Short Term Mortality and Morbidity in Extremely Preterm Babies Born Before 27 Gestational Weeks: Comparison Between Two Birth Cohorts (1999-2003 and 2010-2016) in a Belgian Third Level NICU

Agnese Vicari [a,c], Yoann Marechal [b], Christian Debauche [c]

[a] Clinique Notre Dame de Grace, department of Pediatrics, Charleroi, Belgium
[b] Hôpital Civil Marie Curie, Neonatal Intensive Care Unit, Charleroi, Belgium
[c] Cliniques Universitaires Saint Luc, Neonatal Intensive Care Unit, Brussels, Belgium

Agnese.vicari@gmail.be

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Extremely premature ; mortality ; morbidity.

Abstract

Purpose
To compare mortality and morbidity in a third-level neonatal intensive care unit in 2010-2016 in order to assess changes in outcomes since 1999-2003 and to evaluate possible intervention improvement.

Methods
We retrospectively analyzed data collected between 2010 and 2016 on 109 patients born before 27 gestational weeks among infants hospitalized at the Cliniques Universitaires Saint Luc in Brussels. We compared them with a previous internal study cohort of 75 patients of the same age born between 1999 and 2003. We compared mortality and morbidity at unit discharge between the two periods.

Results
The overall mortality rate of extremely preterm infants decreased by 4% from 1999-2003 to 2010-2016. This is not statistically significant (p=0,66). Neonatal deaths occurred earlier in the period 1999-2003. Between 1999 and 2003 deaths were most often attributed to multiorgan failure. In the 2010-2016 period deaths were most frequently attributed to severe central nervous system injury.

The overall prevalence of survivors without major morbidities decreased by 2% from the 1999-2003 to the 2010-2016 period (p=0,78), also not statistically significant.

Conclusions
Our findings corroborate previous studies suggesting that improved outcomes for infants born before 25 weeks of gestation might be achieved by considering resuscitation before 24 weeks. In order to obtain more statistically significant data, future research should compare the Belgian EPIBEL 1999-2000 cohort with a more recent Belgian cohort, potentially clarifying the impact of advanced interventions and care strategies on mortality and morbidity rates in extremely preterm infants.

Introduction

Very extreme prematurity, considered here as birth before 27 gestational weeks, remains nowadays a huge challenge in terms of mortality and morbidity.

Significant advances were made in the nineties with the generalization of the use of antenatal corticosteroids and surfactant (1 - 3).

In France a large cohort study, EPIPAGE 2, revealed that survival without morbidity for preterm babies born between 25 and 27 gestational weeks has still improved over a 15-year period (1997-2011), but not for babies born at 24 weeks (4). This difference for the infants born at 24 weeks of gestation is linked to the general habit in France of choosing not to reanimate preterm babies before 24 weeks.

A cohort study, made in the U.S., where neonatologists generally intervene from 22 weeks, showed an increase in the rate of survival without neurodevelopmental impairment from 2000 through 2011 in preterm babies born at 23 and 24 weeks, but not for those born at 22 weeks (5).

The aim of the present study was to compare babies born extremely preterm in the Cliniques Universitaires Saint Luc (CUSL) in Brussels between 1999 and 2003 to those born between 2010 and 2016 at the same institute. We wanted to see whether there has been an improvement in terms of morbidity and mortality between the two periods. As in France, the policy of the institution during those years was not to intervene before 24 gestational weeks. This study will be useful to identify possible improvements in the interventions with preterm babies. It will also guide the staff to give a better information to parents facing a preterm birth.

Methods

Study population and definitions

This single center retrospective study at CUSL includes very extremely preterm babies, considered here as babies born before 27 gestational weeks, from 1st January 1999 to 31st December 2003 (75 patients selected), compared to those born from 1st January 2010 to 31st December 2016 (109 patients selected). The data from the first cohort (1st January 1999 to 31st December 2003) were derived from a previous non-published internal study. Consequently, we first analyze the second cohort (1st January 2010 to 31st December 2016) using the same criteria that were used for the first study. In a second time we compared the two cohorts.

We used the neonatal department registry to select patients born before 27 gestational weeks and hospitalized in the third level neonatal center in CUSL. Gestational age was established as the best obstetric estimate based on the last maternal menstrual period date and/or antenatal ultrasonography data.

Patient data were retrospectively collected from the discharge summary.

