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Changes in Perinatal Care and Outcomes in Newborns at the Limit of Viability in Spain: The EPI-SEN Study

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Key Words
Prematurity · Morbidity · Mortality · Limit of viability · Clinical decision making

Abstract
Background: Advances in perinatal care can influence morbidity and mortality in newborns at the limit of viability. Knowledge of these changes over time may help improve clinical decision making, optimize resource allocation and increase quality of care. ***Objectives:*** To evaluate the influence on morbidity and mortality of changes introduced in the perinatal care of preterm infants (22–26 weeks' gestational age, GA) in Spain between two consecutive periods (2002–2006 and 2007–2011). ***Methods:*** An analysis of prospectively collected data in a national database network (SEN1500) was performed. All live newborn infants of 22–26 weeks' GA born in or transferred to referral centers of the SEN1500 network in the first 28 days of life were included. Perinatal interventions, clinical management, neonatal morbidity, and survival until hospital discharge were retrieved. ***Results:*** A total of 5,470 newborns were included (2,533 and 2,937 in each period, respectively). The major changes introduced during the second period were as follows: (1) lower proportion of extramural births (11.0 vs. 8.9%, $p = 0.01$), (2) increase in antenatal steroids (69.5 vs. 80.8%, $p < 0.001$), (3) delivery by C-section (41.8 vs. 48.3%, $p < 0.001$) and (4) use of CPAP during resuscitation (7.8 vs. 20.7%, $p < 0.001$). Death in the delivery room decreased from 5.1 to 3.2% ($p < 0.001$). Survival increased from 49.9 to 57.9% ($p < 0.001$), and survival without major morbidity increased from 18.1 to 21.2% ($p = 0.006$). ***Conclusions:*** During the second period, a greater attachment to practices proven to have a beneficial impact on survival and reduction of morbidity in the extremely preterm infant was noted, and survival and survival without major morbidity increased. A more conservative approach was detected for newborns of 22 weeks' GA.

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Introduction

Prematurity implies a significantly greater risk of mortality and long-term sequelae, with potential compromise for the survivor's neurocognitive development. Currently, many cases of survival at 22 weeks of gestational age (GA) have been reported [1]. However, there are significant differences in survival among countries or centers [2–11]. Table 1 shows the variability in survival until hospital discharge in 4 different geographical areas: North America [3, 6], Europe [1, 5, 7, 8], Oceania [9, 10], and Japan [11]. The difficulty in comparing epidemiological results between different studies resides in the different designs or methodologies employed. Thus, survival rates may be related to all newborns born at a particular GA (including stillborn), to all live births (including those who died in the delivery room, DR) or just to those admitted to the neonatal intensive care unit (NICU) [2–11]. In addition, clinical practice changes over time as new interventions with proven results are incorporated [12]. For these reasons extrapolation of results from different centers or cultural environments does not reflect the reality of a particular region.

In Spain we have an updated population-based database of survival of newborns at the limit of viability [13]. However, to date a systematic evaluation of the changes in interventions and outcomes over time has not been carried out.

The aim of this study was to elucidate the changes that have been introduced in the perinatal care of live newborns of 22–26 weeks' GA in Spain, and to evaluate how these changes have influenced mortality and morbidity to hospital discharge during two consecutive 5-year periods: 2002–2006 and 2007–2011.

Patients and Methods

The Spanish SEN1500 network prospectively collects maternal and neonatal data of live-born infants of ≤1,500 g born in or admitted to the collaborating centers within the first 28 days of life independently of their GA. For the purpose of the present study, data corresponding to all live newborns of 22–26 weeks' GA within the database were retrieved and the results of two periods were compared: 2002–2006 and 2007–2011. During the study period, 38,751 infants of ≤1,500 g were born in Spain [14] and 25,325 were admitted to SEN1500 centers, representing 65% of all infants of ≤1,500 g born in our country during both study periods. The characteristics of the SEN1500 database have been described elsewhere [15]. Data collection and analysis were approved by the IRB of the participating centers.

