Survival of very preterm infants: Epipage, a population based cohort study

B Larroque, G Bréart, M Kaminski, M Dehan, M André, A Burguet, H Grandjean, B Ledésert, C Lévéque, F Maillard, J Matis, J C Rozé, P Truffert on behalf of the Epipage study group

Objective: To evaluate the outcome for all infants born before 33 weeks gestation until discharge from hospital.

Design: A prospective observational population based study.


Patients: All births or late terminations of pregnancy for fetal or maternal reasons between 22 and 32 weeks gestation.

Main outcome measure: Life status: stillbirth, live birth, death in delivery room, death in intensive care, decision to limit intensive care, survival to discharge.

Results: A total of 722 late terminations, 772 stillbirths, and 2901 live births were recorded. The incidence of very preterm births was 1.3 per 100 live births and stillbirths. The survival rate for births between 22 and 32 weeks was 67% of all births (including stillbirths), 85% of live births, and 89% of infants admitted to neonatal intensive care units. Survival increased with gestational age: 31% of all infants born alive at 24 weeks survived to discharge, 78% at 28 weeks, and 97% at 32 weeks. Survival among live births was lower for small for gestational age infants, multiple births, and boys. Overall, 50% of deaths after birth followed decisions to withhold or withdraw intensive care: 66% of deaths in the delivery room, decreasing with increasing gestational age; 44% of deaths in the neonatal intensive care unit, with little variation with gestational age.

Conclusion: Among very preterm babies, chances of survival vary greatly according to the length of gestation. At all gestational ages, a large proportion of deaths are associated with a decision to limit intensive care.

Changes in perinatal management, including increased prenatal referral, prenatal steroid treatment, assisted ventilation at delivery, and surfactant therapy, have been associated with a substantial increase in survival of infants at very low gestational ages. I Immaturity is nonetheless associated with high levels of neonatal morbidity and mortality. Surviving very preterm children appear to have numerous severe disabilities, especially the most immature babies. Data on survival often come from specialized neonatal units, with a selection bias resulting from different criteria for referral, admission, or treatment. This explains in part the better survival rates, especially for the lowest gestational ages, observed in some single or multiple centre networks than in population based studies.

Legislation and practice with respect to late terminations of pregnancy for malformation or severe fetal or maternal disease vary according to country. In France there is no age limit for late terminations, and this may affect death and survival rates.

The ethical issues of withholding/withdrawing care for very preterm infants at high risk of death or serious disabilities are also important. A European study of physician practices and attitudes indicates that the vast majority of European neonatologists have been involved in some limitation of intensive care, although the nature of the decision taken varies from one country to another. Theoretical discussions of the criteria for decision making have been published, and professional guidelines are beginning to appear. In France, a professional group of neonatologists has publish their guidelines, and the National Consultative Bioethics Committee has published advice (http://www.cne-ethique.org advice n 65 of 9/14/2000). However, there are few studies that report data on actual practices with respect to end of life decisions for babies. Clinical decisions as well as information to parents need to rely on the most relevant outcome estimates, and no recent population based data were available in France.

We report the conditions at birth and survival of babies born between 22 and 32 weeks in a geographically defined population in France in 1997, stratified by gestational age. The additional role of birth weight, plurality, and sex is also analysed. Finally, deaths associated with limitation of intensive care in the delivery room or the neonatal intensive care unit (NICU) are reported.

PARTICIPANTS AND METHODS

The study included all births (live births and stillbirths) and late terminations of pregnancy, occurring from 22 to 32 completed weeks gestation, in 1997, to women in the maternity wards of nine French regions, which cover about one third of all births in France. Information was extracted from obstetric and neonatal records.

Only one private maternity hospital refused to participate. All infants who were transferred to an NICU were included. Data on the vital status of two children of 32 weeks gestation are missing; these two cases are excluded from the tables. Gestational age used in this study is the best obstetric estimate of maturity, reported as the number of weeks of amenorrhoea.
Limitation of intensive care was assessed with two questions. The question on “resuscitation in the delivery room” offered the following possible answers: (1) no, not necessary; (2) yes, as planned; (3) yes, despite an earlier decision not to resuscitate; (4) no, as decided before birth; (5) no, decided at birth. The last two answers were considered to be withholding of intensive care in the delivery room and included cases in which resuscitation was either not initiated or withdrawn rapidly in the delivery room. For deaths after admission to an NICU, the question on the “circumstances of death” offered the following answers: (1) despite intensive care; (2) after a decision to withhold or withdraw intensive care, which was considered “limitation of care in the NICU”. Multiple logistic regression was used to estimate odds ratios for death before discharge according to the infant’s sex, birth weight, and plurality, adjusted for gestational age. The statistical analysis used SAS software (SAS Institute Inc, Cary, North Carolina, USA). The study received the approval of the Commission Nationale de l’Informatique et des Libertés.