The primary outcome was infant mortality, defined as the number of children who died before discharge from the department. We also analyzed the cause and timing of death. The secondary outcome was severe neonatal morbidity at discharge. It was defined as one or more of the following outcomes: severe central nervous system (CNS) injury considered as grade III or more intraventricular hemorrhage, according to the Papile et al. classification; periventricular leukomalacia defined as persistent parenchymal hyper echogenicity; severe bronchopulmonary dysplasia (BPD), according to the Jobe and Bancalari definition; stage 3 or higher retinopathy of prematurity with laser treatment, according to the international revisited classification (6 - 8).

As this is a retrospective cohort study, it does not include any personal data of the patients, therefore informed consent was not asked to the parents or guardian of the children. No data can be directly linked to the patient themselves.

Research ethics board agreement has been given by the hospital-faculty Ethics Committee of Cliniques Universitaires Saint Luc on 27th may 2024.

Statistical analysis

For our statistical analysis and creation of graphics, we used Graphpad Prism (V 10.2.1).

We compared the overall and cause-specific mortality and morbidity rates (number of events per total number of patients) and the proportionate mortality and morbidities (relative percentage contribution) for the coded causes of death and neonatal short-term morbidity among infants born in two birth-year periods. We selected a larger second period to ensure a total number of patients greater than 100, aiming to more significant results.

We compared all population characteristics between the two periods using the chi-square test. For the groups where there was at least one N ≤ 5, we used the Fisher's exact test with Graphpad Prism (V 10.2.1). We considered the differences between the two cohorts as statistically significant if p≤0,05.

As we did not have precise gestational age for each patient in the first cohort, we used a nonparametric Mann-Whitney test to compare gestational age in the two cohorts.

We also used the chi-square test and the Fisher's exact test, with the same criteria, to compare the mortality and morbidity rates in our population with those of some national cohort studies, acknowledging the known statistical limit due to the differences in the size and characteristics of the populations studied.

Results

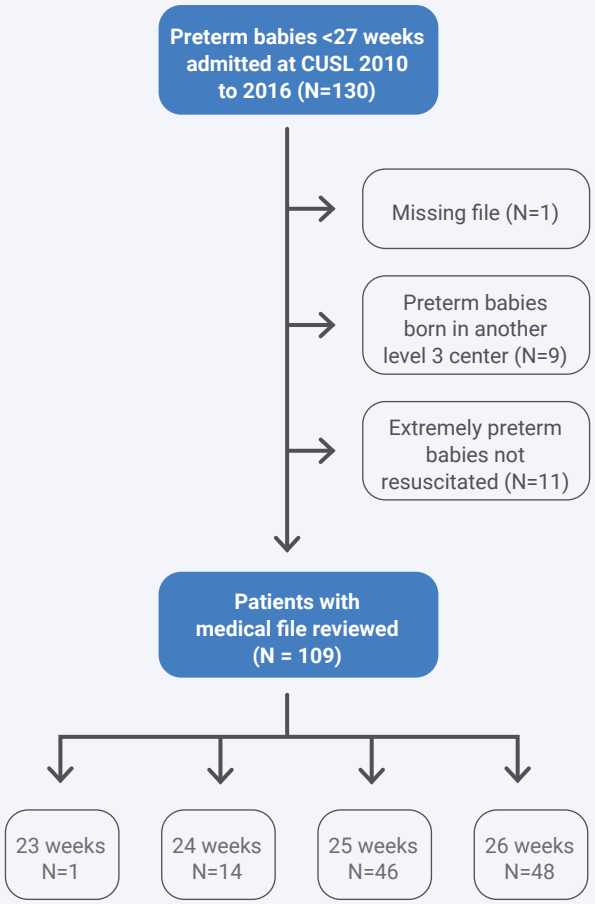
Characteristics of the two cohorts

We initially had 130 patients, one patient was excluded because the report was missing. Nine patients were excluded because they were born and initially hospitalized in another third level neonatal center. They were transferred to the department for ophthalmologic or otorhinolaryngologic advice. Finally, we excluded 11 patients that were not actively reanimated at birth and who received palliative care. These patients were all born before 25 gestational weeks: 8 of them were born before 24 weeks and were not reanimated due to the general policy in the department during our study, while 3 others were born between 24 and 24 weeks 6/7, all of them in a context of chorioamnionitis, and received palliative care in agreement with the parents (Figure 1).

