Variability in the management and outcomes of extremely preterm births across 5 European countries: a population-based cohort study.

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Abstract

**Objective:** To explore international variations in the management and survival of extremely low gestational age and birth-weight births.

**Design:** Area-based prospective cohort of births

**Setting:** 12 regions across Belgium, France, Italy, Portugal and the United Kingdom

**Participants:** 1449 live births and fetal deaths between 22⁺⁰⁻25⁺⁶ weeks gestation born in 2011-2012.

**Main outcome measures:** Percentage of births; recorded live born; provided antenatal steroids or respiratory support; surviving to discharge (with/without severe morbidities).

**Results:** The percentage of births recorded as live born was consistently low at 22 weeks and consistently high at 25 weeks but varied internationally at 23 weeks for those weighing 500g and over (range 33%-70%) and at 24 weeks for those under 500g (range 5%-71%). Antenatal steroids and provision of respiratory support at 22 to 24 weeks gestation varied between countries, but were consistently high for babies born at 25 weeks. Survival to discharge was universally poor at 22 weeks gestation (0%) and at any gestation with birthweight below 500g, irrespective of treatment provision. In contrast, births at 23 and 24 weeks weighing 500g and over showed significant international variation in survival (23 weeks: range: 0%-25%; 24 weeks range: 21%-50%), reflecting levels of treatment provision.

**Conclusion:** Wide international variation exists in the management and survival of extremely preterm births at 22 to 24 weeks gestation. Universally poor outcomes for babies at 22 weeks and for those weighing under 500g suggest little impact of intervention and support the inclusion of birth-weight along with gestational age in ethical decision-making guidelines.
WHAT IS ALREADY KNOWN

Large international differences exist in reported rates of extremely preterm and very low birth weight births.

Variation in survival rates at extremely low gestational age and extremely low birth-weight make counselling parents and decisions to initiate treatment difficult.

WHAT THIS PAPER ADDS

Wide international variation exists in the management of babies born at the limits of viability, which impacts on survival and makes international comparison of survival outcomes problematic.

Birth-weight should be included within ethical guidelines for counselling parents and making decisions around intensive treatment for births before 25 weeks.
INTRODUCTION

Advances in antenatal and neonatal care of very preterm birth have significantly improved the survival of babies who were once seen as non-viable [1-4]. Consequently, reconsideration of the limits of viability has been called for [5]. However, high rates of severe morbidity associated with survival at very early gestational age raise difficult ethical and policy questions when determining management policy, counselling parents and deciding whether to initiate intensive care [3, 6-8].

Wide regional and international differences in reported survival rates of extremely preterm births make these decisions more challenging, as a lack of consistent outcome data at early gestations prevent clear identification of criteria for intervention. The range of definitions of periviable birth has led to differences in the reported prevalence [9], and is likely to contribute to these wide international variations in reported survival rates [10]. The definition of viability based on gestational age, birth-weight and other factors may be influenced by variation in national legal registration criteria [11, 12], and clinical guidelines overlaid by clinicians’ perceived risk and parental opinions[13]. This will also lead to variations in the initiation and continuation of intensive care [10] and may impact on eligibility criteria for maternity and paternity benefits and funeral costs.

Currently little evidence exists regarding the impact of increased intensity of intervention on short and long term outcomes, particularly survival free of major morbidities. According to Lantos and Meadow[14] h policies that limit medical intervention in extremely preterm infants lead to low survival rates that further corroborate these policies and perpetuate the poor outcomes.. In the Netherlands however the national policy of non-resuscitation below 25 weeks gestation has recently been reviewed on the basis of technological progress and results published in the literature[15].

Using the data of a large European population-based study of extremely preterm births, we explore international differences in the frequency of recording of births as live born, provision of active
treatment and subsequent survival by gestational age and birth weight, across twelve regions in five countries.

