The EPICure Study: Outcomes to Discharge From Hospital for Infants Born at the Threshold of Viability

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ABSTRACT. *Objective.* **To evaluate the outcome for all infants born before 26 weeks of gestation in the United Kingdom and the Republic of Ireland. This report is of survival and complications up until discharge from hospital.**

Methodology. **A prospective observational study of all births between March 1, 1995 and December 31, 1995 from 20 to 25 weeks of gestation.**

Results. **A total of 4004 births were recorded, and 811 infants were admitted for intensive care. Overall survival was 39% (n = 314). Male sex, no reported chorioamnionitis, no antenatal steroids, persistent bradycardia at 5 minutes, hypothermia, and high Clinical Risk Index for Babies (CRIB) score were all independently associated with death. Of the survivors, 17% had parenchymal cysts and/or hydrocephalus, 14% received treatment for retinopathy of prematurity (ROP), and 51% needed supplementary oxygen at the expected date of delivery. Failure to administer antenatal steroids and postnatal transfer for intensive care within 24 hours of birth were predictive of major scan abnormality; lower gestation was predictive of severe ROP, while being born to a black mother was protective. Being of lower gestation, male sex, tocolysis, low maternal age, neonatal hypothermia, a high CRIB score, and surfactant therapy were all predictive of oxygen dependency. Intensive care was provided in 137 units, only 8 of which had >5 survivors. There was no difference in survival between institutions when divided into quintiles based on their numbers of extremely preterm births or admissions.**

Conclusions. **This study provides outcome data for this geographically defined cohort; survival and neonatal morbidity are consistent with previous data from the United Kingdom and facilitate comparison with other geographically based data.** *Pediatrics* **2000;106:659–671;** ***extremely preterm infant, survival, cerebral ultrasound scan, intraventricular hemorrhage, parenchymal cysts, hydrocephalus, retinopathy of prematurity, chronic lung disease.***

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ABBREVIATIONS. PMA, postmenstrual age; NNU, neonatal unit; LMP, last menstrual period; EDD, expected date of delivery; ROP, retinopathy of prematurity; CI, confidence interval; HR, heart rate; CRIB, Clinical Risk Index for Babies; RDS, respiratory distress syndrome; IQR, interquartile range; PROM, prolonged rupture of membranes >24 hours; FIO_2, fraction of inspired oxygen; PDA, patent ductus arteriosus.

The care of the fetus considered to be at the threshold of viability raises some of the most difficult clinical problems for obstetricians and pediatricians. Advice given to parents needs to be based on reliable contemporary information drawn from appropriate populations. The number of these infants born in an individual unit is small and conclusions based on their outcome are unreliable. Published reports derive from a range of populations including those from single tertiary centers with selected patients and others based on geographically defined areas. Furthermore, survival and morbidity are defined differently in different studies and show wide variation. For example, since 1990, for infants born at 25 weeks of gestational age, published rates of survival range from 35% to 79%[1,2] and published rates of severe disability range from 12% to 35%.[3,4]

The EPICure study was designed to describe survival and health problems for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland. In this article we describe the progress of these infants during their initial admission for intensive care.

METHODS

Details of all births, between March 1, 1995 and December 31, 1995, believed at the time of delivery to be between 20 and 25 completed weeks of gestation, ie, up to 25 weeks and 6 days' postmenstrual age (PMA) were collected prospectively from all 276 maternity units in the United Kingdom and the Republic of Ireland. A dataset was collected on all births that included the gestational age used by delivery room staff, whether signs of life were noted, and whether the infant was admitted to a neonatal unit (NNU). Full data collection using a standardized form was completed only for those infants who were admitted. The dataset comprised demographic information about the mother, including the date of the last menstrual period (LMP), and details of ultrasound scans performed before 20 weeks' gestation. Neonatal data included descriptions of the early clinical condition of the infant, major interventions, and complications until death or discharge from hospital. A full list of the items collected is provided in the "Appendix." The study involved no interventions; care provided for mothers and infants was at the discretion of the hospital staff. The data were anonymous until discharge from hospital when informed consent for later evaluations was requested.

Records with missing information were returned. When it proved difficult to obtain data, one of the investigators visited the hospital and extracted information from the case notes. Data were regarded as missing only when the investigators concluded that they were unobtainable.

Data Validation

Data were entered into a computer database by 1 of 2 study nurses. Items that were ambiguous or improbable were clarified with the person providing the data and errors corrected. Accuracy was subsequently assessed by double entry of 10% of all record forms. From 15 280 entries, 17 errors were found (.1% error rate). During analysis, outlying points and any that seemed unlikely were checked.

Analysis

All analyses were performed using *Stata, Version 5.0* (Stata Corp, College Station, TX)[5] except for χ^2 analysis for trend for which we used *EpiInfo, Version 6*.[6] Comparisons of continuous outcomes were made using analysis of variance for categorical predictors or linear regression for binary and continuous variables. Comparisons of binary outcomes were analyzed using either χ^2 analysis or logistic regression as appropriate. Gestational age was investigated both as a continuous variable and categorically as completed weeks. The effect of the size of the institution on survival was analyzed by considering hospitals categorized into quintiles based on the total numbers of births and of admissions within the gestational age range of 20 to 25 weeks. A forward stepwise logistic regression was used to investigate independent effects on death before discharge from hospital and of major complications of prematurity in the survivors to discharge. The significance level was not changed when multiple comparisons were performed. Investigation of potential nonlinear effects was made using fractional polynomial regression. The birth weight for gestational age in the logistic regression analyses was calculated as the difference from the predicted birth weight for given gestation, sex, and the interaction term of sex and gestational age where male = 1 and female = 0 in a multiple linear regression, using data from all of the infants admitted to NNUs. It approximates to the difference from average birth weight for a child of that gestation and sex.

The level of statistical significance for all analyses was set at $P \leq .05$ using 2-tailed comparisons.

Calculation of Gestational Age

The gestational age of the 811 admissions was calculated by the investigators using the information on the record form. The expected date of delivery (EDD) was based on the LMP of the mother or on the results of an ultrasound scan performed before 20 weeks' gestation, if only one or the other was available. If both were available and the EDD derived from scans differed from that based on LMP by >14 days, the scan gestation was used. Pediatricians were given the option to include infants for whom reliable dating information was not available when, based on their own clinical assessment, they believed that the gestational age was below 26 weeks.

Outcomes

For infants who died, the primary cause of death was requested using standard definitions listed in the "Appendix." To estimate the number of deaths preceded by active withdrawal of intensive care, clinicians were asked whether a "... formal decision had been made to withdraw care after appropriate discussion...." This did not include occasions when "... the baby is extubated before death following an acute deterioration and unsuccessful resuscitation...." Survival was calculated at 28 days after birth, at the EDD, and at discharge from hospital. Cerebral ultrasound scans were reported locally and classified as to the presence and extent of hemorrhage, ventriculomegaly, and parenchymal cysts. Ventriculomegaly was defined as a Ventricular Index >4 mm above the 97th percentile.[8] For the purpose of this analysis, scans showing major abnormality were defined as those showing unilateral or bilateral parenchymal cysts and/or hydrocephalus. Cases with retinopathy of prematurity (ROP) of sufficient severity to need treatment with laser or cryotherapy were noted. Oxygen dependency was recorded at 36 and 40 weeks' PMA.

RESULTS

All 276 maternity hospitals in the United Kingdom and Ireland provided information. Ten hospitals reported no births between 20 and 25 completed weeks of gestational age during the study. In the other 266 hospitals, 4004 births were recorded. Of the 2112 births believed to be between 20 and 22 weeks' gestation, 11% were reported to show signs of life at birth. This rose to 39% of 622 births at 23 weeks, 60% at 24 weeks, and 67% at 25 weeks. Of those reported to show signs of life, 92% <23 weeks' gestation, 50% at 23 weeks, 18% at 24 weeks, and 8% at 25 weeks' gestation died in the delivery room.