For the purpose of the study, analysis of demographic characteristics and perinatal interventions of all live-born infants were included. For the analysis of survival, infants with major congenital defects (chromosome abnormalities, severe congenital cardiothoracic, central nervous system or abdominal defects) and those who died in the DR were excluded. Mortality was defined as the patient's death before hospital discharge, or until the date of the first birthday, when still hospitalized, at which time data collection ended. Major morbidity was defined as follows: intraventricular

Table 1. Survival of newborn infants of ≤25 weeks' GA as reflected in international updated references expressed as percentages

Cohort	Year(s)	Denominator	GA, weeks			
			22	23	24	25
Neonatal Research Network [3] (survival to corrected age of 18–22 months)	1998–2003	admissions to NICU	5	26	56	75
VON (multinational) [6]	2009	live births	5	33	61	–
EPICure [1]	1995	admissions to NICU	9	20	34	52
		live births + stillbirths	1	11	26	44
Epipage [7]	1997	live births	0	0	31	50
Swiss study [5]	2000–2004	live births	0	11	30	50
EXPRESS [8] (survival to 28 days)	2004–2007	live births	12	54	71	82
		live births + stillbirths	7	34	60	73
EXPRESS [8] (survival to 1 year)	2004–2007	admissions to NICU	26	65	73	84
		live births	10	53	67	82
		live births + stillbirths	4	29	50	67
Australia (regional) [9]	1990–1991	live births	0	20	44	64
New Zealand [10]	1998–1999	live births	0	9	72	
Japan (multicenter) [11] (limited to 90 days)	2005	admissions to NICU	34	54	77	85

All data refer to survival to hospital discharge, unless otherwise indicated.

hemorrhage grades III/IV [16], periventricular leukomalacia (cysts or persistent periventricular echogenicity for more than 14 days), bronchopulmonary dysplasia (BPD) defined as oxygen dependency at 36 weeks' postmenstrual age (PMA) [17], necrotizing enterocolitis ≥stage 2 of Bell [18], and retinopathy of prematurity (ROP) ≥grade 3 [19] and/or the need for laser therapy. We also analyzed and compared the total length of stay (days), survival and survival without major morbidity (severe intraventricular hemorrhage, periventricular leukomalacia, BPD, necrotizing enterocolitis, and ROP ≥3 and/or the need for laser therapy).

Data Analysis

Statistical analyses were performed using SPSS 19 software (IBM, New York, USA) [20]. Continuous variables were expressed as means and standard deviations or medians and interquartile ranges, and qualitative variables were expressed as proportions (percentages). The differences between groups for continuous variables were examined with the Student t test or the Mann-Whitney U test, or the ANOVA or Kruskal-Wallis test, as appropriate. For testing the hypothesis of qualitative variables we used the χ^2 test or Fisher's exact test, when necessary. The level of statistical significance was set at $p < 0.05$ for all comparisons.

Results

A total of 5,470 neonates at a GA ranging from 22 to 26 weeks were included: 2,533 in the first period (2002–2006) and 2,937 in the second period (2007–2011). De-

Table 2. Comparison of demographic characteristics and antenatal interventions in extremely low GA neonates in Spain in two different time periods (2002–2006 and 2007–2011)

Population characteristics	Period 1 2002–2006 (n = 2,533)	Period 2 2007–2011 (n = 2,937)	p
Gestational age distribution			<0.001
22 weeks	46 (1.8)	21 (0.7)	
23 weeks	212 (8.4)	201 (6.8)	
24 weeks	566 (22.3)	610 (20.8)	
25 weeks	755 (29.8)	903 (30.7)	
26 weeks	954 (37.7)	1,202 (40.9)	
Birth weight, g	758.9±160.7	773.8±158.6	0.001
Length, cm	32.9±2.6	33.0±2.5	0.689
Head circumference, cm	23.2±1.7	23.1±1.6	0.763
Male sex	55.7%	54.7%	0.446
Multiple gestation	30.7%	29.6%	0.372
Assisted reproductive techniques	15.7%	17.3%	0.129
Outborn patients	278/2,533 (11.0)	261/2,937 (8.9)	0.01
Antenatal steroids			
At least 1 dose	1,712/2,463 (69.5)	2,330/2,884 (80.8)	<0.001
Complete course	1,106/2,463 (44.9)	1,577/2,884 (54.7)	<0.001
Chorioamnionitis[1]	7/23 (30.4)	668/1,958 (34.1)	0.711
Maternal antibiotics	1,231/2,281 (54.0)	1,568/2,609 (60.1)	<0.001
Cesarean delivery			
22 weeks	6/46 (13.0)	4/21 (19.0)	0.522
23 weeks	33/212 (15.6)	35/201 (17.4)	0.613
24 weeks	183/566 (32.3)	222/610 (36.4)	0.143
25 weeks	313/755 (41.5)	439/903 (48.6)	0.004
26 weeks	523/954 (54.8)	718/1,202 (59.7)	0.022
Total	1,058/2,533 (41.8)	1,418/2,937 (48.3)	<0.001
1-min Apgar score ≤3	34.4%	29.0%	<0.001
5-min Apgar score ≤3	11.2%	7.8%	<0.001
Major congenital defects	3.4%	4.1%	0.216
Died in delivery room	5.1%	3.2%	<0.001

