CHAPTER 3

Ethics of maintaining extremely preterm infants

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Summary

Advances in pharmacology and technology have pushed back the limits of viability to 23–24 weeks of gestation at the expense of an increasing number of survivors with disabilities. Treatment of these extremely preterm infants should be based on a thorough determination of diagnosis and prognosis, followed by decision-making on the basis of futility of treatment or quality-of-life issues and counseling of parents. This paper reviews survival rates and outcome of infants under 26 weeks of gestation born in Europe and the rest of the world and discusses the role of parents and the influence of condition at birth, gender, and birth weight in ethical decision-making on behalf of these infants. Dutch guidelines on treatment of extremely preterm infants at birth are presented to assist the clinician in facing the challenging ethical, moral, legal, and emotional dilemmas that surround this hot topic in perinatology.

Practice points

• Survival at 22 weeks of gestation has not improved over the past three decades
• Higher survival in pro-active treatment versus a more selective approach
• Surviving infants born at 23–24 weeks of gestation show high rates of disabilities
• Condition at birth is only partially related to survival and later outcome
Introduction

Over the past ten years the ethics of maintaining extremely preterm infants has become a hot topic at medical conferences and is discussed frequently in the medical press. Newer ventilation techniques and medication (antenatal steroids and surfactant) have dramatically improved survival of these tiny infants, but at the expense of worries about their neurodevelopment, growth and later academic achievement. More and more controversy has evolved over whether we are doing the right thing in neonatology.\textsuperscript{1} We continue to search for the limits of viability and place it somewhere between 23 and 25 weeks of gestation. Below 23 weeks, it is biologically almost impossible to ventilate a preterm infant because of the immature structure and physiology of the foetal human lung. Inconsistency of pregnancy data or biological variations may account for the occasional survivors who are reported at this gestational age.\textsuperscript{2} Since the mid-1980s a gestation of 23 weeks has been an insurmountable biological barrier and neither surfactant, steroids nor new ventilation modalities have been able to change this.\textsuperscript{2}

In an ideal world, guidelines about the limits of viability should be readily available. To develop these, one needs recent data about survival and later outcome. Data on survival of infants born at the margins of viability are difficult to compare because survival rates are dependent on the denominator used to calculate them, i.e. on the number of all births (including stillbirths), all live born infants or all infants admitted to the Neonatal Intensive Care Unit (NICU). Survival rates for unborn infants are lower than survival rates reported for infants admitted to the NICU.\textsuperscript{3} This should be kept in mind when counselling parents before threatening or imminent preterm delivery. Survival will be higher in a neonatal unit which only admits inborn infants than in a regional referral unit admitting outborn infants. Different attitudes from obstetricians and neonatologists towards resuscitation will also influence survival numbers: a pro-active management results in higher survival rates.\textsuperscript{4,5} However, the ultimate goal reaches beyond mere survival and should be to survive without major disabilities. Despite an increase in survival rates of extremely preterm infants during the last decade, this has not been associated with a reduction in disabilities. Most studies report a steady prevalence of disabilities, i.e. an identical increase in the absolute numbers of survivors with and without disabilities, or an increase in the percentage of infants with disabilities.\textsuperscript{6}
In this paper we present an overview of survival rates and later outcome of extremely preterm infants born in Europe and the rest of the world and discuss the factors which play an important role in decision-making on behalf of them.

Outcome

Survival

Table 1 shows survival of extremely preterm infants, according to gestational age, in various European countries. The reported percentages are the percentages of live born infants who survived until discharge. Survival is relatively high in Norway, Sweden, Germany and Austria. Markestad et al.\textsuperscript{7} from Norway contribute their good outcome to a high percentage (95\%) of inborn infants, good perinatal care and instillation of surfactant in the delivery room in two-thirds of the infants. Serenius et al.\textsuperscript{8} report a survival rate similar to their countryman Hanson in the Northern part of Sweden. The higher survival rate and pro-active attitude is in sharp contrast with the lower survival rate in the Southern part of Sweden, where a more selective approach is used. Herber-Jonat et al.\textsuperscript{5} state that the relatively high survival in Germany is also the result of pro-active treatment. Weber et al. who report the results of 16 NICU’s in Austria found their data to be comparable with the rest of Europe, although at the upper range.\textsuperscript{9} In Denmark, where continuous positive airway pressure (CPAP) is the ventilatory support of choice, survival data are higher when calculated as a percentage of actively treated infants compared to a percentage of the total number of live born infants.\textsuperscript{3}

Table 2 gives some examples of survival of extremely preterm infants born outside Europe, with relatively high survival rates in cases of extremely short gestation (23 weeks).