Infants were admitted for intensive care in 190 (71%) of the units in which births occurred. After transfers for intensive care in the first 24 hours (14% of admitted infants), ongoing intensive care was provided by 137 NNUs in 51% of the hospitals in which the infants were born.

Eight hundred forty-three infants, thought at birth to be between 20 and 25 completed weeks of gestation, were admitted during the study. Calculation of gestational age by the investigators using information on the record form found 29 of these to be $>25^6$ weeks of gestation. An additional 3 infants, who had no information recorded from which gestational age could be estimated, were considered by their pediatrician on clinical assessment to be more mature than 25^6 weeks; these 32 infants were excluded from the analysis. The 811 infants for whom results are presented include 26 infants for whom the estimate of gestational age was made solely on the pediatrician's clinical assessment.

Maternal Characteristics

Of the 705 mothers, 574 had singleton and 131 multiple pregnancies (Table 1). Maternal age did not vary between women with singleton and multiple pregnancies but mothers with multiples were more likely to be white and primiparous. Previous pregnancy loss occurred in 72% of multiparous women (361/501). The reporting of complications of pregnancy particularly of preeclampsia and antepartum hemorrhage was more frequent in singleton, compared with multiple pregnancies. Complication rates did not differ by gestational age. Tocolytics, but not steroids, were used more commonly in multiple pregnancies. The administration of any antenatal steroid was less frequent before 24 weeks' gestation (χ^2 trend, 23–25 weeks: $P < .0005$) in both singleton ($P = .0001$) and multiple pregnancies ($P = .0002$), but the proportion of those before or beyond 24 completed weeks' gestation who had received steroids for >24 hours before delivery was similar ($n = 265$; $P = .59$).

For 700 of the 705 women details of delivery were provided. Cesarean section was more common at higher gestational age (χ^2 trend, $P < .0005$) regardless of whether the woman was in labor ($P = .002$ for those in labor and $P < .0001$ for those not in labor; Table 2). Of those women reported to have complications of pregnancy, 20% (88/442) were delivered by cesarean section, compared with 8% (21/257) of those with no complications ($P < .0005$). Cesarean

TABLE 1. Antenatal Characteristics of Mothers

	Total $n = 705$	Singleton Gestations $n = 574$	Multiple Gestations $n = 131$	P Value (Singletons Versus Multiples)
Maternal age (y)				
Median (number reporting)	28.0 (696)	28 (567)	29 (129)	
[IQR]	[24–32]	24–32	25–33	.2*
{Range}	{14–44}	{14–44}	{17–42}	
Maternal ethnicity	% (n)	% (n)	% (n)	
White	76.7 (541)	74.7 (429)	85.6 (112)	.027†
Black (West Indian, African, and other)	13.1 (92)	14.1 (81)	8.4 (11)	
Indian subcontinent	6.1 (43)	7.1 (41)	1.5 (2)	
Other (including Oriental)	2.0 (14)	1.7 (10)	3.1 (4)	
Not known	2.1 (15)	2.3 (13)	1.5 (2)	
	% (n/n Reporting)	% (n/n Reporting)	% (n/n Reporting)	
Primiparous	28.4 (199/700)	25.1 (143/570)	43.1 (56/130)	<.0001
Complications of pregnancy				
Any complication	63.2 (442/699)	65.4 (372/569)	53.9 (70/130)	.014
APH	28.9 (201/695)	30.7 (174/567)	21.1 (27/128)	.031
PET	3.9 (27/695)	4.6 (26/567)	.78 (1/128)	.04
Cervical suture	8.2 (57/695)	9.0 (51/567)	4.7 (6/128)	.10
PROM	24.0 (167/695)	24.7 (140/567)	21.1 (27/128)	.39
Chorioamnionitis	17.8 (124/695)	18.2 (103/567)	16.4 (21/128)	.64
Antenatal steroids				
Any steroid given	64.9 (451/695)	64.3 (364/566)	67.4 (87/129)	.50
24 and 25 wk gestation	69.6 (385/553)	68.3 (310/454)	75.8 (75/99)	.14
≤23 wk gestation	46.5 (66/142)	48.2 (54/112)	40.0 (12/30)	.42
Steroid >24 h before delivery				
24 and 25 wk gestation	60.5 (233/385)	60.7 (188/310)	60.0 (45/75)	.92
≤23 wk gestation	48.5 (32/66)	51.9 (28/54)	33.3 (4/12)	.25
Tocolysis	22.7 (156/688)	21.1 (118/560)	29.7 (38/128)	.04

* F test, all other comparisons are χ^2.
† White versus all other ethnic groups.
APH indicates antepartum hemorrhage; PET, preeclamptic toxaemia.

section was not more common in multiple pregnancies.

Cephalic presentation occurred in 66% of singleton pregnancies. There was no difference in the proportion of cephalic and breech presentations at different gestations. Cesarean section rates in singleton pregnancies were similar in breech (13.9%) and cephalic (13.5%) presentations.

Infant Characteristics

The proportion of live-born infants admitted for intensive care rose with increasing gestational age (χ^2 trend, $P < .0001$; Table 3). Of the 811 infants whose gestational age was assessed postnatally to be <26 weeks, 237 (29%) were from multiple pregnancies, including 77 complete sets of twins and 11 complete sets of triplets. Within 24 hours of birth, 114 of infants (14%) were transferred to a second hospital for continuing intensive care (postnatal transfers). Fifty-four percent of admissions were male. The proportion of multiples and male infants admitted, and the proportion of admitted infants who were postnatal transfers did not vary significantly with gestational age ($P = .06$, $P = .80$, and $P = .48$, respectively). Of all admitted infants, 631were white (78%), 104 were black (13%; including West Indian, African, and other Afro-Caribbeans), 45 were from the Indian subcontinent (6%; Indian, Pakistani, or Bangladeshi), 15 were from other ethnic groups (2%), and the ethnicity of 16 was unknown. These numbers differ from the proportion of mothers from different ethnic groups in Table 1 because of the effect of multiple birth. The proportion of infants from different ethnic groups did not vary significantly with gestational age (χ^2 trend, $P = .06$).

Of 38 infants (5%) reported to have congenital abnormalities, 14 had malformations that were

TABLE 2. Mode of Delivery (700 Women)

Gestation (Weeks)	Cesarean Section Before Labor		Cesarean Section in Labor		Vaginal Deliveries	
	n	%	n	%	n	%
≤23	6	(4.2)	4	(2.8)	132	(93.0)
24	21	(8.2)	10	(3.9)	225	(87.9)
25	41	(13.6)	27	(8.9)	234	(77.5)
Total	68	(9.7)	41	(5.9)	591	(84.4)

TABLE 3. Distribution of Admissions by Gestation, Plurality, and Postnatal Transfer*

Gestation (Weeks)	Gestation Recorded at Birth		Gestation Recalculated From Record Form Admissions *n*	Singletons *n* (% Admissions)	Twins		Triplets		Quadruplets		Postnatal Transfer
	Total Live Births *n*	Admitted to NNU *n* (%)			Pregnancies	Admissions *n* (%)	Pregnancies	Admissions *n* (%)	Pregnancies	Admissions *n* (%)	
≤21	104	3 (2.9)	3	3 (100)	0	—	0	—	0	—	0
22	138	17 (12.3)	22	13 (59.1)	6	9 (40.9)	0	—	0	—	3 (13.6)
23	241	121 (50.2)	131	96 (73.3)	20	29 (22.1)	3	4 (3.1)	1	2 (1.5)	23 (17.6)
24	382	313 (81.9)	298	213 (71.5)	39	69 (23.2)	7	16 (5.4)	0	—	39 (13.1)
25	424	389 (91.7)	357	249 (69.7)	47	82 (23)	9	24 (6.7)	1	2 (.6)	49 (13.7)
Total	1289	843	811	574 (70.8%)	112	189 (23.3%)	19	44 (5.4%)	2	4 (.5%)	114 (14.1%)

NNU indicates neonatal unit.
* The gestation at birth is that upon which antenatal decisions were based, the effect of recalculation of gestational age after admission using information from the study record form is shown. Percentages are for the numbers admitted by gestational age.

acutely life-threatening. These included 4 with congenital diaphragmatic hernia, 3 with meconium ileus, 2 with pulmonary hypoplasia, and 1 each with tracheo-esophageal fistula, imperforate anus, laryngeal cleft, cystic adenomatoid malformation of the lung, and aortic stenosis. The child with tracheo-esophageal fistula, the child with imperforate anus, and 1 child with meconium ileus survived.