METHODS

The EPICE (Effective Perinatal Intensive Care in Europe) study is an international area-based study aimed at assessing the use of evidence-based interventions for very preterm births[16] The study recruited a cohort of all still- and live births from 22+0 weeks to 31+6 weeks of gestation that occurred over 12 months in the period between April 2011 and September 2012 in 19 European regions (except in France where data were collected for six months) for a total of 7,336 cases covering over 850,000 annual births. Data were abstracted from medical records in obstetric and neonatal units using a standardised questionnaire with common pretested definitions. Gestational age was defined as the best obstetric assessment, using information on last menstrual period and routine ultrasound measures. Infants were followed up until discharge home from hospital or into long-term care or death.

Parental consent and ethics and data protection approval was obtained in each study region as required by national legislation.

For this study we used the data of all reported still- and live births between 22+0 and 25+6 weeks of gestation, with known information on birth-weight at delivery and outcome at discharge. We excluded terminations of pregnancy. Analyses were undertaken for gestation specific (22+0-22+6, 23+0-23+6, 24+0-24+6, and 25+0-25+6 weeks) and birth-weight specific (<500 grams; >=500 grams) groups. EPICE regions were combined by country, including only those countries with 5 or more births in each gestational age and birth-weight group to allow appropriate comparisons. This resulted in the inclusion of 12 regions across 5 countries: Flanders, Belgium; Burgundy, Ile-de-France and Northern regions, France; Emilia-Romagna, Lazio and Marche regions, Italy; Lisbon and Northern
regions, Portugal; East Midlands, Northern and Yorkshire and Humber regions, United Kingdom.

Although the official criteria for registration of stillbirths and live births may differ between these
countries (Table 1), the use of the common EPICE recruitment criteria allowed to overcome these
differences and provide comparable data across the 5 countries.

**Table 1**: Official gestational age and birth weight criteria* for registration of live births and
stillbirths by country.

<table>
<thead>
<tr>
<th>Country</th>
<th>Stillbirths</th>
<th>Live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>$\geq 25^{+5}$ weeks</td>
<td>No limit</td>
</tr>
<tr>
<td>France</td>
<td>$\geq 22^{+0}$ weeks OR $\geq 500$g</td>
<td>$\geq 22$ weeks OR $\geq 500$g</td>
</tr>
<tr>
<td>Italy</td>
<td>$\geq 25^{+5}$ weeks</td>
<td>No limit</td>
</tr>
<tr>
<td>Portugal</td>
<td>$\geq 24^{+0}$ weeks OR $&gt;500$g if gestational age unknown</td>
<td>No limit</td>
</tr>
<tr>
<td>UK</td>
<td>$\geq 24^{+0}$ weeks</td>
<td>No limit</td>
</tr>
</tbody>
</table>

*These criteria may differ from gestational age and birth weight limits for the statistical
recording of live births and stillbirths in some countries.

**Data analysis**

The percentage of births reported as live born was calculated for each country, gestational age and
birth-weight group based on the number of live births divided by the total number of still- and live
births in that group. Here provision of antenatal steroids and of respiratory support (i.e. any CPAP or
mechanical ventilation) were used as indicators of whether the baby was viewed as viable before
and after birth respectively. Survival outcomes were divided into four hierarchical groups: death
before discharge; survival to discharge with severe neonatal morbidity (comprising intraventricular
haemorrhage grade III or IV, cystic periventricular leukomalacia, retinopathy of prematurity stages III
to V, or severe necrotising enterocolitis); survival to discharge with bronchopulmonary dysplasia
(BPD) (defined by receiving oxygen at 36 weeks gestation); or survival without any of these severe
morbidities. BPD was assessed separately because there is large regional variability in respiratory
management and accepted oxygen saturation targets which can affect measurement of this variable
[17]. Information on the fraction of inspired oxygen (FiO₂) that would have allowed standardization
were not available in all regions. For the sake of comparability between countries and across
outcome indicators, unless stated differently the denominator used throughout was the number of
all births (still-and live births by gestational age and birth weight group in each country.), as while this may seem counterintuitive for measures such as respiratory support (since only live births would receive this type of care), it improves the comparability between countries where there are differences in whether a birth is reported as live or not.

