

- **Glucose (mmol/L)**

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- p=0.014
- p=0.047

**Steroid Follow-up Study**
Repeat Courses of Antenatal Steroids

“Time relations of therapy were important; it was effective only if delivery could be delayed for at least 24 hours, and no longer than 7 days … This suggests that if very premature delivery has not occurred within 7 days, and again threatens, therapy might need to be repeated at intervals of not less than 7 days …”

Howie & Liggins 1982
Australasian Collaborative Trial of Repeat Doses of Prenatal Steroids to Women at Risk of Preterm Birth for the Prevention of Neonatal Respiratory Disease.
## Primary Infant Outcomes After Repeat Prenatal Steroids

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Trials</th>
<th>Repeat n</th>
<th>Repeat N</th>
<th>Single n</th>
<th>Single N</th>
<th>RR</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>8</td>
<td>463</td>
<td>1603</td>
<td>565</td>
<td>1603</td>
<td>0.83</td>
<td>0.75 – 0.91</td>
<td>0.0002</td>
</tr>
<tr>
<td>Severe RDS</td>
<td>6</td>
<td>267</td>
<td>2427</td>
<td>321</td>
<td>2399</td>
<td>0.80</td>
<td>0.56 – 1.14</td>
<td>0.22</td>
</tr>
<tr>
<td>Composite serious outcome</td>
<td>7</td>
<td>438</td>
<td>2561</td>
<td>519</td>
<td>2533</td>
<td>0.84</td>
<td>0.75 – 0.94</td>
<td>0.002</td>
</tr>
<tr>
<td>Death</td>
<td>9</td>
<td>96</td>
<td>2791</td>
<td>1102</td>
<td>2763</td>
<td>0.93</td>
<td>0.70 – 1.23</td>
<td>0.60</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>8</td>
<td>181</td>
<td>2709</td>
<td>170</td>
<td>2684</td>
<td>1.06</td>
<td>0.87 – 1.30</td>
<td>0.54</td>
</tr>
<tr>
<td>IVH</td>
<td>6</td>
<td>129</td>
<td>1533</td>
<td>137</td>
<td>1532</td>
<td>0.94</td>
<td>0.75 – 1.18</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Cochrane Review, Crowther, McKinlay, Middleton, Harding 2010
## Effects on Birth Weight

<table>
<thead>
<tr>
<th>Trials</th>
<th>Repeat N</th>
<th>Single N</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>9</td>
<td>2820</td>
<td>2806</td>
<td>-75.8</td>
<td>-1176, -34.0</td>
</tr>
</tbody>
</table>

Birth weight outcomes adjusted for gestational age did not differ statistically between treatment groups.

*Birth weight* *Z scores*: MD -0.11, 95% CI -0.23 to 0.00, p=0.06, 2 trials, 1256 infants.

*Birth weight* *MOM*: MD 0.00, 95% CI -0.03 to 0.03, p=1.00, 1 trial, 590 infants.

*Birth weight* *SGA*: RR 1.18, 95% CI 0.97 to 1.43, p=0.10, 7 trials, 3,973 infants.

Cochrane Review, Crowther, McKinlay, Middleton, Harding 2010
Outcomes at 6-8 Years After Repeat Antenatal Steroids

Growth
• Current size
• Body composition (DEXA)

Cardiovascular
• Ambulatory blood pressure

HPA Axis
• Circadian salivary cortisol pattern
• Basal and insulin-stimulated plasma cortisol

Metabolic
• Frequently sampled IV glucose tolerance test with arginine (minimal model)
Perinatal Research in New Zealand: Why Do We Do It?

