The Future of Preterm Infants
Learning From the Past

Mirjam van Weissenbruch
The Netherlands:

13,000 (7%) preterm newborns (< 37 weeks of gestation)

2,500 (1.4%) preterm newborns < 32 wks of gestation
• 2006: 10 per 1000 births.

• 29% extreme preterms (22.0-25.6 weken)

• Mortality risk 935 per 1000 births (94%).
## Perinatal mortality in the Netherlands

<table>
<thead>
<tr>
<th>Zwangerschapsduur weken* (dagen)</th>
<th>Aantal geborenen*</th>
<th>Foetale sterfte</th>
<th>Neonatale sterfte</th>
<th>Perinatale sterfte #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>voor de geboorte</td>
<td>tijdens baring</td>
<td>totaal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>22°– 24°wk</td>
<td>618</td>
<td>191</td>
<td>188</td>
<td>379</td>
</tr>
<tr>
<td>25°– 31°wk</td>
<td>1908</td>
<td>219</td>
<td>39</td>
<td>258</td>
</tr>
<tr>
<td>32°–36°wk</td>
<td>10.595</td>
<td>149</td>
<td>20</td>
<td>169</td>
</tr>
<tr>
<td>≥ 37°wk</td>
<td>158.911</td>
<td>198</td>
<td>96</td>
<td>294</td>
</tr>
<tr>
<td>Onbekend</td>
<td>1402</td>
<td>40</td>
<td>13</td>
<td>53</td>
</tr>
<tr>
<td><strong>Totaal</strong></td>
<td><strong>173.434</strong></td>
<td><strong>797</strong></td>
<td><strong>356</strong></td>
<td><strong>1153</strong></td>
</tr>
</tbody>
</table>

*Tabel 2 Nederlandse Perinatale Sterftecijfers voor, tijdens en na de bevalling naar zwangerschapsduur

*) = levend en doodgeboren, #) = perinatale sterfte: foetale en vroeg neonatale sterfte / Bron: PRN 2007\textsuperscript{10c}
US birth and mortality rates VLBW infants

EXHIBIT 3

<table>
<thead>
<tr>
<th>Deaths per 1,000 live births</th>
<th>Percent of all live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1.5</td>
</tr>
<tr>
<td>350</td>
<td>1.4</td>
</tr>
<tr>
<td>300</td>
<td>1.3</td>
</tr>
<tr>
<td>250</td>
<td>1.2</td>
</tr>
<tr>
<td>200</td>
<td>1.1</td>
</tr>
</tbody>
</table>


**NOTES:** Dashed line relates to the left y axis and denotes deaths per 1,000 live births among very-low-birthweight infants. Solid line relates to the right y axis and denotes the percentage of live births that were very-low-birthweight infants. Data on infant mortality were unavailable for 1992–1994.

Increased VLBW survival has paralleled improvements in

- **Prenatal care**
  - corticosteroids
- **Obstetric care**
  - standardization of prenatal care, ultrasonography, tocolytic therapy to delay delivery; antibiotic use, antenatal fetal surveillance
- **Neonatal care**
  - ventilatory support, surfactant
Bussemaker wil richtlijn vroeggeborenen

Door een onzer redacteuren

DEN HAAG, 12 MAART. Staatssecretaris Bussemaker (Volksgezondheid, PvdA) wil dat artsen een richtlijn opstellen over het omgaan met extrem vroeg geborenen kinderen. Die richtlijn, zegt zij, kan reden zijn voor een discussie over de levensvatbaarheidsgrens van foetussen.

De levensvatbaarheid van een kind buiten de baarmoeder is gekoppeld aan de termijn waarop abortus nog is toegestaan. Deze termijn ligt nu op 24 weken zwangerschap. Bussemaker ging gisteren in een Kameroverleg over medische ethiek in op de vraag van Kamerlid Ormel (CDA) om een onderzoek naar deze termijn. Volgens Ormel is de levensvatbaarheid van jonge foetussen door medisch-wetenschappelijke ontwikkelingen vergroot, waardoor de abortusgrens wellicht ook moet.