Chi-squared tests were performed to assess whether the outcome measures varied significantly between countries.

Sensitivity analyses were undertaken excluding those fetuses known to have died in the antepartum period since death could have occurred several days before delivery leading to a decrease in birth-weight. Since the results were qualitatively the same only the analysis of all births are presented here.

RESULTS

There were 1500 births between 22rd and 25th weeks gestation across the five countries, of which 51 were excluded due to missing birth-weight (3.4%) leaving 1449 births for analysis. The rates of birth at 22 to 25 weeks gestation were similar across all five countries (Table 2) at 2.8 per 1000 births (range: 2.4 in Italy to 3.0 in France).
**Table 2:** Number and rate of births at 22-25 weeks gestational age in 5 European countries (based on data from 12 regions)

<table>
<thead>
<tr>
<th>Countries*</th>
<th>All gestations</th>
<th>22-25 weeks</th>
<th>Number of births</th>
<th>Rate of births 22-25 weeks per 1000 total births (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>22-23 weeks</td>
<td>24-25 weeks</td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>69395</td>
<td>201</td>
<td>34 51</td>
<td>2.90 (2.51; 3.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;500g &gt;=500g</td>
<td></td>
</tr>
<tr>
<td>France**</td>
<td>132683</td>
<td>399</td>
<td>86 105</td>
<td>3.01 (2.72; 3.32)</td>
</tr>
<tr>
<td>Italy</td>
<td>108679</td>
<td>266</td>
<td>59 65</td>
<td>2.44 (2.16; 2.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;500g &gt;=500g</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>61017</td>
<td>158</td>
<td>32 26</td>
<td>2.59 (2.20; 3.03)</td>
</tr>
<tr>
<td>UK</td>
<td>149241</td>
<td>425</td>
<td>73 73</td>
<td>2.85 (2.58; 3.13)</td>
</tr>
<tr>
<td>Total</td>
<td>521215</td>
<td>1449</td>
<td>284 320</td>
<td>2.78 (2.64; 2.93)</td>
</tr>
</tbody>
</table>

* Regions comprise: Belgium (Flanders); France (Burgundy, Ile-de-France, Northern); Italy (Emilia Romagna, Lazio, Marche); Portugal (Northern region, Lisbon); UK (East Midlands, Northern, Yorkshire)