Values are numbers (with percentages in parentheses) or means ± SD, unless otherwise indicated. [1] Chorioamnionitis data were started to be collected progressively during the second period.

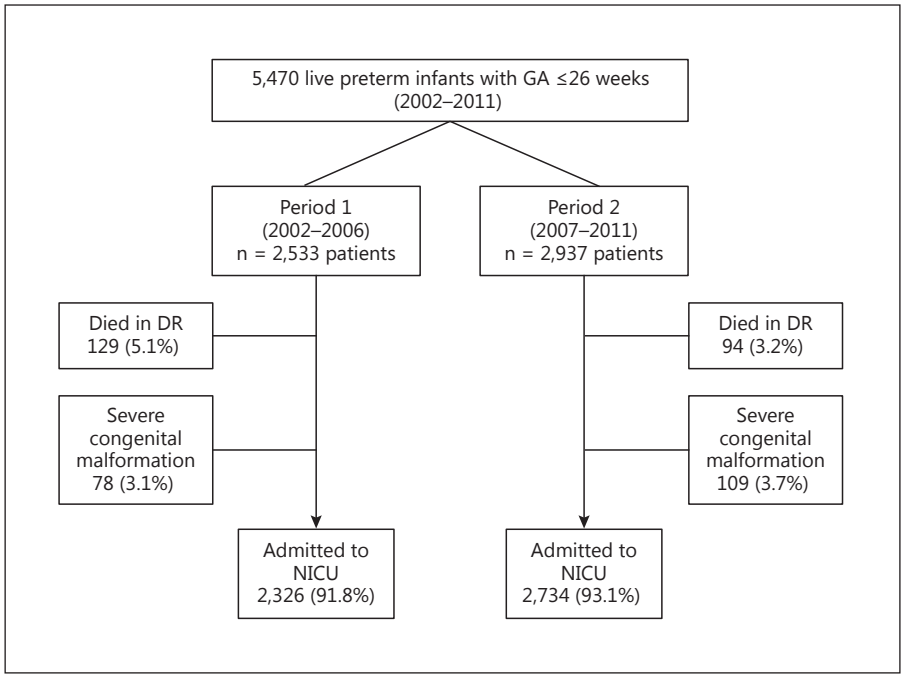

Fig. 1. Distribution of patients and exclusions. Flow diagram describing the number of preterm infants of ≤26 weeks' GA admitted to the NICU in two periods: 2002–2006 (period 1) and 2007–2011 (period 2).

mographic and perinatal characteristics are shown in table 2. The use of CPAP in the DR was significantly higher in the second period ($p < 0.001$), with the exception of neonates of 22 weeks' GA.

Of the 5,470 patients included in both periods, 223 (4.1%) died in the DR and 187 (3.4%) had major congenital anomalies and were excluded from the analysis at discharge (fig. 1). Overall, there were 539 (9.9%) outborn patients and these showed a similar mortality to inborn patients both in periods 1 and 2 (48.2 vs. 47.6%, respectively, $p = 0.764$). A total of 5,060 admitted patients (2,326 and 2,734 in each period, respectively) without major congenital anomalies were included for survival analysis.

No significant differences regarding the patients' temperature on admission to NICU and a temperature of <35°C was found between the two periods. However, physiological stability in the first 12 h of life, as indicated by the CRIB-1 score, was greater during the second period: 7 (4–10) vs. 6 (3–9), $p < 0.05$.