Neurodevelopmental and cognitive outcome

The problem of predicting outcome of these very preterm infants is perfectly described by Jobe in an editorial in which he asks the ultimate question ”Is any very preterm infant normal?”\textsuperscript{10} Predictors of early outcome do not predict later outcome very well. Levene, after reviewing the most recent best available data, is uncertain about whether it is right to provide intensive care for all babies referred to their service: only less than 25\% of babies born alive ≤ 24 weeks survive with-
Table 1. Survival (until discharge, as % of live born infants) and major complications among extremely preterm infants in Europe.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of birth</th>
<th>Survival (% of live born infants)</th>
<th>Major complications (% at time of hospital discharge, &lt; 26 weeks)</th>
<th>Long term outcome in infants &lt;26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>23 wks</td>
<td>24 wks</td>
<td>25 wks</td>
</tr>
<tr>
<td>UK⁴¹ (EPICure)</td>
<td>1995</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France⁵⁵ (EPIPAGE)</td>
<td>1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium¹⁹ (EPIBel)</td>
<td>1999–2000</td>
<td>6</td>
<td>29</td>
<td>56</td>
</tr>
<tr>
<td>Netherlands⁴² (LFUPP)</td>
<td>1996–1997</td>
<td></td>
<td>40</td>
<td>64</td>
</tr>
<tr>
<td>Germany⁵</td>
<td>1999–2003</td>
<td>82</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Austria⁹</td>
<td>1999–2001</td>
<td>24</td>
<td>57</td>
<td>74</td>
</tr>
<tr>
<td>Norway⁷</td>
<td>1999–2000</td>
<td>39</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Sweden⁸</td>
<td>1992–1998</td>
<td>43</td>
<td>63</td>
<td>77</td>
</tr>
<tr>
<td>Finland¹⁸</td>
<td>1995–1996</td>
<td>14</td>
<td>42</td>
<td>75</td>
</tr>
<tr>
<td>Denmark⁴³</td>
<td>1998–2001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wks = weeks; NA = not available; IVH = intraventricular haemorrhage ≥ grade 3; PVL = cystic periventricular leucomalacia; ROP = retinopathy of prematurity ≥ grade 3; BPD = bronchopulmonary dysplasia = oxygen dependence at 36 weeks postmenstrual age; CP = cerebral palsy; IQ = intellectual quotient; MDI = mental development index; PDI = psychomotor development index. * = Infants ≤ 26 wks; † = ROP treated; ‡ = infants < 25 weeks; § = ROP ≥ grade 2.
Table 2. Survival (as % of live born infants) in extremely preterm infants in Canada, USA and Australia.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of birth</th>
<th>Survival (% of live born infants)</th>
<th>Major complications (%) at the time of hospital discharge, &lt; 26 weeks</th>
<th>Long term outcome in infants &lt; 26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>23 wks 24 wks 25 wks Remarks</td>
<td>IVH/PVL ROP BPD</td>
<td></td>
</tr>
<tr>
<td>Canada:</td>
<td>1991-1996</td>
<td>NA 56 68 *: % of infants admitted to NICU</td>
<td>NA 19 NA NA</td>
<td></td>
</tr>
<tr>
<td>Effer et al.</td>
<td>1996-1997</td>
<td>40 57 76</td>
<td>32 32 51</td>
<td></td>
</tr>
<tr>
<td>Chan* et al.</td>
<td>1991-1996</td>
<td>19</td>
<td>6†</td>
<td></td>
</tr>
<tr>
<td>USA:</td>
<td>1993-1997</td>
<td>46 59 82</td>
<td>21 22 35</td>
<td></td>
</tr>
<tr>
<td>El-Metwally et al.</td>
<td>1995-1996</td>
<td>30 50 74</td>
<td>6† NA 35†</td>
<td></td>
</tr>
<tr>
<td>Australia:</td>
<td>1991-1992</td>
<td>10 33 58</td>
<td>8/7 NA 69</td>
<td>11% CP both cohorts; 18 resp. 24% DQ &lt;-2 SD</td>
</tr>
<tr>
<td>Doyle et al.</td>
<td>1997</td>
<td>41 41 73</td>
<td>NA NA NA</td>
<td></td>
</tr>
</tbody>
</table>