The influence of sex, plurality, and gestational age on birth weight of admissions (Table 4) was analyzed using multiple regression analysis. Adjusted mean birth weight rose each completed week of gestation by 75.6 g (95% confidence interval [CI]: 67.2–84.0), boys were 40.8 g heavier than girls (95% CI: 26.5–55.1), and singletons were 37.7 g heavier than multiples (95% CI: 22.0–53.4). These 3 items explained 28% of the variability in birth weight. After adjustment for these 3 items, postnatal transfers were slightly heavier than those receiving continuing intensive care in their hospital of birth (mean difference: 25.9 g; 95% CI: 5.5–46.4; $P = .017$).

Severity of Illness and Interventions

Early indicators of clinical condition were persistent bradycardia defined as a heart rate (HR) <100 bpm 5 minutes after birth, hypothermia defined as the first recorded temperature being <35°C, and the Clinical Risk Index for Babies (CRIB) score[8] (Table 5). One hundred fourteen (15%) had persistent bradycardia and 306 (40%) were hypothermic. The proportion of infants in poor condition decreased with increasing gestational age (persistent bradycardia, $P = .006$; hypothermia, $P < .0001$; increasing CRIB score, $P < .0005$).

Surfactant replacement therapy was used in 682 infants (84%), 58% of whom received an animal derived product (Table 5). The use of surfactant increased with increasing gestational age (χ^2 trend, $P = .013$). Timing and frequency of surfactant therapy were not requested. Information was available on the first chest radiograph of 700 infants. It is not known how many died before a radiograph could be obtained or how many of the radiographs preceded surfactant administration. Of the radiographs reported, 7% showed no abnormality, 45% mild to moderate (grades 1 and 2), and 48% severe changes of respiratory distress syndrome (RDS; grades 3 and 4; see "Appendix"). There was no consistent pattern of chest radiograph grading in relation to gestational age.

Comparing infants who did and who did not receive surfactant therapy, there was no difference in the proportion who were hypothermic ($P = .50$) or in their CRIB scores ($P = .14$). More surfactant-treated infants had a persistent bradycardia at 5 minutes ($P = .02$). There were no differences between the groups who received an animal-derived as opposed to an artificial surfactant in respect of these 3 markers of early condition (persistent bradycardia, $P = .59$; hypothermia, $P = .81$; CRIB score, $P = .10$). None of these markers differed between infants who remained in their hospital of birth and those transferred postnatally (persistent bradycardia, $P = .19$; hypothermia, $P = .62$; CRIB score, $P = .27$). All

TABLE 4. Distributions of Birth Weights by Gestation, Sex, and Plurality

	(*n*)	Birth Weight (Grams)			*n* (%) <500 Grams
		Median	IQR	Minimum to Maximum	
All infants	21 wk (3)	440	—	440–508	2 (66.7%)
	22 wk (22)	540	467–604	364–740	6 (27.3%)
	23 wk (131)	600	560–665	390–980	10 (7.6%)
	24 wk (298)	680	620–759	460–964	7 (2.4%)
	25 wk (357)	760	680–848	370–1040	8 (2.2%)
	Total (811)	695	610–786	360–1040	33 (4.1%)
Gestational age					
22 wk (*n* = 22)	Boys (10)	540	515–590	364–680	—
	Girls (12)	540	456–618	410–740	—
	Singletons (13)	555	520–640	445–680	—
	Multiples (9)	467	423–590	364–740	—
23 wk (*n* = 131)	Boys (70)	615	570–690	400–980	—
	Girls (61)	600	550–650	360–850	—
	Singletons (96)	621	578–683	400–980	—
	Multiples (35)	575	530–630	360–772	—
24 wk (*n* = 298)	Boys (166)	700	640–785	470–950	—
	Girls (132)	660	593–711	460–964	—
	Singletons (213)	680	622–770	470–964	—
	Multiples (85)	670	610–730	460–907	—
25 wk (*n* = 357)	Boys (187)	780	685–875	370–1040	—
	Girls (170)	739	670–810	470–1000	—
	Singletons (249)	770	690–858	470–1040	—
	Multiples (108)	737	646–832	370–994	—
Total (*n* = 811)	Boys (436)	712	632–822	364–1040	12 (2.8%)
	Girls (375)	680	600–758	360–1000	21 (5.6%)
	Singletons (574)	700	622–796	400–1040	16 (2.8%)
	Multiples (237)	670	600–760	360–994	17 (7.2%)

TABLE 5. Markers of Condition Over First 12 Hours and Use of Surfactant Therapy

Gestation Completed Weeks	Heart Rate <100 bpm 5 Minutes After Birth		Admission Temperature °C			CRIB Score (9)		Surfactant Therapy		
	Number Positive/ Number Reporting	%	*n*	Median IQR	% Below 35°C	*n*	Median IQR	Number Receiving/ Number Reporting	%	% of Those Treated Receiving Animal-Derived Surfactant
21	2/3	66.7	3	32.0	66.7	2	13, 17	2/3	66.7	50.0
22	5/21	23.8	20	34.0 33.4–34.8	80.0	20	14 11–17	16/22	72.7	75.0
23	23/125	18.4	120	34.5 33.5–35.6	58.3	111	13 11–17	102/131	77.9	54.9
24	33/291	11.3	279	35.0 34.1–35.8	42.7	276	12 9–15	259/296	87.5	57.5
25	51/344	14.9	335	35.3 34.8–36.0	29.6	329	8 5–11	303/351	85.4	58.9
Total	114/783	14.6	757	35.0 34.1–35.9	40.4	738	11 8–14	682/803	84.1	58.2

admitted infants were ventilated via a tracheal tube; no details of ventilation mode or settings were collected.

Patent ductus arteriosus was reported in 202 of 313 of the infants (65%) who survived to discharge. Of these, 116 (57%) were treated with indomethacin alone, 26 (13%) with indomethacin and ligation, and 6 (3%) with ligation alone.

Corticosteroids were administered postnatally for chronic lung disease to 304 infants (39%), with increasing frequency at higher gestational age (χ^2 trend, $P = .002$; Table 6). There was no difference in the age at which steroids were started in infants of different maturity; however, they were started earlier in those who died (median age: 14 days; interquartile range [IQR]: 8–19), compared with those who survived (21 days; IQR: 12–29; $P < .0001$). Only 5 surviving infants started steroids before day 7. Steroids were given to 72% of survivors with a median use of 24 days (IQR: 15–36).

TABLE 6. Postnatal Treatment With Steroids for Chronic Lung Disease

Gestation (Weeks)	Number Receiving Steroids *n*/*n* Reporting (%)	Age Steroids Started (Days)		Number of Survivors Receiving Steroids *n*/*n* Reporting (%)	Duration of Treatment in Survivors (Days)	
		n	Median; IQR		*n*	Median; IQR
≤23	42/148 (28.4)	40	20.5; 14–29	24/28 (85.7)	22	25; 15–30
24	112/294 (38.1)	111	19.0; 12–35	77/99 (77.8)	74	24.5; 15–42
25	152/347 (43.8)	148	17.5; 11–27	126/186 (67.7)	126	23; 14–35
Total	306/789 (38.8)	299	19.0; 12–29	227/313 (72.5)	222	24; 15–36

Outcomes

Deaths

Of the 811 admissions, 61% died before discharge from hospital ($n = 497$). The mode of death of 11 infants was not recorded. Intensive care was actively withdrawn in 55% of those who died ($n = 269$; Table 7), the frequency did not vary with gestational age (χ^2 trend, $P = .22$). Although most infants died early in their postnatal course, intensive care was actively withdrawn up until the 170th day. Among the 486 infants who did not survive to discharge, 27% ($n = 131$) never had a cerebral ultrasound scan. The median age at death of this group was 1 day (IQR: 0–1 day). Lack of a cerebral ultrasound scan was more common in those whose intensive care was not actively withdrawn (33% vs 22%; $P < .001$). Of the cerebral ultrasound scans performed on these infants ($n = 355$), 113 (32%) showed major abnormality (parenchymal cysts and/or hydrocephalus). Scans with these abnormalities were more frequent in the group whose intensive care was actively withdrawn (40 vs 20%; $P < .0001$). Postmortem examinations were performed on 29% of the infants who died.