About 90% of patients were diagnosed with respiratory distress syndrome in each period. The mode of respiratory support is shown in table 3. Oxygen and invasive mechanical ventilation were less frequently used during the second period, with an increase in the use of noninvasive ventilation, especially after 24 weeks of GA. The total time of invasive mechanical ventilation in survivors was significantly reduced in the second period: 14 days (3.3–32) vs. 12 days (2–28), $p < 0.05$. This was also the case with the total time on oxygen therapy: 57.5 days (30–88.3) vs. 51 days (22.3–77), $p < 0.001$. The incidence of pneumothorax (10.4 vs. 9.5%) and the use of postnatal steroids for BPD (15% in both periods) did not substantially change.

The proportion of ROP ≥3 decreased in the second period (18.0 vs. 14.9%, $p = 0.018$). Laser treatment did not show significant differences.

The incidence of early sepsis and the incidence of nosocomial infections, defined as the presence of compatible clinical symptoms plus a positive blood or cerebrospinal fluid culture before or after 72 h of life, respectively, did not change. However, late-onset neonatal sepsis and/or meningitis, defined as infection with positive culture acquired after 72 h after birth, increased significantly in the second period (47.5 vs. 53.5%, $p < 0.001$). In contrast, Candida infections decreased significantly (13.9 vs. 9.4%, $p < 0.001$).

Birth weight at 28 days (table 2) in survivors was significantly higher in period 2 (991 ± 209 vs. 1,029 ± 211 g, $p < 0.001$) and at 36 weeks' PMA (1,890 ± 365 vs. 1,967 ± 377 g, $p < 0.001$).

Survival and survival without major morbidity increased with GA and in period 2 compared to period 1 (table 4).

The average length of stay (days) of patients who were discharged home significantly decreased in the second

Table 3. Interventions performed in the DR and care given in the NICU to extremely low GA neonates in two different time periods (2002–2006 and 2007–2011) as retrieved from the Spanish Neonatal Registry SEN1500

	Period 1	Period 2	p
Interventions performed in DR	n = 2,533	n = 2,937	
Oxygen			
22 weeks	18/46 (39.1)	8/21 (38.1)	0.936
23 weeks	152/211 (72.0)	149/198 (75.3)	0.461
24 weeks	515/561 (91.8)	555/609 (91.1)	0.683
25 weeks	707/746 (94.8)	816/897 (91.0)	0.003
26 weeks	852/941 (90.5)	1,047/1,188 (88.1)	0.075
Total	2,244/2,505 (89.6)	2,575/2,913 (88.4)	0.166
CPAP[1]			
22 weeks	–	–	–
23 weeks	0/22 (0)	6/56 (10.7)	<0.001
24 weeks	14/136 (10.3)	47/282 (16.7)	<0.001
25 weeks	19/245 (7.8)	116/546 (21.2)	<0.001
26 weeks	26/351 (7.4)	187/839 (22.3)	<0.001
Total	79/757 (7.8)	357/1,725 (20.7)	<0.001
Intubation			
22 weeks	14/46 (30.4)	4/17 (19.0)	0.329
23 weeks	129/211 (61.1)	142/198 (71.7)	0.024
24 weeks	470/562 (83.6)	517/610 (84.8)	0.598
25 weeks	598/750 (79.7)	693/900 (77.0)	0.180
26 weeks	674/941 (71.6)	819/1,199 (68.3)	0.097
Total	1,885/2,510 (75.1)	2,175/2,928 (74.3)	0.490
Surfactant in DR			
22 weeks	4/42 (9.5)	1/21 (4.8)	0.510
23 weeks	29/207 (14.0)	32/199 (16.1)	0.559
24 weeks	143/551 (26.0)	161/607 (26.5)	0.825
25 weeks	154/734 (21.0)	208/898 (23.2)	0.291
26 weeks	183/931 (19.7)	251/1,197 (21.0)	0.456
Total	513/2,465 (20.8)	653/2,922 (22.3)	0.173
Surfactant at any time			
22 weeks	16/39 (41.0)	4/21 (19.0)	0.085
23 weeks	142/204 (69.6)	149/199 (74.9)	0.238
24 weeks	492/553 (89.0)	534/610 (87.5)	0.451
25 weeks	671/750 (89.5)	765/899 (85.1)	0.008
26 weeks	792/946 (83.7)	980/1,198 (81.8)	0.244
Total	2,113/2,492 (84.8)	2,432/2,927 (83.1)	0.089
Interventions in NICU	n = 2,326	n = 2,734	
Oxygen therapy			
22 weeks	20/20 (100)	7/7 (100)	–
23 weeks	144/154 (93.5)	140/160 (87.5)	0.07
24 weeks	513/524 (97.9)	537/567 (94.7)	0.006
25 weeks	682/706 (96.6)	788/849 (92.8)	0.001
26 weeks	869/904 (96.1)	1,015/1,141 (89.0)	<0.001
Total	2,228/2,308 (96.5)	2,487/2,724 (91.3)	<0.001
Noninvasive ventilation before intubation			
22 weeks	0/17 (0)	1/7 (14.3)	0.111
23 weeks	6/149 (4.0)	11/161 (6.8)	0.278
24 weeks	23/512 (4.5)	69/571 (12.1)	<0.001
25 weeks	51/697 (7.3)	171/853 (20.0)	<0.001
26 weeks	72/884 (8.1)	280/1,142 (24.5)	<0.001
Total	152/2,259 (6.7)	532/2,734 (19.5)	<0.001