75 extremely preterm babies (24 to 26 6/7 weeks of gestation) that meet the inclusion criteria were born in our center from January 1st, 1999, to December 31st, 2003, and 109 from January 1st, 2010, to December 31st, 2016. Among these infants 51 (68%) survived to discharge in the first cohort and 78 (72%) survived to discharge in the second cohort.

Mean birthweights were similar in the two groups, but there were more infants considered extremely small for gestational age from the point of view of birthweight (20% vs 6% p=0,007) and birth length (19% vs 6%, p=0,006) in the first group compared to the second one. (Table 1). This difference is mainly due to the different growth chart used for the two populations: Usher and McLean growth curves were used for the first group and Fenton preterm growth chart for the second one (9, 10).

FIGURE 1: Flow chart of inclusion criteria.



Gestational age and sex were similar in the two groups, with the only difference that the second cohort included a 23 weeks' gestation patient (Table 1).

There was a small and non-significant difference in the overall age at birth (babies were younger in the cohort 1 (25,2 +/- 0,8 vs 25,5 +/- 0,9). There was no difference in the age at birth of the survivors 25,9 +- 0,7 in the two cohorts (Table 1).

There were less multiple gestations in the first group than in the second one (24% vs 30%) but siblings in the first cohort tend to be younger than in the second one (55% born at 24 gestational weeks vs 12%) (Table 1).

Regarding obstetrical problems as chorioamnionitis, eclampsia and metrorrhagia, there was no significant difference between the two populations (Table 1).

Between the two periods we detected a significant increase in the percentage of women who delivered by cesarean section (from 51% to 78%, p=0,001) (Table 1). There was also a significant decrease in the number of women not receiving antenatal corticosteroids at all (24% in the first period and 10% in the second period, p=0,01). However the number of women that underwent a complete course of antenatal corticosteroids was not significantly different (52% vs 62% p=0,22) (Table 1).

Finally, during the second period there was a significant increase of intubated neonates in the delivery room (from 69% to 89%, p=0,006) and of neonates that underwent surfactant therapy (from 20% to 86%, p<0,001). Mean APGAR score at 1, 5 and 10 minutes was similar in the two groups (Table 1).

TABLE 1: Characteristics of the two cohorts.

	1999-2003	2010-2016	p value
	(N=75)	(N=109)	
Gestational age (GA) - weeks	25,13 +/- 0,8	25,29 +/- 0,8	0,177
23 weeks – no. (%)	0	1 (1)	
24 weeks – no. (%)	19 (25)	14 (13)	
25 weeks – no. (%)	27 (36)	46 (42)	
26 weeks – no. (%)	29 (39)	48 (44)	
Birth weight – g (median +/- standard deviation)	762 +/- 167	759 +/- 166	
Extremely small for GA (<P3) – no. (%)	15 (20)*	7 (6)¶	0,007
Birth length – cm (median +/- standard deviation)	33 +/- 3 cm	33 +/- 2	
Extremely small for GA (<P3) – no. (%)	14 (19)*	6 (6)¶	0,006
Head circumference – cm (median +/- standard deviation)	23 +/- 2	23 +/- 2	
Extremely small for GA (<P3) – no. (%)	3 (4)*	5 (5)¶	1
Male sex – no. (%)	44 (59)	66 (59)	
Multiple gestation – no. (%)	18 (24)	33 (30)	
Mother received prenatal glucocorticoids		N= 106	
None – no. (%)	18 (24)	11 (10)	0,01
Incomplete course – no. (%)	18 (24)	27 (25)	0,91
Complete course – no. (%)	39 (52)	68 (62)	0,22
Chorioamnionitis – no. (%)	33 (44)	39 (36)	0,3
Pre-eclampsia/HELLP/Eclampsia – no. (%)	14 (19) §	16 (15)	0,46
Metrorrhagia – no. (%)	31 (41)	39 (36)	0,48
Premature rupture of membrane – no. (%)	27 (36)	38 (35)	0,88
Inborn – no. (%)	65 (87)	102 (94)	0,2
Cesarean section – no. (%)	38 (51)	85 (78)	0,001
Intubated in delivery room – no. (%)	52 (69)	97(89)	0,006
Surfactant therapy no. (%)	15 (20)	94 (86)	<0,001
Apgar score			
1 min – median (+/- standard deviation)	4 (2)	3 (2)	
5 min – median (+/- standard deviation)	6 (2)	7 (2)	
10 min – median (+/- standard deviation)	7 (2)	7 (2)	
Length of stay – mean +/- std.dev (median)	82+/-27 (79)	103+/-33 (94)	
Term at discharge (weeks)	37,7+/-3,8	40,5+/-4,5	
Return home – no./total no. survivors (%)	28/51 (55)	63/78 (81)	0,07
Post-term return home > 40 gestational weeks	10/28 (36)	19/63 (30)	0,62
Post-term return home > 44 gestational weeks	4/28 (14)	5/63 (8)	0,71

* Usher and McLean growth curves (16); ¶ Fenton preterm growth chart (17);
§ N=74: data missing for one patient.