The most frequently cited cause of death was "pulmonary insufficiency" (Table 8), defined as ". . . ventilatory support unsatisfactory from the outset."

The results of logistic regression analysis to evaluate the independent association of the recorded variables with death are shown in Table 9. When the analysis was adjusted by including the descriptors of early postnatal clinical condition, gestational age, birth weight, multiple birth, and tocolysis were no longer independently associated with death. Death rates were not affected by the use of any surfactant or in the subgroup of infants treated with an animal-derived surfactant product.

TABLE 8. Primary Cause of Death Excluding Those With Lethal Congenital Abnormalities

Pulmonary insufficiency	167 (34.4%)
RDS ± IVH ± infection	150 (30.9%)
Late sequelae of ventilation	40 (8.2%)
Infection	40 (8.2%)
Intracranial bleeding	28 (5.8%)
Necrotizing enterocolitis	17 (3.6%)
Other*	43 (8.9%)
No cause stated	15 (3.1%)

IVH indicates intraventricular hemorrhage.
* Including 13 pulmonary hemorrhage, 4 air leak, 2 severe hypotension, 2 hypernatraemia, 2 sudden collapse, 1 pulmonary hypoplasia, 1 pulmonary hypertension, 1 brain stem infarct, 1 periventricular leukomalacia, and 1 intraperitoneal bleed.

Survival

Rates of survival to 28 days of age, to EDD, and to discharge from hospital are shown in Table 10, in gestational age, and in birth weight groups. Expressed as a percentage of reported live births, survival to discharge at 23 weeks was 11% (95% CI: 7.0–15), at 24 weeks was 26% (95% CI: 22–31), and at 25 weeks was 44% (95% CI: 39–49). Most deaths occurred early in the postnatal course (Fig 1). The proportions of those infants alive on the 7th and on the 28th day who survived until discharge were

TABLE 7. Comparison of Age at Death, Ultrasound Findings, and Autopsy Rate Among Infants Who Did and Did Not Have Intensive Care Actively Withdrawn

	Active Withdrawal of Intensive Care *n* = 269 (55.3%) Age at Death (Days)				Care Not Actively Withdrawn *n* = 217 (44.7%) Age at Death (Days)				
	n	Median	75th Percentile	Maximum	*n*	Median	75th Percentile	Maximum	
Gestation (wk)									
21	2	1	2	—	1	2	—	—	
22	13	1	5	40	7	2	23	26	
23	51	1	2	168	54	2	15	225	
24	101	3	12	168	97	2	13	164	
25	102	4	15	170	69	2	8	325	
All	269	3	11	170	217	2	13	325	
Cerebral ultrasound scans									*P* Value
None recorded			60 (22.3%)				71 (32.7%)		<.0001
Cysts and/or ventriculomegaly			84/209 (40.2%)				29/146 (19.9%)		<.0001
Autopsy performed			71/269 (26.4%)				68/215 (31.6%)		.23

TABLE 9. Results of Univariate and Multivariate Analyses of Factors Associated With Death Before Discharge

Variable (All Yes/No Unless Stated)	(*n*)	Univariate Analysis		Multivariate Analysis (Variables Known at Birth) *n* = 781		Multivariate Analysis (All Variables) *n* = 712	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Known at birth							
Gestation (per wk)	(811)	.47 (.38–.57)	<.0005	.47 (.38–.58)	<.0005		
Birth weight (per 100 g)	(811)	.60 (.53–.68)	<.0005				
Birth weight for gestation (per 100 g)	(811)	.68 (.59–.79)	<.0005	.68 (.58–.79)	<.0005		
Multiple	(811)	1.39 (1.01–1.90)	.044	1.55 (1.08–2.22)	.018		
Male sex	(811)	1.31 (.98–1.74)	.066	1.41 (1.03–1.94)	.033	1.64 (1.10–2.36)	.008
Any obstetric problems	(804)	.78 (.58–1.05)	.100				
Preeclampsia	(798)	1.63 (.71–3.75)	.250				
PROM (>24 h)	(798)	.68 (.49–.95)	.023				
Cervical suture	(798)	.57 (.34–.97)	.040				
APH	(798)	1.33 (.97–1.84)	.081				
Chorioamnionitis	(798)	.47 (.33–.68)	<.0005	.49 (.32–.73)	.001	.51 (.32–.82)	.005
Antenatal steroid	(800)	.38 (.28–.53)	<.0005	.50 (.35–.73)	<.0005	.57 (.38–.85)	.006
Tocolytics	(792)	.57 (.41–.79)	.001	.66 (.45–.97)	.034		
Maternal age (per y)	(801)	.98 (.96–1.01)	.460				
Ethnic group = white	(811)	1.13 (.81–1.59)	.130				
Postnatal variables							
Cesarean vs vaginal delivery	(805)	1.07 (.73–1.58)	.720				
HR at 5 min <100 bpm	(811)	3.21 (1.95–5.28)	<.0005			1.99 (1.07–3.67)	.029
Admission temperature ≥35°C	(757)	.31 (.23–.43)	<.0005			.58 (.39–.85)	.006
CRIB score (per point; 9)	(738)	1.35 (1.29–1.42)	<.0005			1.31 (1.25–1.38)	<.0005
Postnatal transfer	(804)	1.32 (.87–2.01)	.190				
Surfactant therapy	(811)	.95 (.64–1.41)	.790				

OR indicates odds ratio of dying; APH, antepartum hemorrhage.

greater at higher gestational age (χ^2 trend, $P < .0001$ and $P = .0005$, respectively; Table 11).

Major Complications of Prematurity Among Survivors

A report was received on at least 1 cerebral ultrasound scan from all survivors to discharge. Fewer scan reports were received at EDD because many infants were already at home (Table 12). The last scan performed on 52 of the infants showed major abnormality (groups 3–5, Table 12). There was no significant association of major abnormality on the scan with decreasing gestational age (χ^2 trend, $P = .16$).

Forty-five infants received treatment for ROP, 44 to both eyes (Table 13). At 36 weeks' PMA, 74% of infants were still receiving supplementary oxygen, as were 51% at 40 weeks; 32% were discharged with home oxygen therapy. Both treated ROP and oxygen dependence at 40 weeks' PMA were more common in the more preterm infants (Table 13).

All 3 of these adverse outcomes occurred in 7 infants (2%) and 2 of the 3 in 46 (15%; Fig 2). Infants of lower gestational age were more likely to have 2 or more adverse outcomes than were more mature infants (χ^2 trend, $P = .007$).

Logistic regression analysis was performed using the same variables as in the previous analysis (Table 9) with, on this occasion, the 3 major complications of prematurity: major abnormality on the last cerebral ultrasound scan available, treated ROP, and oxygen dependence at EDD as separate outcomes (Table 14). Major scan abnormality was less common in infants whose mothers had received steroids for >24 hours before delivery and more common if the mother had received tocolytics or if the infants were transferred postnatally. In contrast, severe ROP was more common at shorter gestation but was less common in black babies and after pregnancies with no obstetric complication. Supplementary oxygen at EDD was more commonly needed after shorter gestation, in boys, and after tocolysis. Among postnatal variables, there were no associates with ROP but chronic oxygen dependency was associated with hypothermia, higher CRIB score, and the use of surfactant.