Table 3 (continued)

	Period 1	Period 2	p
Invasive mechanical ventilation (conventional or high-frequency ventilation)			
22 weeks	18/20 (90.0)	6/7 (85.7)	0.756
23 weeks	140/155 (90.3)	142/160 (88.8)	0.649
24 weeks	511/525 (97.3)	550/570 (96.5)	0.422
25 weeks	683/710 (96.2)	798/850 (93.9)	0.038
26 weeks	835/909 (91.9)	1,002/1,139 (88.0)	0.004
Total	2,187/2,319 (94.3)	2,498/2,726 (91.6)	<0.001

Values are numbers (with percentages in parentheses).
[1] Data were started to be collected progressively at the end of the first period.

period: 96 days (80–115) vs. 92 days (78–110), $p < 0.05$. In addition, the PMA at discharge decreased with increasing GA at birth, this reduction being more evident during the second period (table 4). Finally, the proportion of patients fed exclusively mother's milk at discharge increased significantly in the second period, from 18.3 to 36.6% ($p < 0.001$).

The mean time to death in patients who did not survive was similar during both periods: 4 days (1–14) and 6 days (2–17), respectively. Overall, 57.8% patients died in the first week of life and 85.7% in the first 28 days. The main identified causes of death were respiratory (37.6%), infectious (23.3%), neurological (14.9%), others (18.8%), and unspecified (5.5%).

Data concerning withholding or withdrawing therapy in the DR were collected in 45% of patients during the first period and in 75.5% in the second. In most patients who died in the DR a decision to withhold or withdraw resuscitation was recognized (87.9 and 90.1%, respectively, in each period; table 5).

Data regarding decisions to limit therapy were available for 44% of patients during the first period and for 95.3% during the second. Withdrawing therapy was similar in both periods (34.9 and 37.7%, respectively; table 5). The main reason related to discontinuation of intensive care was the presence of major brain damage (71.2% of patients).

Discussion

This is the first multicenter study about morbidity and mortality in extremely low GA neonates carried out in Spain that compares how changes in perinatal interventions introduced over a substantial period of time (5 years) have influenced relevant clinical outcomes such as survival and survival without major morbidity. During the second study period (2007–2011), there was a 17.5% increase in the number of patients born in or admitted to our units. According to the INE (Spanish Statistics Institute), the prematurity rate remained stable in Spain during the 10 years of the study (7.7% of all births), but the proportion of neonates of <28 weeks' GA increased by 18% (from 2.95% during the first period to 3.48% in the second). An interesting finding in our study was that the increase in the absolute number of patients admitted during the second period was due to infants of 24 weeks' GA or greater, with a lower number of admissions of infants of 22 and 23 weeks' GA (table 2). In fact, patients of 22 weeks' GA received less oxygen in the DR, were less frequently intubated and received less surfactant in the DR or later (table 3), indicating that to some extent therapeutic limitation was implemented in this GA group (table 5). This is in agreement with other studies in which the proportion of live-born babies for whom active stabilization was withheld at birth decreased with increasing gestation from 73% at 22 weeks to <2% at 24–26 weeks [21].

In recent years, a number of interventions, including antenatal steroids, oxygen titration in the DR, noninvasive ventilation, regionalization of preterm deliveries, strict use of postnatal steroids, and extensive use of human milk, may have contributed to improving survival and short- and long-term clinical outcomes [12, 22, 23].