RESULTS

In the regions and period defined above, 4395 inclusions were recorded between 22 and 32 weeks gestation: 722 (16%) late terminations of pregnancy, 772 stillbirths (18%), and 2901 (66%) liveborn children (table 1). The total number of births for the studied regions and period was obtained from the National Institute for Statistics and Economic Studies, and allowed us to calculate the rate of births between 22 and 32 weeks gestation: 1.3 per 100 live births and stillbirths, 1.1 per 100 live births. The proportion of late terminations of pregnancy decreased with gestational age, from 50% at 22 weeks to 3% at 32 weeks. The number of live births increased with gestational age. The proportion of stillbirths was high: 21% overall, 17% antepartum, and 4% intrapartum; both decreased with increasing gestational age. Live births accounted for 79% of all births, ranging from 16% at 22 weeks to 92% at 32 weeks. At 25 weeks, more than half of all births showed signs of life, and at 27 weeks, 80% showed signs of life.

Overall, 127 babies (4% of live births) died in the delivery room shortly after birth; the more immature the infant, the greater the likelihood of death in the delivery room (table 1). A total of 2774 infants were admitted to NICUs (96% of live births), 315 of whom died before discharge, giving a rate of survival to discharge of 89% of those admitted for intensive care, 85% of live births, and 67% of all births. No infants born at 22 or 23 weeks survived; 13 of the 42 infants (31%) born alive at 24 weeks survived until discharge; half of all infants born alive at 25 weeks survived, and 78% born at 28 weeks
survived. Figure 1 shows the survival percentages by gestational age with three different denominators: infants admitted to NICUs, infants born alive, and all births. The difference between survival of all births and live births was about 20% at 24–26 weeks, and this decreased to 8% at 31–32 weeks. The difference between survival of live births and infants transferred to NICU was more than 10% at 24–26 weeks, and this decreased with gestational age to under 1.5% at 28–32 weeks.

Liveborn infants with birth weight less than the 10th centile had a higher death rate than infants with a higher birth weight (table 2). Multiple births accounted for 28% of all births (table 3). At each gestational age, the stillbirth rate was lower and the hospital death rate higher for multiple births than for singletons. In a multivariate model adjusted for gestational age and birth weight below the 10th centile, a birth weight below the 10th centile was associated with an increase in mortality of liveborn infants (odds ratio (OR) = 3.2 (95% confidence interval (CI) 2.3 to 4.6)) for multiple births (OR = 1.9 (95% CI 1.0 to 1.7)) and for boys (OR = 1.3 (95% CI 1.0 to 1.7)).

Of the 127 deaths in the delivery room, 66% involved a decision to limit care in either the delivery room or the NICU—from 81% for those born at 22–24 weeks to about 40% at 31–32 weeks.

DISCUSSION

The strength of this study comes from the population based recruitment of the cohort and the large sample size over a short period, which provides a detailed picture of the birth and survival of infants of 22–32 weeks gestation in the context of current medical practices.

All children admitted to NICUs were included as confirmed from hospital registration. Only one small private maternity hospital refused to participate, where the occasional stillbirth may have occurred. Gestational age was estimated by the obstetric team from all available information (last menstrual period, ultrasound examination, clinical assessments).

Ultrasonography during pregnancy is nearly universal in France: the 1998 French national perinatal survey found that 99.8% of women had at least one ultrasound assessment, and 96.3% at least three. Differences in methods (type of study, length of follow up) and actual care (according to time period and country) may account for the wide variations in reported survival rates. Geographically based population studies that include all births, including stillbirths, produce the most accurate and comparable estimates of gestational age specific mortality. In our study, the overall difference in survival rates according to whether the denominator was all births or live births was 8% for the whole sample but about 20% for the lower gestational age groups (fig 1). The accurate identification of an infant as live born in the case of few signs of life also affects both the ratio of stillbirths/live births and neonatal mortality. Calculating survival rates by gestational age based on all births in addition to live births provides interesting information for comparison between studies, but is possible only in geographically based studies that document all deaths before and during delivery. Few studies present survival rates including stillbirths. Some include antepartum deaths or differentiate between antepartum and intrapartum deaths, whereas others include only the latter.

Some studies excluded “lethal congenital malformations”, “major malformations”, malformations without specifying severity, “antenatally diagnosed malformations”, or registered terminations of pregnancy. We chose to record terminations of pregnancy but to exclude them in the estimation of survival rates. Few data are available to measure the incidence of late terminations, but compared with other European countries, the rate seems to be high in France.

Comparison of the distribution of live births at 25–32 weeks in the Paris area in 1985–1986 and in the Epipage...
data in 1997\textsuperscript{11–14} shows that the proportion of births at 25–26 weeks has increased from 4% to 14%, whereas the proportion of births at 30–32 weeks has decreased from 70% to 60%. Because of the higher proportion of extremely low gestational ages, the global survival rate has increased only slightly, although survival has increased substantially at each gestational age. For comparisons over time and between studies, survival rates by week of gestation are more informative than global mortality.

Infants below the 10th centile of weight for gestational age had a higher risk of mortality. Other studies have reported a similar association.\textsuperscript{15–19} Among liveborn infants, mortality was higher for multiples than singletons. Results of previous studies differ, with some reporting a similar risk excess for multiples,\textsuperscript{20–21} no difference,\textsuperscript{11,22} or a lower risk.\textsuperscript{19} These conflicting results could be explained in part by differences in care of multiples between studies: a variable proportion of inclusions in the Epipage study, and as much as 50% at 22–24 weeks. Babies who would have been stillborn with less active obstetric care are alive in the delivery room, and, as they are more frail, they contribute to an increase in neonatal mortality. An active policy of immediate resuscitation reduces the number of early neonatal deaths but may increase both the number of late deaths among these fragile infants and the number of decisions to limit intensive care.