Hospital stay

The median length of stay in hospital and the term at discharge among survivors increased from the 1999-2003 period (82 +/- 27 days and 37,7 +/- 3,8 weeks) to the 2010-2016 period (103 +/- 33 days and 40,5 +/- 4,5 weeks). Meanwhile the transfer in other departments of CUSL or in a first or second level neonatal center decreased. Overall post-term discharge home, considered as a return home after 40 gestational weeks, decreased in the second population compared with the first one (Table 1). All these differences are not statistically significant.

Trends in mortality

The overall in hospital mortality rate of the extremely preterm babies decreased by 4% in the CUSL from 1999-2003 to 2010-2016, but this is not statistically significant (p=0,66). In the cohort 2010-2016 the mortality decreased especially in babies born at 24 gestational weeks (from 63% to 43%, p=0,32), and also in babies born at 25 gestational weeks (from 32% to 30%, p=0,9). Mortality seems to increase slightly in babies born at 26 gestational weeks (from 16% to 21%, p=0,55). Nevertheless all these differences are not statistically significant (Table 2 and Figure 2). The only reanimated 23 weeks of gestation baby died at 6 days of life.

The mortality rate among babies born of multiple pregnancies from 1999 to 2003 was higher than from 2010 to 2016 (61% vs 15% p= 0,001). For babies with antenatal chorioamnionitis, eclampsia or premature rupture of membrane there was no significant difference in the mortality rate between the two groups (Table 2).

Neonatal deaths occurred earlier in the 1999-2003 period compared with the 2010-2016 period. 66% of babies died before 48 hours in the first group compared with 18% in the second group (p<0,001). 79% of babies died before 72 hours in the 1999-2003

TABLE 2: Mortality rate comparison.

	1999-2003	2010-2016	p value
Mortality – no. deaths /total no. (%)	24/75 (32)	31/109 (28)	0,63
23 weeks – no. deaths /total no. (%)	-	1/1 (100)	-
24 weeks – no. deaths /total no. (%)	12/19 (63)	6/14 (43)	0,34
25 weeks – no. deaths /total no. (%)	8/27 (30)	14/46 (30)	1
26 weeks – no. deaths /total no. (%)	4/29 (14)	10/48 (21)	0,55
Origin of the baby			
Inborn – no. deaths /total no. (%)	19/65 (29)	29/102 (28)	0,91
Outborn – no. deaths /total no. (%)	5/10 (50)	2/7 (29)	0,62
Number of babies per pregnancy			
Singleton – no. deaths /total no. (%)	13/57 (23)	26/76 (34)	0,18
Multiple pregnancies – no. death /total no. (%)	11/18 (61)	5/33 (15)	0,001
Chorioamnionitis§			
No chorioamnionitis – no. deaths/total no. (%)	17/41 (41)	20/70 (29)	0,19
Proved chorioamnionitis – no. death/total no. (%)	6/33 (18)	11/39 (28)	0,35
Premature rupture of membrane			
No premature rupture of membrane – no. deaths/total no. (%)	14/47 (30)	20/71 (28)	0,86
Premature rupture of membrane – no. deaths/total no. (%)	9/27 (33)	11/38 (29)	0,72
Pre-eclampsia, HELLP or eclampsia			
None – no. deaths/total no. (%)	20/60 (33)	27/93 (29)	0,6
Pre-eclampsia, HELLP or eclampsia – no. deaths/total no. (%)	3/14 (21)	4/16 (25)	1
Antenatal corticosteroid use Δ			
None – no. deaths /total no. (%)	8/18 (44)	6/11 (55)	0,71
Incomplete course – no. deaths/total no. (%)	7/18 (39)	8/27 (30)	0,55
Complete course – no. deaths/total no. (%)	9/39 (23)	16/68 (24)	0,96
Other ◊ corticosteroids – no. deaths/total no. (%)	0	1/3 (33)	1

§ Data unknown for one death patient in the 1999-2003 cohort; Δ Betamethasone complete course = 2 doses at 24 h distance; ◊ Dexamethasone initially used as treatment of HELLP syndrome.

period compared with 35% in the 2010-2016 period (P=0,002). In the second period, most babies died between 3 and 7 post-natal days (35% vs 4% in the first period, p=0,007) (Figure 3).