Our study shows that during the second period there was greater attachment to practices (table 2) proven beneficial such as antenatal steroid administration and regionalization, which avoids complications associated

Table 4. Discharge disposition of extremely low GA neonates born in two different time periods (2002–2006 and 2007–2011)

Discharge disposition	Period 1 (n = 2,326)	Period 2 (n = 2,734)	p
Survival			
22 weeks	1/20 (5)	1/7 (14.3)	0.419
23 weeks	19/155 (12.3)	32/161 (19.9)	0.066
24 weeks	191/526 (36.3)	205/571 (35.9)	0.888
25 weeks	356/713 (49.9)	509/853 (59.7)	<0.001
26 weeks	594/912 (65.1)	837/1,142 (73.3)	<0.001
Total	1,161/2,326 (49.9)	1,584/2,734 (57.9)	<0.001
Survival without major brain damage			
22 weeks	1/20 (5)	1/7 (14.3)	0.419
23 weeks	14/155 (9.0)	23/158 (14.6)	0.130
24 weeks	150/522 (28.7)	145/562 (25.8)	0.278
25 weeks	274/706 (38.8)	389/827 (47.0)	0.001
26 weeks	470/895 (52.5)	640/1,101 (58.1)	0.012
Total	909/2,298 (39.6)	1,198/2,655 (45.1)	<0.001
Survival without BPD			
22 weeks	0/20	0/7	–
23 weeks	7/154 (4.5)	11/156 (7.1)	0.346
24 weeks	81/511 (15.9)	78/556 (14.0)	0.404
25 weeks	164/682 (24.0)	244/762 (32.0)	0.001
26 weeks	338/831 (40.7)	465/1,004 (46.3)	0.015
Total	590/2,198 (26.8)	798/2,485 (32.1)	<0.001
Survival without major morbidity[1]			
22 weeks	0	0	–
23 weeks	2/155 (1.3)	5/159 (3.1)	0.266
24 weeks	49/514 (9.5)	33/562 (5.9)	0.024
25 weeks	109/690 (15.8)	181/791 (22.9)	0.001
26 weeks	242/844 (28.7)	321/1,024 (31.3)	0.210
Total	402/2,223 (18.1)	540/2,543 (21.2)	0.006
PMA at discharge in survivors, weeks			
22 weeks	–	–	–
23 weeks	40.9±3.1	43±4.9	0.109
24 weeks	41.7±5.1	41.1±3.8	0.163
25 weeks	40.5±4.1	40.2±4.6	0.317
26 weeks	39.5±4.7	39±3.3	0.013

Values are numbers (with percentages in parentheses) or means ± SD.

[1] Major morbidity: major brain damage, BPD, ROP ≥3 and/or need of laser therapy and/or necrotizing enterocolitis.

with neonatal transport [24]. Spain has a regionalized National Health Service covering its entire territory. Perinatal centers are classified according to the availability of technology and the degree of severity of patients who can be admitted. This organizational structure clearly facilitates regionalization of perinatal conditions [25]. In addition, obstetric practice changed and the rate of C-section in preterm births, which was associated with a higher survival ratio, significantly increased in the second period, primarily in gestations of >24 weeks (table 2).

Recommendations to avoid lung overdistension and unnecessary exposure to high concentrations of oxygen during CPR and subsequent management of patients [12] were better followed during the second period. In our study, the early use of CPAP in the DR increased significantly in all groups, except for infants of 22 weeks' GA (table 3). The administration of oxygen and invasive me-