Additionally, 7% survivors (23/308) were reported to have pulmonary hemorrhage of sufficient severity to necessitate adjustment of ventilator settings and 4% (13/308) had either peritoneal drainage for suspected intestinal perforation or a laparotomy for necrotizing enterocolitis and/or intestinal perforation. The frequency of these complications did not vary with gestational age.

DISCUSSION

This is the largest population-based study of infants of very low gestation to have been reported. The majority of previously published outcome data for extremely immature infants are based on birth weight and inevitably include both appropriately grown and small for gestational age infants. In order for professionals to work with parents to plan care around the time of birth reliable outcome data based on gestational age are needed. The aim of this study was to gain complete information about the outcome of births between the 20- to 25-week gestational age range in the United Kingdom and Ireland. Details of deliveries were recorded down to 20 completed weeks of gestation to ensure inclusion of the most immature live-born infants. The option for infants to be included when neither certain menstrual dates nor an early scan was available was agreed before the study started because some pediatricians thought this was likely to be a common occurrence. In the

TABLE 10. Survivors (% of Admissions) at 28 Days, Expected Date of Delivery, and Discharge From Hospital by Gestation and Birth Weight*

	Total Population	Infants Not Transferred	Postnatal Transfers	Singletons	Multiples	Singletons Not Transferred
Gestation						
21 wk	$n = 3$; no survivors					
22 wk	$n = 22$	$n = 19$	$n = 3$	$n = 13$	$n = 9$	$n = 10$
28-d survivors (%)	3 (13.6%)	2 (10.5%)	1 (33.3%)	2 (15.4%)	1 (11.1%)	1 (10.0%)
EDD survivors (%)	2 (9.1%)	2 (10.5%)	0	1 (7.7%)	1 (11.1%)	1 (10.0%)
Discharged (%; 95% CI)	2 (9.1%; 0–21.1)	2 (10.5%; 0–24.2)	0	1 (7.7%; 0–22.2%)	1 (11.1%; 0–31.6)	1 (10.0%; 0–28.5)
23 wk	$n = 131$	$n = 105$	$n = 23$	$n = 94$	$n = 35$	$n = 79$
28-d survivors (%)	38 (29.2%)	30 (28.6%)	8 (36.4%)	31 (34.3%)	7 (20.0%)	25 (31.7%)
EDD survivors (%)	28 (21.4%)	22 (21.0%)	6 (26.1%)	23 (24.5%)	5 (14.3%)	19 (24.1%)
Discharged (%; 95% CI)	26 (19.9%; 13.1–26.7)	20 (19.1%; 11.6–26.6)	6 (26.1%; 8.2–44.0)	22 (23.4%; 14.8–32.0)	4 (11.3%; 0.8–21.8)	18 (22.8%; 13.5–32.1)
24 wk	$n = 298$	$n = 253$	$n = 39$	$n = 211$	$n = 83$	$n = 180$
28-d survivors (%)	129 (43.3%)	111 (43.9%)	16 (41.0%)	101 (47.9%)	26 (31.3%)	87 (48.3%)
EDD survivors (%)	107 (35.9%)	95 (37.6%)	12 (30.8%)	86 (40.8%)	21 (25.3%)	76 (42.2%)
Discharged (%; 95% CI)	100 (33.6%; 28.2–39.0)	88 (34.8%; 32.9–40.7)	12 (30.8%; 16.3–45.3)	81 (38.4%; 31.8–45.0)	19 (22.9%; 14.9–31.3)	71 (39.4%; 32.3–46.5)
25 wk	$n = 357$	$n = 299$	$n = 49$	$n = 244$	$n = 108$	$n = 211$
28-d survivors (%)	209 (59.2%)	185 (62.7%)	22 (44.9%)	145 (60.4%)	64 (59.3%)	131 (63.3%)
EDD survivors (%)	192 (53.8%)	171 (57.2%)	20 (40.8%)	134 (54.9%)	58 (53.7%)	121 (57.4%)
Discharged (%; 95% CI)	186 (52.1%; 46.9–57.3)	165 (55.2%; 49.4–60.8)	20 (40.8%; 27.0–54.6)	131 (54.7%; 46.2–54.7)	55 (50.9%; 41.5–60.3)	118 (55.9%; 49.2–62.6)
Birth weight						
<500 g	$n = 33$	$n = 29$	$n = 4$	$n = 16$	$n = 17$	$n = 14$
28-d survivors (%)	3 (9.1%)	3 (10.3%)	0	0	3 (17.7%)	0
EDD survivors (%)	3 (9.1%)	3 (10.3%)	0	0	3 (17.7%)	0
Discharged (%; 95% CI)	2 (6.1%)	2 (6.9%; 0–34.0)	0	0	2 (11.8%; 0–27.1)	0
500–749 g	$n = 497$	$n = 419$	$n = 65$	$n = 338$	$n = 151$	$n = 293$
28-d survivors (%)	201 (40.8%)	174 (41.8%)	24 (37.5%)	148 (44.3%)	51 (33.8%)	131 (45.2%)
EDD survivors (%)	164 (33.0%)	147 (35.1%)	17 (26.2%)	120 (35.5%)	44 (29.1%)	111 (37.5%)
Discharged (%; 95% CI)	157 (31.6%; 27.5–35.7)	140 (33.4%; 28.9–37.9)	17 (26.2%; 15.5–36.9)	116 (34.3%; 29.2–39.4)	41 (27.2%; 20.1–34.3)	106 (36.2%; 30.7–41.7)
750–999 g	$n = 276$	$n = 228$	$n = 43$	$n = 206$	$n = 67$	$n = 173$
28-d survivors (%)	172 (62.6%)	149 (65.6%)	22 (51.2%)	128 (62.4%)	44 (65.7%)	111 (64.5%)
EDD survivors (%)	159 (57.6%)	138 (60.5%)	20 (46.5%)	121 (58.7%)	38 (56.7%)	105 (60.7%)
Discharged (%; 95% CI)	152 (55.1%; 48.6–61.6)	131 (57.5%; 51.1–63.9)	20 (46.5%; 31.6–51.4)	116 (56.3%; 49.5–63.1)	36 (53.7%; 41.8–65.6)	100 (57.8%; 48.1–67.5)
>999 g	$n = 5$	$n = 3$	$n = 2$	$n = 5$	$n = 0$	$n = 3$
28-d survivors (%)	3 (60.0%)	2 (66.7%)	1 (50.0%)	3 (60.0%)		2 (66.7%)
EDD survivors (%)	3 (60.0%)	2 (66.7%)	1 (50.0%)	3 (60.0%)		2 (66.7%)
Discharged (%; 95% CI)	3 (60.0%)	2 (66.7%)	1 (50.0%)	3 (60.0%)		2 (66.7%)
Total	$n = 811$	$n = 679$	$n = 114$	$n = 565$	$n = 235$	$n = 483$
28-d survivors (%)	379 (47.0%)	328 (48.7%)	47 (41.6%)	279 (49.8%)	98 (41.7%)	244 (50.9%)
EDD survivors (%)	329 (40.6%)	290 (42.7%)	38 (33.3%)	244 (43.2%)	85 (36.2%)	217 (44.6%)
Discharged (%; 95% CI)	314 (38.7%; 35.3–42.1)	275 (40.5%; 36.8–44.2)	38 (33.3%; 24.6–42.0)	235 (41.6%; 37.5–45.7)	79 (33.6%; 27.3–40.6)	208 (43.1%; 38.7–47.5)

* Total population includes 3 born outside hospital; the remaining columns exclude these 3 and those with lethal congenital anomalies.