Between 1999 and 2003, deaths were most frequently attributed to multi-organic failure (MOF) that represented 42% of deaths against only 10% during the 2010-2016 period (p= 0,009). In contrast, between 2010 and 2016, deaths were most frequently attributed to severe CNS injury (32% against 8% in the first period, p=0,048). There was no significant difference between the two periods in the other mortality causes as pulmonary or cardiac failure (Figure 4).

Neonatal morbidity

Strikingly, the overall prevalence of survivors without major morbidities decreased by 2% from the 1999-2003 period to the 2010-2016 period, but this is not statistically significant (p=0,78) (Table 3, Figure 5). This prevalence decreased for patients surviving without CNS bleeding (from 92% to 88%, p=0,56), but increased for those surviving without severe BPD (from 73% to 80%, p=0,43) or without severe retinopathy of prematurity, considered here as retinopathy needing a laser treatment, (from 83% to 92%, p=0,23) (Table 3).

Of all extremely preterm babies that where initially reanimated, 60% in the 1999-2003 cohort and 52% in the 2010-2016 cohort (p=0,09) survived without CNS lesions (bleeding and/or permanent hyper echogenicity). 45% vs 48% (p=0,84) survived without CNS lesions and without chronic lung disease. Finally 45% vs 43% (p=0,78) survived without any severe condition.

FIGURE 2: Mortality rate for babies born before 27 weeks (% of total patients).

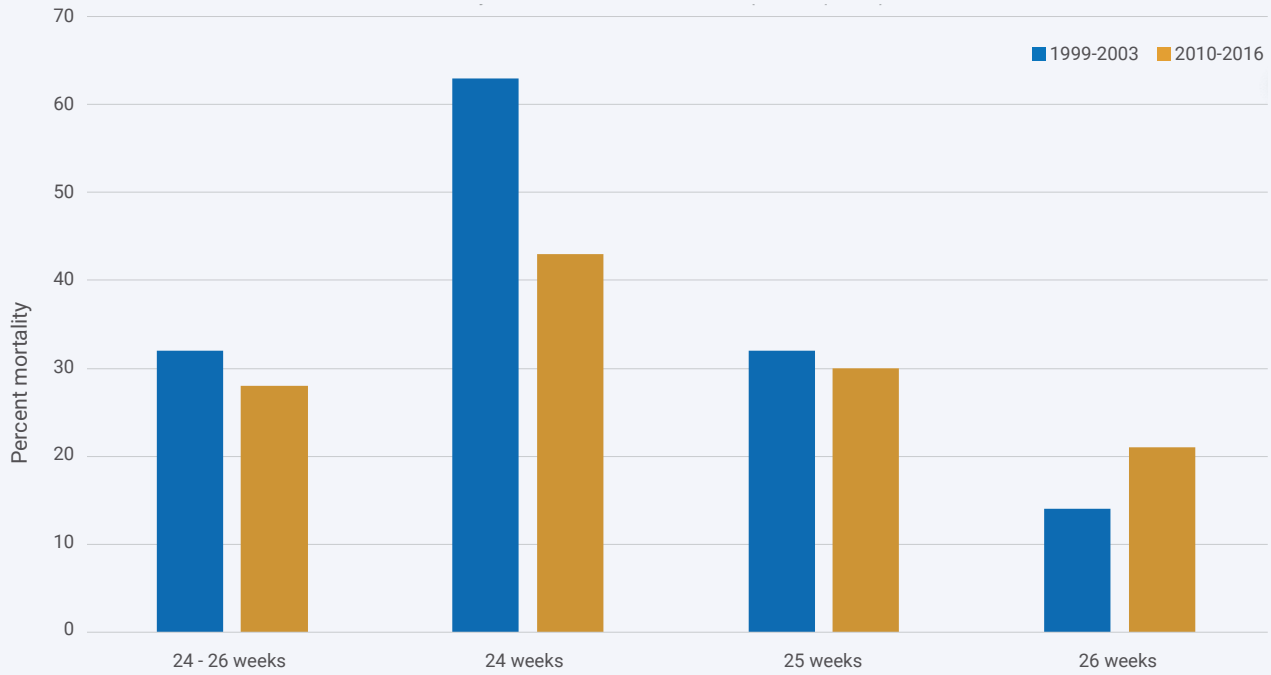


FIGURE 3: Timing of death comparaison.