Table 5. Mortality and withholding or withdrawing therapy

	Period 1	Period 2	p
Total born alive	n = 2,533	n = 2,937	
Mortality in DR			
22 weeks	26/46 (56.5)	14/21 (66,7)	0.432
23 weeks	51/212 (24.1)	34/201 (16.9)	0.073
24 weeks	32/566 (5.7)	25/610 (4.1)	0.215
25 weeks	15/755 (2.0)	12/903 (1.3)	0.292
26 weeks	5/954 (0.5)	9/1,202 (0.7)	0.519
Total	129/2,533 (5.1)	94/2,937 (3.2)	<0.001
Withholding or withdrawing therapy in DR			
22 weeks	11/11 (100)	11/11 (100)	–
23 weeks	24/27 (88.9)	22/23 (95.7)	0.380
24 weeks	12/13 (92.3)	18/20 (90.0)	0.822
25 weeks	3/5 (60.0)	10/10 (100)	0.032
26 weeks	1/2 (50.0)	3/7 (42.9)	0.858
Total	51/58 (87.9)	64/71 (90.1)	0.688
Patients admitted to NICU	n = 2,326	n = 2,734	
Mortality in NICU			
22 weeks	19/20 (90.5)	6/7 (85.7)	0.419
23 weeks	136/155 (87.7)	129/161 (80.1)	0.066
24 weeks	335/526 (63.7)	366/571 (64.1)	0.888
25 weeks	357/713 (50.1)	344/853 (40.3)	<0.001
26 weeks	318/912 (34.9)	305/1,142 (26.7)	<0.001
Total	1,165/2,326 (50.1)	1,150/2,734 (42.1)	<0.001
Withholding or withdrawing therapy in NICU			
22 weeks	2/6 (33.3)	2/5 (40.0)	0.819
23 weeks	28/59 (47.5)	58/120 (48.3)	0.912
24 weeks	37/117 (31.6)	139/337 (41.2)	0.066
25 weeks	63/98 (39.1)	106/314 (33.8)	0.247
26 weeks	45/120 (37.5)	88/280 (31.4)	0.238
Total	179/513 (34.9)	413/1,096 (37.7)	0.280

Values are numbers (with percentages in parentheses).

chanical ventilation were reduced, with an increase in the use of CPAP before intubation in all groups, but significantly in newborns of 24–26 weeks' GA (table 3).

As shown in table 4, survival and survival without major morbidity were significantly increased in patients of 25 and 26 weeks. In contrast, we observed a higher morbidity and mortality among infants of 24 weeks' GA. The decision to limit therapeutic efforts was substantially increased in this group (35.3 vs. 44.1%, p = 0.07) and may have influenced these results. Other studies have also found an overall increase in survival in infants of <26 weeks' GA when comparing temporal series. Costeloe et al. [21] found, however, that increased survival disappeared when comparing the subgroups of patients alive at 7 days of life. Notably, there was an increased morbidity among survivors, probably at the expense of infants who would not have previously survived. Among the strategies proposed by Costeloe et al. [21] to reduce morbidity and mortality, the optimization of antenatal transfer of preterm pregnant women was emphasized because the proportion of outborn patients of <26 weeks in their area was still very high (42%). In addition, they significantly reduced the use of postnatal steroids from 71 to 21% [21]. In contrast, the use of postnatal steroids did not change in our NICUs but was altogether lower than that referred to by these authors.

Overall, we did not find changes between periods in the decision to actively limit therapy (34.9 vs. 37.7%, p = 0.280). These data are similar to the EPIBEL study, in which all life supportive measures were maintained in 50% of patients until death occurred, while in 39% some type of limitation was implemented [26]. In comparison,

in the EPICure study, conducted in patients at a GA ranging from 21 to 25 weeks, the proportion of patients who died after active withdrawal of intensive therapy was 55.3% [21].

Our results highlight specific areas of concern that should be addressed if we are to improve neonatal mortality and short- and long-term morbidities. These include disseminating strategies to avoid nosocomial infections or drastically increasing the number of patients on human milk.

There are limitations in our study. Outborn patients represented 11% in the first period while they represented 8.9% in the second period (table 2). We lack information on the mortality rates relative to the outborn infants who died before NICU admission. Therefore, there could be a selection bias relative to the sickest infants who might have died before transfer to the referral centers where the data were collected. Another limitation of our study is that approximately 35% of the newborns of 22–26 weeks' GA born during the study period were not included.

In conclusion, during the second period, survival increased and major morbidities were reduced. Simultaneously, a greater attachment to practices associated with improved outcomes was noted. However, a more conservative approach was detected for newborns of 22 weeks' GA. These results should be helpful in implementing national perinatal guidelines, thus minimizing intercenter variability in the management of women at high risk of extremely preterm birth and their infants, and increasing the quality of clinical care and ethical decisions.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Erratum

The following Appendix should be included in the paper entitled 'Changes in perinatal care and outcomes in newborns at the limit of viability in Spain: the EPI-SEN study' by García-Muñoz Rodrigo et al. [Neonatology 2015;107:120–129, DOI: 10.1159/000368881].