Bussemaker noemde dit de meest ingewikkeldte medisch ethische discussie. Hoewel zij de deur op een kiertje zette voor een discussie over de verlaging van de abortusgrens, zei zij ook dat de evaluatie van de abortuswet geen aanleiding gaf om de grens te bekorten. Een meerderheid in de Tweede Kamer steunt haar daarin.

In Nederland is afbreking van een zwangerschap toegestaan tot 24 weken. Die termijn staat niet in de wet, maar is de uitkomst van het politiek-maatschappelijk debat over de afbreking van zwangerschap. Toen de wet in 1981 van kracht werd, gingen artsen er van uit dat kinderen levensvatbaar waren vanaf 6 maanden zwangerschap. Kinderen die vóór 6 maanden worden geboren, worden niet behandeld, waardoor zij overlijden. Vanwege een zekerheidsmargin van 2 weken, kan er nu abortus plaatsvinden tot 24 weken.
Active care of the newborn from 24 0/7 weeks, unless...
- parental consent is required
Developments in Neonatology

Although the survival rate will increase it remains important that medical professionals continue keep asking whether a reasonable minimal quality of life can be expected.
Mortality and long-term sequelae are disproportionally more prevalent among infants born very early.

Over the last decades:
Survival rates have increased dramatically (modern medical technology)
Incidence of serious morbidity does not decrease!!

At 19 years of age:\(^1\):
- 13% has moderate to severe handicaps
- 53% has at least a mild problem
- 3x more unemployed/ not in school

more focus on short- and long-term outcome

\(^1\) Hille et al. Pediatrics 2007
Infants with the lowest gestational age are at greatest risk for short-term morbidities:

- Respiratory distress syndrome
- Patent ductus arteriosus
- Intraventricular hemorrhage
- Necrotizing enterocolitis
- Late onset sepsis
- Bronchopulmonary dysplasia
- ROP
length of hospitalization and PCA at discharge according to GA at birth among VLBW infants and who survived to discharge.

![Bar chart showing length of stay or PMA at discharge vs Gestational Age at Birth]


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Survival to discharge according to GA among VLBW infants