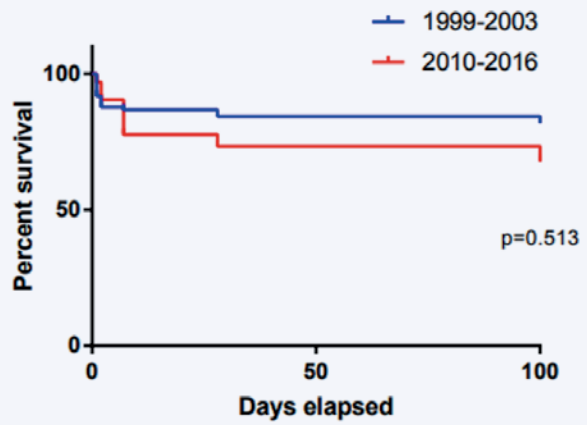
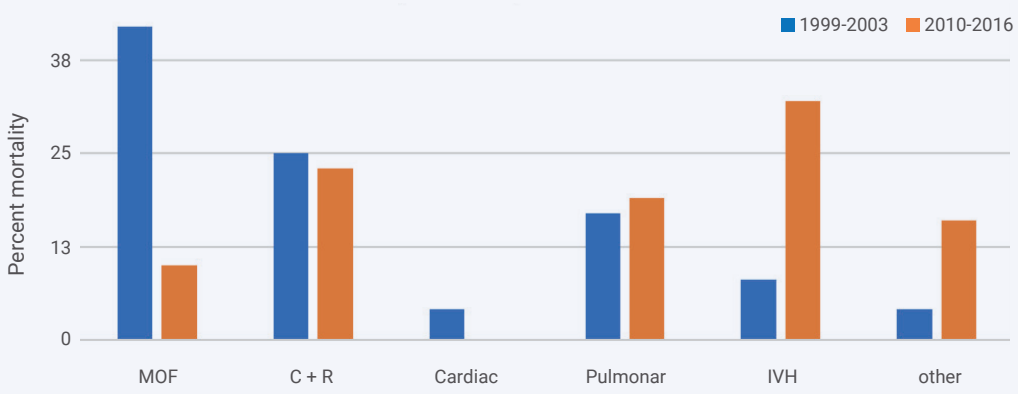
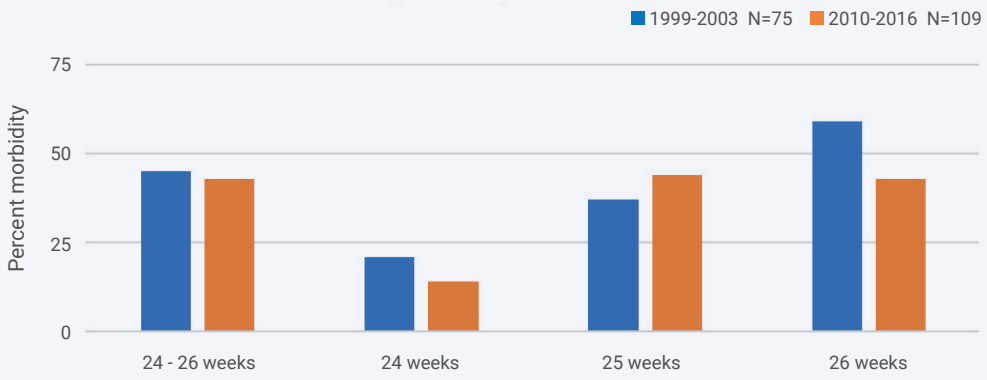


FIGURE 4: Principal causes of death (% of total dead patients).



MOF = Multiple Organ failure; C + R = Cardiac and respiratory failure; IVH = Intraventricular Hemorrhage; Other reason of death: dysmaturity, digestive failure and severe sepsis.

FIGURE 5: Survival without major morbidity (% total patients).



Discussion

Considering gestational age, morphology, obstetrical history, there is no significant difference in the characteristics of the two population studied. There seems to be a difference in the number of extremely small for birthweight and birth length infants. This is probably due to a different growth chart used in the two periods.