Appendix

The hospitals, investigators and coordinators of the Spanish Neonatal Network SEN1500 are as follows:

Complejo Hospitalario Albacete (Andrés Martínez Gutiérrez); Complexo Hospitalario A Marcide (José Luaces González); Corporació Parc Taulí (Juan Badia); Fundación Hospital De Alcorcón (Ana Martín Ancel); Hospital Basurto (Gabriel Saitua Iturriaga); Hospital Bierzo (María Teresa González Martínez); Hospital Cabueñes (Adela Rodríguez Fernández); Hospital Cantabria (Javier Gómez-Ullate Vergara); Hospital Carlos Haya (Tomás Sánchez Tamayo); Hospital Central Asturias (C. Moro Bayón); Hospital Clínic Barcelona (Josep Figuera Aloy); Hospital Clínico San Carlos (Tamara Carrizosa Molina); Hospital Cruces (Carolina de Castro Laíz); Hospital de Granollers (Israel Anquela Sanz); Hospital de la Santa Creu i Sant Pau (Gemma Ginovart Galiana); Hospital de la Zarzuela (Marisa López Gómez); Hospital Donosita (Luis Paisan Grisolía); Hospital Elche (Josep Mut Buigues); Hospital Germans Trias i Pujol (Antonio Natal Pujol); Hospital Getafe (Marta Muro Brussi); Hospital Infanta Margarita (José María Barcía Ruiz); Hospital Trueta (Alberto Trujillo); Hospital Jerez (Joaquín Ortiz Tardío); Hospital Juan Canalejo (José Luis Fernández Trisac); Hospital Juan Ramón Jiménez (José Ángel Morilla Sánchez); Hospital Juan XXIII (Juan Manuel Carretero Bellón); Hospital León (Emilio Álvaro Iglesias); Hospital Miguel Server (José Julián Beltrán Crouset); Hospital Montepríncipe (Marta García San Miguel); Hospital Móstoles (Lorenzo Sánchez de León); Hospital Mutua de Terrassa (Ángel Moral García); Hospital Nuestra Sra. de Sonsoles (Antonio Martín Sanz, Manuel Marrero); Hospital San Juan de Deu (Martín Iriondo Sanz); Hospital San Pedro (Fermín Cucalón Manzanos); Hospital San Pedro de Alcántara (Ana Barrio Sacristán); Hospital Severo Ochoa (María José Santos Muñoz); Hospital Son Dureta (Pere-Ramón Balliu Badía); Hospital Txagorritxu (María Mercedes Martínez Ayucar); Hospital Universitario Arnau de Vilanova (Eduard Solé Mir); Hospital Vall Hebron (Anna Fina Martí); Hospital Valme (Antonio Gutiérrez Benjumea); Hospital Virgen de la Concha (Víctor Marugán Isabel); Hospital Virgen de la Luz (Elisa Cueto Calvo); Hospital Virgen de la Macarena (Mercedes Granero Asencio); Hospital Virgen de la Salud (Alicia de Ureta Huertas); Hospital Virgen de las Nieves (Luis Fidel Moltó Ripio); Hospital Xeral Vigo (Socorro Ocampo Cardalda); Hospital Universitario de Valencia (Javier Estañ Capell); Hospital Universitario de Zaragoza (Purificación Ventura Faci); Hospital Universitario Santiago (José María Fraga); Hospital General Castellón (Ramón Aguilera Olmos); Hospital General Segovia (Miryam Hortelano); Hospital General Yagüe (Bruno Alonso Álvarez); Hospital General Universitario Alicante (Manuela López Azorín); Hospital Universitario Gregorio Marañón (Amparo Rodríguez Herreras); Hospital Universitario La Paz (Jesús Pérez Rodríguez); Hospital Materno Infantil de Canarias (Fermín García-Muñoz Rodrigo); Hospital Universitario Canarias (Pedro Amadeo Fuster Jorge); Hospital Universitario de San Cecilio (Eduardo Narbona); Hospital Universitario La Fe (Vicente Roqués); Hospital Universitario Reina Sofía (Juana María Guzmán Cabañas); Hospital Universitario Río Hortera (Carmen González Armengol); Hospital Universitario Salamanca (Pilar García González); Hospital Universitario San Juan (Javier Gonzalez de Dios); Hospital Universitario Valladolid (José Luis Fernández Calvo); Hospital Universitario Virgen del Rocío (Carmen Macías Díaz); Institut Dexeus (Roser Porta); Scias-Hospital Barcelona (Xavier Demestre).

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