** Study period: 01/06/2011-31/05/2012, except France: 01/04/2011-31/09/2011

**Recording of births as live born**

The percentage of births recorded as live born increased with increasing gestation and birth-weight (Figure 1 and table 3) but this trend varied between countries. There was a consistently low percentage recorded as live born for all births at 22 weeks gestation (<500g: 12.8%; >=500g: 24.5%)(Figure 1a) and for those at 23 weeks weighing less than 500g (18.2%) (Figure 1b). In contrast there was a significantly varied approach for births at 23 weeks gestation and birth weight 500g and over, with the UK and Italy having higher percentages of births recorded as live born (69.6% and 59.2% respectively) than in France, Belgium and Portugal (33.3% for all) (Figure 1b). Similarly there was a variation in approach to babies born at 24 weeks gestation weighing less than 500g with the lowest rates in France (5.0%) and the UK (12.5%) compared to Italy (71.4%) (Figure 1c).
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Less than 500g</th>
<th>500g or over</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Belgium</td>
<td>France</td>
</tr>
<tr>
<td>Births</td>
<td>N (All births)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>N (Live births)</td>
<td>2</td>
</tr>
<tr>
<td>Gestation</td>
<td>N (All births)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>N (Live births)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>% live born</td>
<td>0</td>
</tr>
<tr>
<td>Active</td>
<td>% (All births)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment</td>
<td>Any survival</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>Mortality free</td>
<td>0</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>Morbidity free</td>
<td>N (All births)</td>
</tr>
<tr>
<td></td>
<td>N (Live births)</td>
<td>3</td>
</tr>
<tr>
<td>Gestation</td>
<td>N (All births)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>N (Live births)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>% live born</td>
<td>0</td>
</tr>
<tr>
<td>% (All births)</td>
<td>Respiratory support</td>
<td>0</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>Mortality free</td>
<td>% (All births)</td>
</tr>
<tr>
<td>% (All births)</td>
<td>Mortality free</td>
<td>N (All births)</td>
</tr>
<tr>
<td></td>
<td>N (Live births)</td>
<td>2</td>
</tr>
<tr>
<td>Gestation</td>
<td>N (All births)</td>
<td>40</td>
</tr>
<tr>
<td>% live born</td>
<td>N (All births)</td>
<td>40</td>
</tr>
<tr>
<td>Active</td>
<td>N (All births)</td>
<td>40</td>
</tr>
<tr>
<td>Treatment</td>
<td>N (All births)</td>
<td>20</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>N (All births)</td>
<td>0</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>N (All births)</td>
<td>9</td>
</tr>
<tr>
<td>% live born</td>
<td>N (Live births)</td>
<td>2</td>
</tr>
<tr>
<td>Gestation</td>
<td>N (All births)</td>
<td>22</td>
</tr>
<tr>
<td>% (All births)</td>
<td>N (All births)</td>
<td>22</td>
</tr>
<tr>
<td>Treatment</td>
<td>N (All births)</td>
<td>22</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>N (All births)</td>
<td>11</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>N (All births)</td>
<td>0</td>
</tr>
</tbody>
</table>

NB Regions comprise: Belgium (Flanders); France (Burgundy, Ile-de-France, Northern); Italy (Emilia Romagna, Lazio, Marche); Portugal (Northern region, Lisbon); UK (East Midlands, Northern, Yorkshire)
There was a consistently higher percentage recorded live born for births at 24 and 25 weeks gestation weighing over 500g (74.1% and 79.8% respectively) (Figure 1c and 1d).

Initiation of medical treatment

For babies born at 22 weeks gestation the percentage of all births associated with antenatal steroids prophylaxis (table 3) was consistently very low (2%) for those weighing less than 500g (Figure 1a), while there were significant differences for births weighing 500g and over ranging from 25% of births in Italy to 0% in the UK, France and Belgium. At 23 weeks gestation the rate of prophylaxis increased to 16% for births below 500g with no significant differences between countries, but again there was variation for births ≥500g (from 0% in Belgium to 58% in Italy and the UK). Rates were higher in all countries at 24 and 25 weeks gestation, but significant variability persisted for birthweights ≥500g, with France and Belgium having consistently lower rates of provision.

Respiratory support at 22 weeks gestation (Figure 1a and table 3) varied significantly internationally for both birthweight groups with no interventions in Belgium, France and the UK compared to Italy (<500g: 9%; ≥500g: 25%) and Portugal (<500g: 0%; ≥500g: 13%). This variation in approach persisted at 23 and 24 weeks gestation (Figure 1b and 1c). Italy had consistently high rates of initiation of respiratory support than the other countries while France had the lowest rates. For babies born at 25 weeks gestation the rates of initiation of treatment were substantially higher particularly for those born weighing 500g or over and were consistent across the five countries (Range: 72% to 82%)(Figure 1d).

Survival to discharge

Survival to discharge was universally poor across all 5 countries for babies born at 22 weeks gestation (0.0% for both <500g and ≥500g)(Figure 1a) and for all births at 23, 24 and 25 weeks gestation weighing less than 500g (1%, 2% and 7% respectively)(Figure 1b-1d) irrespective of
variations in the medical treatment provided to these babies. However at 23 and 24 weeks gestation for babies weighing over 500g there was significant variation between countries in survival to discharge, ranging from 0% to 25% of all births at 23 weeks and 21% to 50% at 24 weeks gestation (Figure 1b and 1c). Those countries with higher rates of respiratory support and antenatal steroid provision had generally higher levels of survival. However the percentage of infants surviving without severe morbidity was low particularly at 23 weeks (1% of all births). In contrast at 25 weeks gestation where the initiation of active treatment had not been shown to vary, there was no evidence of a difference in the survival between countries and 52% of all births survived to discharge (Figure 1d). For those surviving without severe morbidity, there was variation between countries in the proportion with BPD or no reported morbidity, with high rates of BPD in the UK.