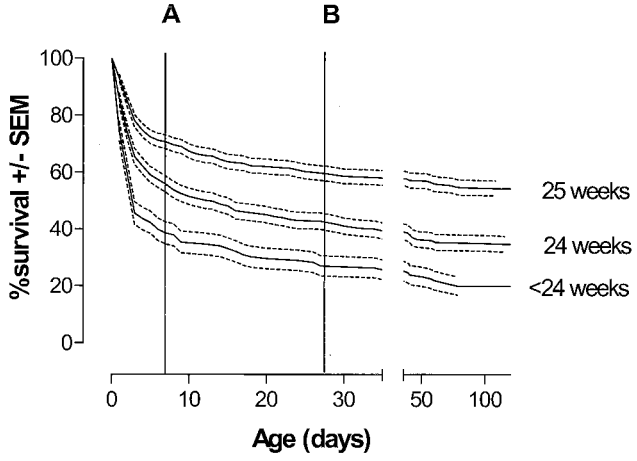

Fig 1. Survival curves for all infants admitted to neonatal intensive care units (n = 357 at 25 weeks, 298 at 24 weeks, and 156 at <24 weeks' gestation). The probability of survival to discharge from hospital for survivors to 7 days (point A) and 28 days (point B) is given in Table 11.

event, this situation arose only for 26 infants (.3% of admissions). The birth weights of these infants fell within the normal range for gestational age and they were included in the analysis.

We found discrepancies between the gestational ages entered on the delivery room records and those subsequently calculated by the investigators despite the fact that all of the information on the record form should have been available to delivery room staff. It seems inevitable that a few infants whose birth was not included in the delivery room record because they were considered to be 26 or more completed weeks' gestation were in fact more immature. The number of such infants will be small and their exclusion will not effect the conclusions of this study.

In interpreting the results it is important to remember that this is an epidemiologic study with both obstetric and neonatal care provided entirely at the discretion of the attending staff. We restricted the collection of data to items that were objective and easily defined. For instance it was agreed that to attempt to record details of resuscitation efforts would yield unreliable data that could not be validated.

We know nothing of the rates of obstetric complications among the mothers whose infants were not admitted for intensive care (stillbirths and delivery room deaths). The incidence of such complications in women whose infants were admitted was high (63%), with particularly high rates of previous pregnancy loss, similar to the findings of the detailed population based study from western Australia.[9] The high proportion of multiple pregnancies, with rates higher among white than among black women, is likely to be attributable to fertility treatments. The use of antenatal steroids seen in this study will probably have increased further since these infants were born. This is particularly important, not only because of the survival advantage seen for even the most immature infants but also because of the significant association with the finding of fewer major abnormalities on the cerebral ultrasound scans. It will be important to determine whether this is reflected as an outcome advantage when they are assessed later.

Information on the use of tocolytics was collected because it was thought that it might indicate pregnancies toward which obstetricians had a more positive attitude. It is interesting that although there was an advantage for survival, tocolysis was associated with an increased incidence of abnormal cerebral scans and more oxygen dependency. The cesarean section rates are modest irrespective of presentation. The excess number of cesarean sections in pregnancies with obstetric complications suggests that the majority are performed for maternal rather than for fetal reasons. Attempts to mount randomized, controlled trials of operative delivery in uncomplicated very preterm pregnancies to improve neonatal outcome have proved difficult to complete[10]; the data from this study do not strengthen arguments in favor of operative delivery for fetal indications.

Four percent of the infants (n = 33) admitted for intensive care, including 8 at 25 weeks of gestation had a birth weight below the recommended lower limit of 500 g set by the World Health Organization for routine collection of perinatal data. Only 2 of these (6%) survived to be discharged from hospital. Mortality was high in the first few days at all gestational ages but particularly in the most immature infants, the construction of survival curves for this large population (Fig 1; Table 11) will help clinicians in their discussions both with parents and with those responsible for planning service requirements.

Caution is required in the interpretation of the regression analysis examining for associations between maternal and early neonatal items with death because only infants born in good enough condition to be admitted to NNUs are included. Nonetheless, it is of clinical interest that the significant associations of low gestational age and low birth weight with death, found when only considering those items known at birth, disappear when adjusted for the early postnatal indicators of clinical condition.

The complications of prematurity that were recorded were selected not only because of their importance as antecedents of later disability, but also because it was thought that they would be reported reliably in a situation when the resources to validate data from each contributing center were not available. The standardized system used for reporting cerebral ultrasound scans has been used previously in large multicenter studies.[11] National guidelines for screening for ROP were in existence in 1995, but it is known that the service was variable, and so we are reporting only the most severe cases. The criteria used in different centers to determine the need for oxygen supplementation beyond 36 weeks' PMA were not requested.

Among the 39% of this study population who were discharged from hospital, 62% had one or more cerebral parenchymal cyst and/or hydrocephalus, treated ROP, or oxygen dependence at 40 weeks' PMA. The significance of these findings for the future health and development of the children will only become apparent after further assessment.

Early markers of neonatal clinical condition dis-

TABLE 11. Survival to 7 and 28 Days for All Admissions and Probability of Survival to Discharge for Survivors at Both Ages

Gestation (Weeks)	*n* Admissions	7 Days After Birth (Fig 1, Point A)		28 Days After Birth (Fig 1, Point B)	
		% Alive at 7 Days (*n*)	% [95% CI] of 7-Day Survivors Discharged From Hospital (*n*)	% Alive at 28 Days (*n*)	% [95% CI] of 28-Day Survivors Discharged From Hospital (*n*)
≤23	156	38.1 (59)	47.5 [34.8–60.2] (28)	26.5 (41)	68.3 [54.1–82.5] (28)
24	298	56.0 (167)	59.9 [52.5–67.3] (100)	43.3 (129)	77.5 [70.3–84.7] (100)
25	357	70.5 (249)	74.7 [69.3–80.1] (186)	59.2 (209)	88.9 [84.6–93.2] (184)
Total ≤25	811	58.9 (475)	66.1 [61.8–70.2] (314)	47.0 (379)	82.7 [78.9–86.5] (312)

TABLE 12. Cerebral Ultrasound Scan Appearances in Those Discharged From Hospital

	First Scan		Scan at ~1 Week		Scan at ~6 Weeks		Scan at ~EDD	
	n	%*	*n*	%*	*n*	%*	*n*	%*
No scan performed	7	2.2	29	9.2	11	3.5	51	16.2
Not interpretable	4	1.3	3	1.2	4	1.3	5	1.9
Classification of scans								
Group 1, no abnormality seen	176	57.3	128	44.9	163	53.8	167	63.5
Group 2, IVH without ventriculomegaly	109	35.5	119	41.9	83	27.4	45	17.1
Group 3, ventriculomegaly without parenchymal changes	1	.3	6	2.1	9	3.0	9	3.4
Group 4, unilateral parenchymal cysts (± ventriculomegaly)	14	4.6	25	8.8	34	11.2	27	10.3
Group 5, bilateral parenchymal cysts (± ventriculomegaly)	3	1.0	4	1.4	10	3.2	10	3.8

IVH indicates intraventricular hemorrhage.
* Percentages for the numbers of those who had no scan performed are expressed in terms of all survivors ($n = 314$). All other results are expressed as a percentage of the scans performed at that age.

TABLE 13. Treatment of ROP and Oxygen Dependence Among Survivors

Gestational Age (Weeks)	Treated ROP	Supplemental Oxygen	
		at 36 Weeks' PMA	at 40 Weeks' PMA
	n/Number Reporting (%, 95% CI)	*n*/Number Reporting (%; 95% CI)	*n*/Number Reporting (%, 95% CI)
≤23	7/27 (25.9; 11.1–46.3)	24/28 (85.7; 67.3–96.0)	21/28 (75.0; 55.1–89.3)
24	20/100 (20.0; 12.7–29.2)	77/100 (77.0; 67.5–84.8)	62/100 (62.0; 51.7–71.5)
25	18/182 (9.9; 6.0–15.2)	130/186 (69.9; 62.8–76.4)	78/186 (41.9; 34.8–49.4)
Total discharges	45/309 (14.6; 10.8–19.0)	231/314 (73.6; 68.3–78.4)	161/314 (51.3; 45.6–56.9)
χ^2 for trend	8.2	3.99	17.1
P value	.004	.046	.00004

placed low gestational age and low birth weight from the logistic regression analysis that considered chronic oxygen dependency as the outcome just as they had done in the analysis of items associated with death. These associations with early clinical condition suggest that attention to the quality of care immediately around the time of birth may enhance survival and respiratory outcomes. Because the details and the timing of interventions in the delivery room were not requested, it is not known how many of these infants had not been successfully intubated by 5 minutes. However, it is of concern that 15% of admitted infants were bradycardic at 5 minutes and that 40% were hypothermic when the temperature was first taken.