Overall, we do not observe any significant difference in the mortality and morbidity rates between the two populations studied. This is probably explained by the small size of the analyzed populations, especially when divided in subgroups by gestational age. Furthermore, we suppose that the lack of difference is also due to the fact that our populations are separated only by 7 years from the end of the first period (2003) to the beginning of the second period (2010). Moreover during such a period there has not been any major advance in neonatal medicine. Nevertheless, we observe a significant increase in the use of surfactant therapy and in the number of patients intubated in the delivery room in the 2010-2016 cohort. We can correlate it to a decrease in the severe bronchopulmonary dysplasia at 36 gestational weeks, but these data are not significant. Furthermore, the decrease in BPD can also be linked to the protective ventilation strategies developed in recent years (11). These data are not shown in the current study.

The other significant difference in the mortality rate between the two groups concerns a decrease in the mortality of babies born from multiple pregnancies. This is probably due to the fact that in the 1999-2003 cohort there was a larger number of siblings born at 24 gestational weeks compared to the 2010-2016 cohort. Moreover 8 of them were triplets in the first group while in the second one they were all twins.

Finally, we found a significant difference in the time of death: preterm babies died earlier in the first cohort than in the second one (Figure 3). This is probably due to the more aggressive reanimation at birth in the 2010-2016 period with an increase in intubation and surfactant therapy in the delivery room. Due to this more aggressive reanimation, the causes of death were significantly different in the two groups. Babies in the first cohort died mainly of multiple organ failure, while in the second one of severe CNS bleeding. Similar data on change of causes and timing of death were already reported in an American cohort study in 2015 (12).

In contrast with the Epipage 2 study in France, we do not observe any significant improvement in mortality rate over time (4). However the survival rate in our first cohort was already considerably higher compared to what is described in that study. The required number of patients to evidence some differences between the two cohorts of our study should have been approximately 2050 children per group, based on our observations (survival difference of 4%, p at 0,05 and power at 0,8). Indeed, our figures are closer to what has been observed in the Epicure English cohort in 2006, but they are still far off from the Australian, Japanese and Swedish figures (Table 4) (13 – 16). The main difference we can observe with these countries

is that they start to reanimate babies born before 24 gestational weeks. Therefore, as the authors of the Epipage 2 study concluded, if we want to improve mortality and morbidity of extreme preterm babies we should probably change the institutional policy and start to reanimate babies before 24 weeks of gestation (4).

Moreover, another difference we noticed is a slight increase in the length of hospital stay in the second group that was probably due to a smaller number of transfers to other departments as the overall discharge to home time decreased in the second cohort. Anyway, the median hospitalization length, 95 days, in the 2010-2016 cohort was similar to the 111 days reported in the EPICURE cohort study for their 2006 population (13).

Conclusion

Our study shows that, in absence of major technical or medicinal advance, it is difficult to improve mortality and morbidity in extreme preterm babies. The countries with the best results are those who reanimate babies from 23 weeks of gestation, with potential extension to 22 weeks, based on favorable conditions.

To improve mortality and morbidity rates in neonatal intensive care units (NICU), especially for babies born before 25 gestational weeks, we should start to reanimate from 23 gestational weeks. The policy at CUSL nowadays considers resuscitating preterm babies from 23 weeks of gestation.

Future studies, including a comparison with a more recent CUSL NICU cohort and the realization of an "EPIBEL 2" study, are planned to assess the impact of these changes on mortality, morbidity, and long-term outcomes of extremely preterm newborns. These efforts aim to contribute to the ongoing debate on peri-viability and to refine parental guidance on resuscitation and survival expectations for extremely premature infants.

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

TABLE 3: Morbidity rate comparison.