**DISCUSSION**

Our study shows that international variation exists in the recording of live births and levels of intervention, suggesting differences in the initiation of early medical treatment for extremely preterm births between countries. This variation had a varying impact on survival outcomes by gestation and birth-weight.

We have shown variation in the recording of births as live born at 23 and 24 weeks. This may relate to *real* differences in the percentage of births that are live born; or *artefactual* differences due to variation in the criteria used to decide whether a birth is viable. This will have an impact on observed neonatal mortality rates which are based only on live births only, a problem highlighted elsewhere[11, 18]. Since the outcomes of these births are relatively poor, countries where there is a high percentage of births at this gestation recorded as live born will have an inflated rate of neonatal mortality compared to those where more births are recorded as stillborn. This finding emphasises the need to use perinatal mortality rates when comparing outcomes for births at this gestation or to introduce a gestational age threshold to prevent inappropriate comparisons.
Our findings suggested that for births of 23 and 24 weeks gestation weighing over 500g there was significant variation in the levels of respiratory support provided and survival was higher in those countries with higher levels of intervention although this was not formally tested. In this group, survival rates appear to be determined partially by the implementation of management guidelines, as shown by corroborating studies [10] [14]. However while survival rates were improved in this group for those with high levels of intervention, rates of survival free of severe morbidity were low. This raises important questions concerning the long term outcomes of these infants and the burden versus benefits balance over the decision to provide intensive treatment. Only for babies born at 25 weeks gestation was there no evidence of international variation in respiratory support initiation or survival. This finding shows a shift in the gestational age at which variation is most pronounced since 10 years ago when Kollee et al found the widest variation in intervention rates across Europe was at 24 and 25 weeks gestation[19] and suggests a gestational age change in the perception of viability. The provision of respiratory support varied for babies weighing less than 500g. However for these babies, survival was universally poor with those countries having higher levels of intervention seeing no evidence of improved outcomes. This confirms the findings of studies of preterm babies born with extreme growth restriction [20]. However the level of care provided for these infants may be high and raise false hope for parents regarding their baby’s chance of survival.

The Nuffield Council[21] and American Academy of Pediatrics [8] guidelines highlight that generally there is a consistent approach to extremely low birth-weight and gestational age births and similarly at higher gestations and birth-weights but in between a “grey area” where survival is possible but infrequent and accompanied by a high risk of severe morbidity. We found this grey area differed between countries, with wide international variation in practice and outcomes, suggesting differences in whether birth-weight or gestational age or both are used to determine management. Italy had a much lower threshold for the initiation of intensive care than other countries while France had the highest threshold. These differences in intervention levels across countries are in
agreement with previous studies and are likely to reflect variation in providers’ attitudes[22] and in
guidelines on management [23] [24, 25]. Recent research has questioned the ethical implications of
basing life and death decisions only on gestational age before 25 weeks in France [26]. Factors that
drive guideline development in ethically and emotionally sensitive areas of clinical practice are
difficult to quantify, but variation is likely to reflect local differences in religious and cultural values
as well as the legal environment[24], and personal experiences of the health care professionals.
These different values and national contexts will influence not only perceptions of fetal viability and
outcomes[27], but also of concepts of “disability” and “quality of life” and “best interests”. Other
influential factors may be of a more practical nature, such as differences in eligibility of maternity
and paternity pay or costs of funeral and burial arrangements. France and Belgium have high burial
costs to parents for neonatal deaths but not stillbirths at these early gestations which could
influence the low number of babies being declared live born in these countries to help parents avoid
these costs (CIRCULAIRE DHOS/DGS/DACS/DGCL n° 2001/576 du 30 novembre 2001, http://social-
sante.gouv.fr/fichiers/bo/2001/01-50/a0503302.htm; accessed 10/03/2016). In contrast in the
UK there is no assistance for parents of stillbirths before 24 weeks gestation and so a higher rate of
live births at this gestation would enable greater access to maternity benefits
(https://www.gov.uk/maternity-pay-leave/eligibility accessed 01/03/2016) while in France benefits
are provided regardless of whether the baby is live born or stillborn after 22 weeks gestation.