The planned withdrawal of intensive care in 55% of the infants who died may have influenced the pattern of morbidity in survivors, although it is probable that many of these infants would have died regardless of whether intensive care was actively withdrawn. The frequency of major abnormality on the cerebral ultrasound scan among the infants who died was higher than among survivors, particularly in the group where intensive care was actively withdrawn (Table 7). It seems likely that the presence of parenchymal pathology or significant ventricular dilatation is being used as an indication to advise withdrawal of intensive care and is thereby reducing the numbers of survivors with major intracerebral lesions.

Increased survival with surfactant therapy was not observed but the use of surfactant was associated with a higher frequency of chronic oxygen dependency. This finding was true both for artificial and animal-derived surfactants and has not been possible to explain based on increased illness severity among treated infants.

During the clinical evaluation of surfactants, some

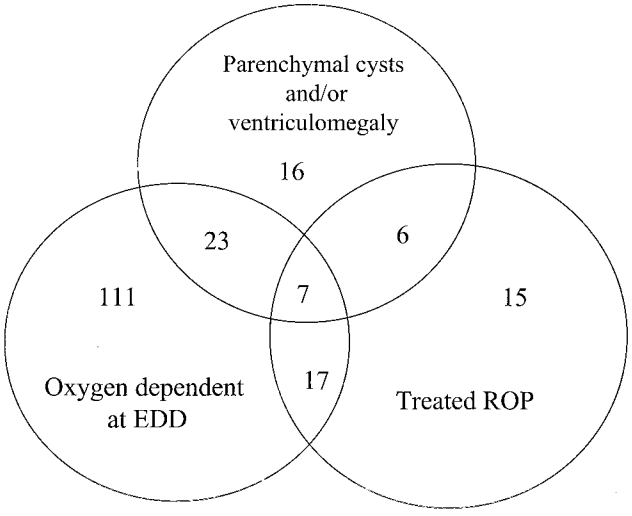

Fig 2. Diagram to show the incidence of multiple major morbidity (parenchymal cysts and/or hydrocephalus on last available cerebral ultrasound scan, oxygen dependence at EDD, and treated ROP) in all survivors to discharge from hospital.

infants were recruited into randomized, controlled trials based on their gestational age but most were recruited based on birth weight.[12] Many infants between 500 and 1000 g were involved in trials, and although some of these will have been <26 weeks, there will also have been more mature infants who were small for gestational age. There has not been a study comparing ventilation with and without surfactant confined to infants <26 weeks with adequate statistical power to assess the impact of surfactant on survival or morbidity. Before 26 weeks there is no significant pulmonary alveolarisation and absence of a beneficial effect of surfactant treatment might be predicted. The high rates of surfactant administration in this study confirm that its use is common. There is evidence of improved survival over time of infants <26 weeks' gestational age in North America, Europe, and Australia during the period of increased use of surfactant in the 1990s.[1,13–15] However, other changes have taken place during this time, in particular, increased use of antenatal steroids and probably more subtle slow improvements in ventilation, control of temperature, and fluid management increasing further the rise in survival that was already apparent in the presurfactant era.[16] To estimate how much, if any, contribution to increased survival has been made by surfactants and to investigate further any association with chronic lung disease is not possible from this study and would necessitate a randomized, controlled trial focused on this patient group.

A comprehensive review of previous reports has been published recently.[17] After exclusion of the few infants with lethal congenital anomalies, survival for the whole population of infants who were admitted for intensive care is 41%, representing only 30% of live-born infants between 23 and 25 weeks' gestational age. These survival rates are comparable to previous population based studies in the United Kingdom[1,13,18] and in Victoria, Australia.[15] Two further studies from Australia[19] and the United States[20] report higher survival rates in this gestational age range. These populations differ in several ways from

TABLE 14. Results of Univariate and Multivariate Analyses for Major Morbidity in Survivors to Discharge

Variable (All Yes/No Unless Stated)	(*n*)	Severe Scan Abnormality		Treated Retinopathy of Prematurity		Supplemental Oxygen at 40 Weeks' PMA	
		Univariate (*n* = 314) OR (95% CI)	Multivariate (*n* = 306) OR (95% CI)	Univariate (*n* = 309) OR (95% CI)	Multivariate (*n* = 309) OR (95% CI)	Univariate (*n* = 314) OR (95% CI)	Multivariate (*n* = 283) OR (95% CI)
Known at birth							
Gestation (per wk)	(314)	.78 (.53–1.17)		.59 (.39–.91)*	.53 (.34–.84)*	.50 (.35–.70)[c]	.57 (.37–.86)*
Birth weight (per 100 g)	(314)	.99 (.77–1.29)		1.00		.72 (.59–.89)[b]	
Birth weight ratio	(314)	1.13 (.84–1.52)		.70 (.52–.93)*		.81 (.64–1.01)	
Multiple	(314)	.85 (.42–1.69)		.50 (.21–1.18)		1.45 (.87–2.44)	
Male sex	(314)	.81 (.45–1.46)		.71 (.37–1.34)		1.51 (.97–2.35)	2.31 (1.35–3.93)**
Any obstetric problems	(314)	.49 (.27–.90)*		(1.49–8.07)*		1.35 (.85–2.16)	
Preeclampsia	(312)	1.65 (.32–8.4)		1.98 (.39–10.2)		.94 (.23–3.81)	
PROM	(312)	.48 (.22–1.04)		.87 (.42–1.81)		1.18 (.72–1.95)	
Cervical suture	(312)	.93 (.34–2.55)		1.53 (.59–3.97)		1.00 (.48–2.1)	
APH	(312)	1.01 (.51–2.01)		2.69 (1.39–5.21)**		1.13 (.67–1.90)	
Chorioamnionitis	(312)	.50 (.22–1.1)		.98 (.47–2.05)		.92 (.55–1.54)	
Antenatal steroid	(313)	.90 (.44–1.82)		.71 (.34–1.47)		1.16 (.67–2.00)	
Steroid >24 h before birth	(313)	.39 (.21–.73)**	.39 (.20–.77)**	1.00 (.54–1.90)		1.25 (.80–1.94)	
Tocolytics	(308)	1.51 (.81–2.8)	2.02 (1.04–3.94)*	.71 (.34–1.09)		1.74 (1.06–2.84)*	2.53 (1.42–4.51)**
Maternal age (per y)	(313)	1.00 (.95–1.05)		1.03 (.98–1.09)		.98 (.94–1.01)	.95 (.91–1.00)*
Ethnic group = black	(314)	.42 (.15–1.24)		.12 (.02–.81)*	.09 (.01–.69)*	.94 (.50–1.76)	
Postnatal variables							
Vaginal delivery	(314)	.63 (.25–1.56)		1.03 (.43–2.47)		.94 (.51–1.72)	
HR at 5 min, <100 bpm	(314)	.81 (.23–2.85)		.98 (.28–3.46)		1.05 (.43–2.54)	
Admission temperature, ≥35°C	(298)	1.00 (.50–2.00)		.68 (.33–1.40)		.40 (.23–.69)***	.50 (.27–.96)*
CRIB score[8] (per point)	(296)	1.07 (.98–1.16)		1.07 (.97–1.19)		1.17 (1.09–1.26)***	1.12 (1.03–1.22)*
Postnatal transfer	(314)	3.06 (1.44–6.46)**	2.61 (1.20–5.71)*	1.38 (.57–3.35)		1.47 (.76–2.84)	
Surfactant therapy	(314)	1.42 (.57–3.54)		.75 (.32–1.75)		3.13 (1.58–6.21)***	3.20 (1.42–7.23)**

* $P \leq .05$; ** $P \leq .001$; and *** $P \leq .0001$.
OR indicates odds ratio of developing condition; APH, antepartum hemorrhage.

the EPICure population, most strikingly in the centralization of care: in western Australia[19] 89% of all births <33 weeks gestational age occurred in a single center, and in North Carolina[20] all neonatal intensive care was provided by 2 centers. Reported survival rates from single centers in the United States[17] are consistently higher than the results of this study, but patient selection makes extrapolation to our geographically defined population difficult.