We have something to offer
We need the skills
We can’t afford not to
Babies With Brain Damage

January 1994: Three babies with unusual and severe brain damage

Post mortem similar to that of a baby born June 1993: Thought to be middle cerebral artery infarction

Enquiries to pathologists, other causes sought, literature reviews, changes in practice reviewed

1994: further cases occurred

Mid-1994: First case-control study
First Case Control Study

Eleven babies, mean 884g, 26 weeks gestation
Two controls for each case, 50 variables compared
Association with  Low blood pressure
Breech presentation
Maternal infection

Presented at Perinatal meeting in Dunedin 1.12.94
No recognition of appearances
Discussion of possible causes included non-accidental injury
Contacted by a paediatrician after the meeting who pointed out the Birmingham article
“Postnatal encephaloclastic porencephaly - a new lesion?”
Cross et al, Archives of Disease in Childhood, 1992

Fifteen extremely preterm infants over 20 months
Previously unrecognised and distinctive pattern of severe brain injury
Fourteen died, one severely disabled

“It seems probably that they represent the effects of an as yet unidentified postnatal event”
Second Case Control Study

Birmingham contacted mid December 1994:
   ECPE related to the condition of baby at birth, hypotension
   and head movement from chest physiotherapy

Chest physiotherapy stopped on babies <1500g and <28 days old

Cerebral ultrasound results for last 3 years reviewed.
   Further cases identified

Case control study repeated to include numbers of chest physiotherapy treatments
<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 13)</th>
<th>Controls (n = 26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation</td>
<td>26 wk</td>
<td>26 wk</td>
<td>ns</td>
</tr>
<tr>
<td>Birth weight</td>
<td>870g</td>
<td>881g</td>
<td>ns</td>
</tr>
<tr>
<td>Cephalic</td>
<td>31%</td>
<td>81%</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypotension</td>
<td>92%</td>
<td>58%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CPT number &lt;4 weeks</td>
<td>79</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Chest Physiotherapy
National Women’s Hospital
1993-2002

1992-1994  Babies with brain damage
1995-1998  ACC claims
1999       Ministerial Inquiry
1999-2000  Lookback programme
2000-2002  Professional Council complaints
2001-2002  Legal suit
Perinatal Research in New Zealand: Why Do We Do It?

We need the skills:

- Chest physiotherapy
- SIDS
- Meningococcal vaccine
Perinatal Research in New Zealand: Why Do We Do It?

We can’t afford not to:
- Training and staffing
- Good healthcare
- Economics
New Therapies in Retrospect in 1997

**New Therapies Introduced**
- Surfactant*
- Extracorporeal membrane oxygenation
- High frequency oscillatory ventilation
- Patient triggered ventilation
- Nitric oxide

**Equipment Changes**
- Ventilators
- Phototherapy units
- Pulse oximeters
- Incubators
- CPAP circuits

**Changes in Use of Existing Therapies**
- Indomethacin*
- Dexamethasone*
- Intravenous amino acid mixtures, vitamins, trace elements*
- Phototherapy
- Oxygen monitoring
- Antenatal drug therapy: Indomethacin*, antibiotics*, TRH*
- Endotracheal suctioning
- Inotropes and pressors
- Volume expanders
- Antibiotics
- Management of central venous and arterial catheters
- Chest physiotherapy
- Skin care
- Apnoea management
- Intravenous immunoglobulin*
Remaining (Changed) “New” Therapies in 2010

New Therapies Introduced
(Surfactant*)

(High frequency oscillatory ventilation)
(Patient triggered ventilation*)
(Nitric oxide*)

Equipment Changes
(Ventilators)
Phototherapy units
(Pulse oximeters)
(Incubators)
(CPAP circuits)

Changes in Use of Existing Therapies
(Indomethacin*)

(Intravenous amino acid mixtures, vitamins, trace elements**)
Phototherapy
(Oxygen monitoring*)
(Antenatal drug therapy: antibiotics*)

Endotracheal suctioning
(Inotropes and pressors)

(Antibiotics)
(Management of central venous and arterial catheters)

(Skin care)
(Apnoea management)
If you think research is expensive, try disease.

Mary Lasker, 1901-94