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### Long term outcome 24 w

<table>
<thead>
<tr>
<th></th>
<th>Tyson 2y</th>
<th>Kutz 30mo</th>
<th>Robertson 3y</th>
<th>De Groote 3y</th>
<th>Steinmache 6y</th>
<th>Wood 30mo</th>
<th>Marlow 6y</th>
<th>Johnson 11y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival as % of all live borns</strong></td>
<td>56 %</td>
<td>63 %</td>
<td>x</td>
<td>36 %</td>
<td>68 %</td>
<td>26 %</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td><strong>Survival as % of all admitted to the NICU</strong></td>
<td>x</td>
<td>63 %</td>
<td>77%</td>
<td>39 %</td>
<td>68 %</td>
<td>33 %</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td><strong>Died or severe impairment as % of all live borns</strong></td>
<td>57 %</td>
<td>56 %</td>
<td>33 %</td>
<td>79 %</td>
<td>45 %</td>
<td>55 %</td>
<td>54 %</td>
<td>53 %</td>
</tr>
<tr>
<td><strong>Severe impairment as percentage of all survivors</strong></td>
<td>23 %</td>
<td>29 %</td>
<td>12 %</td>
<td>36 %</td>
<td>20 %</td>
<td>25 %</td>
<td>29 %</td>
<td>21 %</td>
</tr>
<tr>
<td><strong>Survival without severe impairment as percentage of all survivors</strong></td>
<td>77 %</td>
<td>71 %</td>
<td>88%</td>
<td>64 %</td>
<td>80 %</td>
<td>75 %</td>
<td>79 %</td>
<td>81 %</td>
</tr>
<tr>
<td><strong>Survival with mild impairment as percentage of all survivors</strong></td>
<td>x</td>
<td>Other 47%</td>
<td>x</td>
<td>x</td>
<td>35 %</td>
<td>x</td>
<td>36 %</td>
<td>33 %</td>
</tr>
<tr>
<td><strong>Survival without any impairment as percentage of all survivors</strong></td>
<td>50 %</td>
<td>24 %</td>
<td>88 %</td>
<td>27 %</td>
<td>30 %</td>
<td>46 %</td>
<td>14 %</td>
<td>16 %</td>
</tr>
<tr>
<td><strong>MDI/MPC</strong></td>
<td>x</td>
<td>76 ± 24</td>
<td>x</td>
<td>x</td>
<td>Median 84 (39-111)</td>
<td>85 ± 11</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>PDI</strong></td>
<td>x</td>
<td>82 ± 23</td>
<td>x</td>
<td>x</td>
<td>GMFCS normal 50 %, more than GMFCS 2 in 15 %</td>
<td>87 ± 12</td>
<td>Normal 7% Minimal funct loss 11% CP 18%</td>
<td>x</td>
</tr>
<tr>
<td><strong>Qualified for regular school as percentage of all survivors</strong></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>45 %</td>
<td>x</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
<td><strong>Survival as % of all live borns</strong></td>
<td>75 %</td>
<td>79 %</td>
<td>X</td>
<td>62 %</td>
<td>83 %</td>
<td>43 %</td>
<td>=</td>
<td>=</td>
</tr>
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<td>X</td>
<td>82 %</td>
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<td>89 %</td>
<td>51 %</td>
<td>=</td>
<td>=</td>
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<td>63 %</td>
<td>61 %</td>
</tr>
<tr>
<td><strong>Severe impairment as percentage of all survivors</strong></td>
<td>17 %</td>
<td>6 %</td>
<td>24 %</td>
<td>29 %</td>
<td>21 %</td>
<td>22 %</td>
<td>18 %</td>
<td>11 %</td>
</tr>
<tr>
<td><strong>Survival without severe impairment as percentage of survivors</strong></td>
<td>83 %</td>
<td>94 %</td>
<td>76 %</td>
<td>71 %</td>
<td>79 %</td>
<td>78 %</td>
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<td>X</td>
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<td>16 %</td>
</tr>
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<td><strong>MDI/MPC</strong></td>
<td>X</td>
<td>96 ± 11</td>
<td>X</td>
<td>Normal 44% Mild 26% Moderate 11% Severe 19%</td>
<td>Median 91 (20-122)</td>
<td>84 ± 12</td>
<td>Normal 33% Mild 32% Moderate 19% Severe 17%</td>
<td>X</td>
</tr>
<tr>
<td><strong>PDI</strong></td>
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<td>87 ± 13</td>
<td>Normal 79 Minimal func. Loss 11 CP 10</td>
<td>X</td>
</tr>
<tr>
<td><strong>Qualified for regular school as percentage of all survivors</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>61 %</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Long-term morbidities

Infants with the lowest gestational age are at greatest risk for long-term morbidities:

- increased incidence of cerebral palsy
- mental retardation
- sensory impairments
- minor neuromotor dysfunction
- language delays
- visual-perceptual disorders
- learning disability
- behavior problems
- Metabolic syndrome
Risk factors for metabolic syndrome in (ex)preterms
Embryo and Fetal Growth

- Embryo
- Blastocyst
- Ovum
- 11 weeks
- 7 1/2 weeks
- 4 weeks
- 18 days
- 24 days
- 6 1/2 weeks
- 9 weeks
- 15 weeks

Fertilization age

Menstrual age in weeks

- Last menstrual period
- Ovulation
- Implantation
- First missed period
- Second missed period
- Hegar's sign
Programming describes the process whereby a stimulus or insult, e.g. changes in the nutritional, hormonal and metabolic environment afforded by the mother at a sensitive or critical period of development has lasting or lifelong significance on the structure and physiology of her offspring.
critical windows?