At the EDD, 1 or more of 3 markers for serious morbidity were found in 64% of the EPICure population. Rates of major cerebral ultrasound scan abnormality and severe ROP in this study are similar to those reported by others,[1,21] but the rates of prolonged oxygen dependency are high.

The extent of centralization of neonatal services in the United Kingdom and Ireland varies from region to region, but few hospitals provide care for more than a few extremely preterm infants. The postnatal transfers reported within 24 hours of birth represent only a fraction of the total transfer activity because the majority of transfers occur before birth and were not identified by this study. In 1995 only 15 hospitals had 10 or more intensive cots and, after postnatal transfer, ongoing intensive care for the infants in this study was provided by no fewer than 137 NNUs. Only 16 units reported >10 births within the gestational age range of the study during the 10-month period and only 8 had >5 survivors; the highest number in a single center being 10. This emphasizes the impossibility, in the United Kingdom or Ireland, of making reliable predictions of survival and morbidity using data from a single institution and the need for aggregated data to provide reliable information for clinicians and parents.

In this study, survival was not increased in those centers with higher numbers of extremely premature births and admissions. However, no institution in the United Kingdom has a large experience, compared with neonatal referral centers in Australia and North America. Whether survival and quality of survival in this patient group would be improved by a service reconfigured so that infants were looked after in fewer larger centers is unclear. However, survival free of major morbidity in this vulnerable patient group is so poor that it can be argued that further centralization would, at the very least, enable more experience to be gained and research programs to be developed aimed at improving their prospects.

APPENDIX

Data items included in the standardized form for all infants admitted to an NNU. Items requiring an answer yes or no are indicated y/n and ranges of options are given in parentheses. Throughout the record there were opportunities for the information to be amplified with free text.

For all admissions: center number; 6-digit patient identifier; EDD by LMP; EDD by scan <20 weeks' gestation; maternal age; ethnic origin (white, black African, black Caribbean, black other, Indian, Pakistani, other-specified, not known); number of previous pregnancies; number of live births; any obstetric problems in this pregnancy, y/n; preeclampsia = hypertension (untreated diastolic >90 mm Hg) appearing in pregnancy with proteinuria, y/n; antepartum hemorrhage = any vaginal bleeding >20 weeks gestation after exclusion of local hemorrhage from the genital tract, y/n; prolonged rupture of membranes >24 hours (PROM) = membranes ruptured for >24 hours, y/n; chorioamnionitis suspected or with bacteriologic or histologic proof (these were combined for analysis); antenatal steroids, y/n; steroids started >24 hours before birth, y/n; maternal thyroid releasing hormone, y/n; tocolysis, y/n; mode of delivery (vaginal, cesarean section in labor, cesarean section not in labor); presentation (cephalic, breech, other); hospital of birth; hospital providing continuing intensive care; age (hours) at admission to hospital providing continuing intensive care; plurality (singleton, twin, triplet, other); birth order; date and time of birth; sex; birth weight (g); occipito-frontal circumference (cm); maximum base-deficit in first 12 hours[9]; minimum appropriate fraction of inspired oxygen (F_{IO_2}) in first 12 hours[6]; maximum appropriate F_{IO_2} in first 12 hours[9]; HR: >100 bpm at 5 minutes, y/n; congenital anomalies—free text; first recorded temperature; time of first chest radiograph; radiograph score (0 = normal; 1 = fine reticulo-granular mottling, good lung expansion; 2 = mottling with air bronchograms; 3 = diffuse, mottling, heart borders just discernible, prominent air bronchograms; and 4 = bilateral confluent opacification of lungs—whiteout); received surfactant, y/n; type (Survanta, Abbott Laboratories Ltd, Kent, United Kingdom; Curosurf, Serono Laboratories (UK) Ltd, Hertfordshire, United Kingdom; Exosurf, Wellcome UK, Middlesex, United Kingdom; ALEC, Britannia Pharmaceuticals Ltd, Surrey, United Kingdom; other); date of last tracheal intubation; date of last continuous positive airway pressure; last day of supplemental oxygen; systemic steroids for chronic lung disease, y/n; date of starting steroids; total number of days of steroids; pulmonary hemorrhage = acute onset of bloody tracheal secretions with acute deterioration requiring change of ventilator management, y/n; patent ductus arteriosus (PDA), y/n; indomethacin to treat PDA, y/n; ligation of PDA, y/n; insertion of abdominal drain for suspected perforation, y/n; laparotomy for necrotizing enterocolitis, y/n; other surgical procedures—free text; medications at EDD and/or discharge (systemic steroids, diuretics, anticonvulsants, methyl xanthines, others excluding nutritional supplements—specify); received total parenteral nutrition, y/n; age amino acids started; age lipids started; age enteral feeding started; received breast milk, y/n; weight, length, and occipito-frontal circumference at 4 weeks and EDD; developed any signs of ROP at any time, y/n; ROP right eye treated (cryotherapy, laser, date of first treatment); ROP left eye treated (cryotherapy, laser, date of first treatment); cerebral ultrasound—first after birth and closest to 1 week, 6 weeks, and EDD-scoring—each side separately: hemorrhage (0 = none, 1 = subependymal or choroidal, 2 = intraventricular, and 3 = parenchymal), ventricular size (0 = no dilatation, 1 = <4 mm >97th percentile,[5] and 2 = >4 mm >97th percentile), parenchymal cysts (0 = none, 1 = porencephalic cyst(s), and 2 = cystic leukomalacia); discharge before EDD, y/n; date of discharge; transfer(s) before EDD, y/n; destination(s) after transfers and/or discharge; death, y/n; date of death; active withdrawal of intensive care, y/n (asked only to tick yes if a formal decision had been made to withdraw care after appropriate discussion with family and staff and not to include occasions when the infant was extubated before death after an acute deterioration and unsuccessful resuscitation); postmortem examination, y/n (full, limited); and principal category of death (congenital anomaly + details; pulmonary immaturity = structural immaturity of the lung so gross as to render sustained ventilatory support unsatisfactory from the outset; RDS; RDS with intracerebral hemorrhage; RDS with infection; late sequelae of ventilation; intraventricular hemorrhage; other intracranial hemorrhage; necrotizing enterocolitis; other infections; and other, specify).

Throughout the form opportunities were given for free text to amplify the information.

For survivors to discharge: name at birth and discharge; National Health Service number; mother's National Health Service number; name and address of mother/principal carer; and name and address of general practitioner and of responsible pediatrician.

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NURSE PRACTITIONERS GAIN IN ACCEPTANCE

. . . Nurse practitioners are able to prescribe medicine and, in some states, admit patients to the hospital. They pride themselves on their ability to spend more time with patients, focusing on illness prevention.

. . . The nurses' practice was the focus of a study published in January in the *Journal of the American Medical Association*. The study found no significant differences in the quality of care received by patients randomly assigned either to doctors or nurse practitioners.

. . . Dr Mary O. Mundinger, dean of the Columbia University Nursing School and the study's lead author, said the research had profound implications. "For those looking to get primary care from a nurse practitioner, they can feel increasingly safe and confident in doing so, as a result of this study," she said.

Kelley T. *New York Times* (Health and Fitness Section). April 25, 2000:D7

Noted by JFL, MD