Strengths and limitations of the study

International comparisons of mortality using official birth and death registrations are limited by the
differential practices regarding registration criteria [11]. The strength of this study is the use of
consistently recorded, locally collected international data on all stillbirths and live births from 22 to
25 weeks gestation irrespective of national official registration rules, babies allowing for valid
comparisons across countries. Many other studies of active management only focus on live births
and this can severely bias the survival rates where there is a differential approach to whether a birth
is reported as live born or not. By undertaking analyses using all births as a denominator we have been able to explore in more detail the impact of perceived viability and active management on outcomes. We believe this cohort of births to be broadly representative of births occurring in the five countries whose data are analysed here. A standardised questionnaire was used to collect data from the medical records in obstetric and neonatal units with common pretested definitions. However this limited the number of measures of both perceived viability and interventions included in the study. We analysed outcomes by gestation and birth-weight alone and could not explore other factors which may influence clinicians’ perceptions of viability such as the baby’s physical appearance, response to first treatment, or parental preferences. Intervention measures such as provision of antenatal steroids and respiratory support are limited in their scope but adequately reflect policies and general attitude of units towards viability and intention to treat prior to and following birth. It is possible the lack of administration of antenatal steroids may be due to organisational aspects of care such as limited time between the start of care during labour and delivery but this is unlikely to vary significantly between countries. Before delivery obstetricians and neonatologists frequently use estimated fetal weights to determine potential viability and decisions around management in addition to gestational age. In this study we were restricted to using birth weight which is not known until birth. Research is needed to assess whether both estimated fetal weight and birth weight contribute to the management decisions seen here.

**Implications for policy**

Preterm birth survival rates are widely used for counselling parents, decisions to initiate treatment and making international comparisons of care. The variation seen here in international survival rates of extremely preterm births make these decisions more challenging. Furthermore our findings support Lantos and Meadow’s assertion [14] that while protocols are frequently agreed based on survival rates, their implementation also determine survival rates since the withholding of intensive care leads to a perpetuation of poor survival. In our study, however this only seemed to be true for
some gestational age and birth-weight combinations. Variations in practice also have a major impact on the associated economic costs of each birth. While the numbers of births at these gestations are low, the length of stay and care provision can be extremely high and future long-term needs are uncertain.

Most guidelines on the early management of very preterm births focus on gestational age only, without considering birth weight (18). Until recently, the American Academy of Pediatrics Neonatal Resuscitation Programme[8] recommended that resuscitation should be withheld when the gestational age is less than 23 weeks or a birth-weight of less than 400 grams, but this has now been amended to recommend that resuscitation should be withheld only below 22 weeks (http://www2.aap.org/nrp/docs/15535_NRP%20Guidelines%20Flyer_English_FINAL.pdf accessed 22/03/2016) on the basis of improved reported survival in some countries[28, 29]. Our findings support a higher gestational age criteria of 23 weeks, but also suggest the importance of a birth-weight threshold. This is particularly relevant since the exact assessment of gestational age has in most cases a margin of imprecision that may be crucial to management at 22-24 weeks gestation. Clinical estimates of birth weight in the delivery room may be inaccurate, and weighing a baby could delay resuscitation and impact on survival. However, birth-weight is routinely measured at admission to the neonatal unit, and its prognostic value for infants of borderline viability suggests that it can be a useful criterion in counselling parents and in decisions about continuation of intensive treatment.

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References