Exogenous vs genetic

Stimulus or insult in a critical window has permanent effect on structure and function

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Godfrey 2010
Low birth weight is associated with chronic diseases in adulthood:

- hypertension
- cardiovascular diseases
- insulin resistance
- type II diabetes
- male infertility
- polycystic ovary syndrome

Consequences of IUGR
Insulin sensitivity in prepubertal children

SGA vs AGA

Insulin sensitivity

MA Veening JCEM 2002;87:4657-4661
Consequences of Extra Uterine Third Trimester

- Growth failure
- Short stature
- Reduced final height
- Increased fat mass
- Insulin resistance
- Glucose intolerance
- Hypertension

Risk factors for cardiovascular disease

Third trimester programming of body functions by

‘Golden window’
Changes in weight SDS in preterms from birth until 3 months corrected age
Long-term morbidities

Risk factors metabolic syndrome
Glucose Regulation in Young Adults with Very Low Birth Weight

Petteri Hovi et al

Risk factors metabolic syndrome

N=163 VLBW; N=169 normal birth weight

Oral glucose tolerance test
Blood pressure
lipids
HOMA +18.9%

Hovi NEJM 2007

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2-hrs glucose +6.7%

P. Hovi NEJM 2007

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fasting insulin +16.7%
2-hrs insulin +40%
Systolic blood pressure

P. Hovi NEJM 2007

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Diastolic blood pressure

![Graph showing diastolic blood pressure comparison between VLBW and CON groups.](image-url)

P. Hovi NEJM 2007

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POPS

project on preterm and small for gestational age 1983

Walther FI, den Ouden AL, Verloove-Vanhorick SP

early human development 2000
POPS cohort

- 1338 young adults
- 94% <32 wks < 1500 gr

In sub cohort metabolic risk factors:
- Insulin sensitivity (M-value)
- 24 hrs blood pressure
- Lipids (mixed meal test)
Insulin sensitivity
Hyperinsulinemic euglycemic clamp

Insulin bolus 6 mU/kg iv

Insulin infusion (60 mU/kg/hr)

20 % glucose infusion

Time (min) →
Insulin sensitivity in young adults born preterm

![Bar chart showing insulin sensitivity in prem SGA, prem AGA, and CON groups. The x-axis represents the groups (prem SGA, prem AGA, CON), and the y-axis represents the M-value. The chart includes data from J. Rotteveel Pediatrics 2008.]
height and insulin sensitivity

J. Rotteveel Pediatrics 2008

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Weight and insulin sensitivity

The Future of Preterm Infants. Learning From the Past

J. Rotteveel Pediatrics 2008
Systolic blood pressure

- Prem SGA
- Prem AGA
- CON

mmHg

J. Rotteveel Pediatrics 2008

The Future of Preterm Infants. Learning From the Past
height and systolic blood pressure

J Rotteveel Pediatrics 2008

The Future of Preterm Infants. Learning From the Past
Weight and systolic blood pressure

The Future of Preterm Infants. Learning From the Past

J. Rotteveel Pediatrics 2008
MIXED MEAL TEST
Males

The Future of Preterm Infants. Learning From the Past

J.Rotteveel Diabetologia 2008
The Future of Preterm Infants. Learning From the Past

J. Rotteveel, Diabetologia 2008
The Future of Preterm Infants. Learning From the Past

J. Rotteveel Diabetologia 2008
Preterm born young adults compared to term born young adults have

- a lower insulin sensitivity
- higher blood pressure
- Basal lipids normal; only effect after mixed meal

- Catch up growth is a risk factor
The goal of nutrition in the preterms

- 50 studies now support the concept that faster growth in infancy increases later risk factors for CVD (Nobili 2008)

- to optimize growth and neurodevelopmental outcomes while avoiding both short-term and long-term toxicities and adverse outcomes.

- Overall feeding strategies have focused on growing the very preterm infant at the rate of the fetus, or along a growth curve determined by the birth weight.
Postnatal growth in preterms

The neonatologist's dilemma:

1. what are optimal growth rates

2. catch-up growth after critical growth windows or beneficial "undernutrition" in preterm infants

3. key nutrients for which timing and amount of nutrient delivery will effect optimal growth and neurodevelopmental outcome
Postnatal growth in preterms

Improve early nutrition of the preterm infant, and follow the minimal requirements for nutrition established by the growth of the normal fetus at the same gestational age

- amino acids 3-4 g/kg/day (< 30 weeks)
- glucose 6-10 mg/kg/min
- lipids 2-3 g/kg/day

W. Hay Neonatology 2008
The Impact of Timing