NA = not available; IVH = intraventricular haemorrhage ≥ grade 3; PVL = cystic periventricular leucomalacia; ROP = retinopathy of prematurity ≥ grade 3; BPD = bronchopulmonary dysplasia = oxygen dependence at 36 weeks postmenstrual age; CP = cerebral palsy; IQ = intellectual quotient. † = birth weight 500-750 grams (gestational age not available)
out major disability.\textsuperscript{11} MacDonald \textit{et al.}\textsuperscript{12} describe that 30-50\% of the survivors among live born infants <25 weeks have moderate or severe disability. Hintz \textit{et al.}\textsuperscript{13} found that in a cohort from the National Institute of Child Health Development [NICHD] Neonatal Research Network, born between 1996-1999 with gestational age <25 weeks and birth weight > 500 grams, 47\% had a Mental Developmental Index <70 (-2 SD) and 31\% had a Psychomotor Developmental Index <70 at 18-22 months; only 21\% was unimpaired. McElrath \textit{et al.} found a 33\% survival rate among live born 23-weekers and none were free from substantial morbidity.\textsuperscript{14} In a Canadian study of infants admitted to the NICU, only 11\% born at 23 weeks of gestation survived without major neonatal morbidity, 21\% at 24 weeks and 29\% at 25 weeks.\textsuperscript{15} Yu found a comparable 33\% severe disability rate in survivors born at 23 and 24 weeks.\textsuperscript{16}

In many European studies neonatal morbidity (Table 1) is used as a measure for short-term outcome, but, as mentioned before, early outcome does not predict later outcome very well. Hakanson \textit{et al.}\textsuperscript{4} from Sweden found that 43\% of infants born at or below 25 weeks who were actively treated, survived without broncho-pulmonary dysplasia (BPD), severe retinopathy (ROP) or severe intraventricular haemorrhage (IVH), compared to 28\% of the infants who were more selectively treated. Another Swedish study with an active treatment approach reported that 81\% of the survivors went home without severe ROP/IVH or periventricular leucomalacia and 36\% with BPD.\textsuperscript{17} Markestad \textit{et al.} from Norway described that 44\%, 49\% and 67\% of infants born at respectively 23, 24 and 25 weeks survived “without severe illness”.\textsuperscript{7} In a Finnish study 100\% of the infants born at 22–23 weeks and 62\% of the infants born at 24–25 weeks had at least one morbidity, defined as severe ROP/BPD/abnormal neurological examination at 36 weeks.\textsuperscript{18} In the EPIBel-study (gestational age <26 weeks) the chance to survive free from serious neonatal morbidity was less than 15\%.\textsuperscript{19} In the EPICure-study 49\% of survivors were disabled at 30 months (23\% were severe disabled).\textsuperscript{20} At 6 years of age cognitive impairment (<-2 SD) was present in 21\%, but this value rose to 41\% when the results were compared with those for their classmates.\textsuperscript{21} These high rates of disabilities remain a major challenge.
Decision-making

Role of the parents

Codes of medical ethics require doctors to give absolute priority to their patient’s welfare and have advocated that a physician has no duty to treat, especially when the treatment is futile (no chance, no purpose, unbearable) and that in this event the physician, and not the parents, has the authority to decide. Involvement of the parents in the decision-making process implies that they have a correct insight as to whether care is ethically justified, optional or still the subject of investigations.

In 2000 the results of a large European study were published in which a hypothetical case of extreme prematurity was presented to physicians and nurses (EURONIC group). In Great Britain and the Netherlands, parental wishes appeared to exert influence on the treatment decision. In many countries resuscitation guidelines mention an individual approach at a gestational age less than 24 weeks, with the goal of a parental consult. Recently Peerzada et al. published a survey in which they reported that 93% of the neonatologists in Sweden would resuscitate a very preterm infant if they considered treatment clearly beneficial, despite parental requests to withhold treatment. When the respondents considered treatment to be of uncertain benefit, only 25% would honour parental requests to withhold treatment. Thus in general the respondents envisioned a very limited parental role in delivery room decision-making for extremely preterm infants. This same survey was done earlier in the USA, also by Peerzada, and here 76% of the respondents would honour parental requests to withhold treatment when it was considered to be of uncertain benefit. Fear of litigation however, especially in the USA, might increase resuscitation of infants born near the limits of viability: Ballard et al. showed that there was a strong disposition among neonatologists towards respecting parental wishes in a hypothetical case of a 23-weeker and that this disposition was stronger when neonatologists were given additional reasons to be concerned about litigation.