We have attempted to compare gestation specific survival rates of liveborn very preterm infants from geographically based studies in the 1990s (table 5). Some studies report survival to discharge home,\textsuperscript{11,15–18} and others to one year\textsuperscript{10,25–26} and two years of age,\textsuperscript{21} but increasing length of follow up is considered to introduce only limited variations, as most deaths occur before discharge home. The gestation specific survival rates for live births in our study were similar to those in other populations, except for two Australian studies with higher survival rates.\textsuperscript{15,27} Survival rates at 23 weeks range from 0% to 20%, at 24 weeks from 17% to 44%, and at 25 weeks from 35% to 64%; they tended to be more consistent thereafter. These younger gestational ages are also those for which decisions on intensive care are most discussed.

The high incidence of disability among survivors, particularly for the most immature, has prompted much ethical discussion. The interpretation of differences in neonatal mortality statistics is difficult because of the impact of practices of resuscitation at birth and/or limitation of intensive care. Decision making criteria may vary both across and within countries.\textsuperscript{3} These decisions may occur at different

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Proportions of deaths after a decision to limit (withhold/withdraw) intensive care, by gestational age, among infants born alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>Deaths in delivery room</td>
</tr>
<tr>
<td></td>
<td>No*</td>
</tr>
<tr>
<td>&lt;24</td>
<td>55</td>
</tr>
<tr>
<td>25–26</td>
<td>42</td>
</tr>
<tr>
<td>27–28</td>
<td>14</td>
</tr>
<tr>
<td>29–30</td>
<td>12</td>
</tr>
<tr>
<td>31–32</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>127</td>
</tr>
</tbody>
</table>

*Number of deaths among liveborn children.†Number of deaths after decision to limit intensive care.‡Percentage of deaths after decision to limit intensive care.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Survival rates (%) of very preterm infants born alive in the 1990s in geographically based studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of birth</td>
<td>France</td>
</tr>
<tr>
<td>First author</td>
<td>Epipage</td>
</tr>
<tr>
<td>Survival At discharge</td>
<td>22</td>
</tr>
<tr>
<td>No of live births</td>
<td>2899</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>At discharge</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>27</td>
<td>56</td>
</tr>
<tr>
<td>28</td>
<td>71</td>
</tr>
<tr>
<td>29</td>
<td>78</td>
</tr>
<tr>
<td>30</td>
<td>89</td>
</tr>
<tr>
<td>31</td>
<td>92</td>
</tr>
<tr>
<td>32</td>
<td>97</td>
</tr>
</tbody>
</table>

*Calculated from data provided in the paper.
stages in time: decisions whether or not to initiate intensive care in the delivery room; various attitudes when the treatment appears futile, or the neurological prognosis too poor. In the Epipage study, half the deaths in the delivery room or the NICU were reported to have occurred after a decision to limit intensive care. The literature describes only occasionally, and quantifies very rarely, these aspects of perinatal care, the measurement of which is sensitive and difficult. The EPICure study reports that, among children under 26 weeks, 55% of the deaths in the NICU occurred after intensive care was withheld/withdrawn; the corresponding percentage in the Epipage study is very similar, 51%. As expected, in our study, the percentage of deaths after limitation of intensive care was highest for the most immature infants, in both the delivery room and the NICU. In the NICU, however, the percentage of deaths associated with limitation of care remained high at all gestational ages. Whereas only 3% of those born at 31–32 weeks admitted to the NICU died, 38% of these deaths followed a decision to withdraw further care. In France, there is some consistency in obstetric and neonatal policies and practices aiming to reduce the risk of survival of extremely handicapped children: in the case of major congenital malformation by termination of pregnancy late in the third trimester, and in the case of poor neurological prognosis in very immature babies by limitation of intensive care.

Currently in France, 13% of babies are born before 33 weeks gestation. The overall survival rate to discharge was 89% of the infants admitted to intensive care, 85% of live births, and 67% of all births. Chances of survival among these babies vary greatly according to the length of gestation. At the lowest gestational ages, a large proportion of deaths follow a decision to limit intensive care for babies with the poorest prognosis. A follow up of this cohort is currently carried out in order to assess the impact of perinatal decisions in care on health and development of very preterm babies.

ACKNOWLEDGEMENTS

We thank all those who have contributed to the coordination of the study at the national or regional level, all medical doctors and midwives who took time to fill in the medical questionnaires, and the mothers who agreed to participate in the study.

REFERENCES


This month in the Archives of Disease in Childhood

The following paper appearing in the March 2004 issue of ADC may be of interest to readers of Fetal and Neonatal.
The neurodevelopmental progress of infants less than 33 weeks into adolescence. F O’Brien, S Roth, A Stewart, L Rifkin, T Rushe, J Wyatt.