Influence of condition at birth

There is much controversy about whether cardiopulmonary resuscitation in the delivery room always indicates a uniformly bad prognosis. However, the characteristics of the resuscitation may predict outcome. The question is if there is any ethically relevant information that can be obtained by examining an infant
of 23 or 24 weeks’ gestation immediately after birth and whether this information is critical in making a decision to resuscitate or not. Nevertheless, 75% of the Swedish physicians in the earlier mentioned study of Peerzada\textsuperscript{24} found the condition of the infants at delivery to be (very) important in delivery room decision-making. Shankaran studied 1,016 infants born with a gestational age $\leq 24$ weeks, birth weight $\leq 750$ grams and a 1-minute Apgar score $\leq 3$. She found 60% to have a severe neurological impairment at 18–22 months.\textsuperscript{27} Janvier and Barrington suggest that extensive resuscitation can be followed by intact survival if the resuscitation required is brief. After 3 minutes of active resuscitation and a continuous heart rate $< 100$ beats/minute, short-term outcome is very poor.\textsuperscript{28} Often the decision to continue intensive care is based on the efficacy of positive pressure ventilation in the delivery room, but this is not really evidence-based as nearly all publications on the efficacy of neonatal resuscitation define “resuscitation” as external cardiac massage, epinephrine administration or both.\textsuperscript{29}

**Influence of gender and birth weight**

Males tend to be at a disadvantage: most studies show significant better survival in preterm infants of female gender\textsuperscript{8,30–35} and a greater risk for impaired outcome in males.\textsuperscript{13,20} Morse\textsuperscript{36} described the best survival in black females and the worst survival in white males. Because of this male disadvantage, some authors advise to start active treatment in males one gestational age-week later than in females.\textsuperscript{37}

The question remains whether survival without severe disabilities is possible when birth weight is below 500 grams. Lucey \textit{et al.}\textsuperscript{38} described an overall survival rate of 17% in a large cohort of infants who weighed 401–500 grams at birth. The survivors experienced a high rate of serious morbidities in the neonatal period. Because there is very little information about long-term outcomes of these foetal infants, Professor Jerold Lucey concluded we are all engaged in a large uncontrolled experiment.\textsuperscript{38}

**Conclusion**

There is widespread agreement that the aim of neonatal resuscitation should be a qualitatively acceptable survival of the child. In the USA guidelines state that it is inappropriate to resuscitate infants $< 400$ grams or $< 23$ weeks.\textsuperscript{12} Most
European and Canadian guidelines propose an active approach at 25 and 26 weeks, and a flexible approach at 23 and 24 weeks, depending on the opinion of the parents and the condition of the infant at birth. Nevertheless, more and more infants born at 23 and 24 weeks are resuscitated, especially in Sweden, Norway and Germany. In future studies the qualities of life of these infants, their neuro-developmental outcome and later academic achievements have to be shown.

In the Netherlands, extremely preterm infants are not routinely resuscitated and intensive care will be withdrawn if treatment is clearly futile. This policy is based on reports from the Dutch Medical Association and the Dutch Paediatric Association, which argue that withholding or withdrawing life-sustaining treatment in newborn infants with extremely poor prognoses is justifiable medical practice and that decisions should be taken by the medical and nursing team, together with well-informed parents. In Table 3 the Dutch guidelines are illustrated.

**Table 3.** Consensus on treatment of extremely premature infants at birth in the Netherlands (Dutch Paediatric Association, November 2005).

<table>
<thead>
<tr>
<th>Gestational age in weeks &amp; days</th>
<th>Intrauterine referral to level 3 perinatal center</th>
<th>Antenatal steroids</th>
<th>Caesarean section</th>
<th>Neonatal treatment in the delivery room</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24+0</td>
<td>No</td>
<td>No</td>
<td>Only on maternal indication</td>
<td>Family-centred comfort care</td>
</tr>
<tr>
<td>24+0 – 24+6</td>
<td>Indicated</td>
<td>Can be considered</td>
<td>Only on maternal indication</td>
<td>Family-centred comfort care, unless an active approach seems justified</td>
</tr>
<tr>
<td>25+0 – 25+6</td>
<td>Indicated</td>
<td>Yes</td>
<td>Rarely on foetal indication</td>
<td>Active approach, unless comfort care seems more justified</td>
</tr>
<tr>
<td>≥ 26+0</td>
<td>Indicated</td>
<td>Yes</td>
<td>Yes, unless an active approach does not seem justified</td>
<td>Active approach, unless comfort care seems more justified</td>
</tr>
</tbody>
</table>

If a child weighs less than 500 grams at birth, neonatal treatment will be withheld, except for family-centred comfort care.
Lorentz reminds us how difficult it is to decide before delivery, so an option could be to start intensive care to extremely preterm infants, then reconsider and eventually withdraw treatment. There are little data to support the predictive value of the condition at birth for survival. Levene warns us to keep in mind that treatment of extremely preterm infants (23 and 24 weeks of gestation) should be viewed as an experimental therapy with properly informed consent rather than the automatic process that it often becomes. Because of the often poor long-term neurological and mental outcome of these very immature infants, decisions about justified care should include the alternative of no life-supporting treatment.

References

32. Effer SB, Moutquin JM, Farine D, Saigal S, Nimrod C, Kelly E et al. Neonatal survival rates in