	1999-2003	2010-2016	p value
Survival without major morbidity – no. /total no. survivors (%)	34/51 (67)	47/78 (60)	0,52
24 weeks – no./total no. survivors (%)	4/7 (57)	2/8 (25)	0,31
25 weeks – no./total no. survivors (%)	10/19 (52)	20/31 (65)	0,46
26 weeks – no./total no. survivors (%)	17/25 (68)	25/39 (64)	0,78
Survival without major morbidity – no. /total no. (%)	34/75 (45)	47/109 (43)	0,78
24 weeks – no./total no. (%)	4/19 (21)	2/14 (14)	0,31
25 weeks – no./total no. (%)	10/27 (37)	20/45 (44)	0,46
26 weeks – no./total no. (%)	17/29 (59)	25/49 (51)	0,78
Intraventricular hemorrhage			
Absence of severe CNS bleeding* – no./total no. (%)	58/69 (84)‡	82/106 (77)§	0,37
Survival without severe CNS bleeding* – no./total no. survivors (%)	47/51 (92)	69/78 (88)	0,56
24 weeks – no./total no. survivors (%)	6/7 (86)	6/8 (75)	1
25 weeks – no./total no. survivors (%)	18/19 (95)	27/31 (87)	0,64
26 weeks – no./total no. survivors (%)	23/25 (92)	36/39 (92)	1
Survival without severe BPD at 36 gestational weeks ¥ – no./total no. survivors (%)	32/44 (73)†	64/80 (80)	0,43
24 weeks – no./total no. survivors (%)	4/6 (67)	4/7 (57)	1
25 weeks – no./total no. survivors (%)	11/15 (73)	26/31 (84)	0,45
26 weeks – no./total no. survivors (%)	17/23 (74)	34/42 (81)	0,57
Survival without laser treatment for retinopathy** – no./total no. survivors (%)	39/47# (83)	67/73# (92)	0,23
24 weeks – no./total no. survivors (%)	6/7 (86)	4/7 (57)	0,56
25 weeks – no./total no. survivors (%)	13/17 (76)	28/30 (93)	0,17
26 weeks – no./total no. survivors (%)	20/23 (87)	36/37 (97)	0,15

* Severe CNS bleeding considered as a stage ≥ 3 of Papile classification (6)
‡ CNS ultrasonography not performed for 6 patients (death before 24 hours)
§ CNS ultrasonogrphy not performed for 3 patients (death before 24 hours)
¥ Severe bronchopulmonary dysplasia (BPD) according to Jobe and Bancalari definition (7)
† Data missing for 7 patients transferred in another hospital before 36 gestational weeks
** Retinopathy classification according the international revisited classification (8)
# Data missing for 4 patients in the cohort 1 and 5 patients in the cohort 2

TABLE 4: Comparison to international literature figures.

	CUSL 2010-16	EPIPAGE 2 (4)
Mortality 23-26 weeks – no. deaths /total no. (%)	31/109 (28)	444/996 (45)
23 weeks – no. deaths /total no. (%)	1/1 (100)	88/89 (99)
24 weeks – no. deaths /total no. (%)	6/14 (43)	128/186 (69)
25 weeks – no. deaths /total no. (%)	14/46 (30)	126/308 (41)
26 weeks – no. deaths /total no. (%)	10/48 (21)	102/413 (25)

	CUSL 2010-16	EPICURE (13)
Survival without major morbidity 24-26 weeks – no. /total no. (%)	34/75 (45)	407/972 (42)
24 weeks – no./total no. (%)	4/19 (21)	52/178 (29)
25 weeks – no./total no. (%)	10/27 (37)	133/346 (38)
26 weeks – no./total no. (%)	17/29 (59)	222/448 (50)

	CUSL 2010-16	Australia 2005 (14)
Mortality 23-26 weeks – no. deaths /total no. (%)	31/109 (28)	71/178 (40)
23 weeks – no. deaths /total no. (%)	1/1 (100)	25/32 (78)
24 weeks – no. deaths /total no. (%)	6/14 (43)	21/43 (49)
25 weeks – no. deaths /total no. (%)	14/46 (30)	15/46 (33)
26 weeks – no. deaths /total no. (%)	10/48 (21)	10/57 (18)
Survival without major morbidity 23-26 weeks – no. /total no. (%)	31/76 (41)	225/492 (46)
23 weeks – no./total no. (%)	0/1 (0)	9/53 (17)
24 weeks – no./total no. (%)	4/19 (21)	30/96 (31)
25 weeks – no./total no. (%)	10/27 (37)	75/167 (45)
26 weeks – no./total no. (%)	17/29 (59)	111/176 (63)

	CUSL 2010-16	Japan 2003-05 (15)
Mortality 24-25 weeks – no./total no. (%)	20/60 (33)	139/737 (19)

	CUSL 2010-16	EXPRESS 2009 (16)
Mortality 23-26 weeks – no. deaths /total no. (%)	31/109 (28)	125/617 (20)
23 weeks – no. deaths /total no. (%)	1/1 (100)	28/81 (35)
24 weeks – no. deaths /total no. (%)	6/14 (43)	36/132 (27)
25 weeks – no. deaths /total no. (%)	14/46 (30)	33/200 (16)
26 weeks – no. deaths /total no. (%)	10/48 (21)	28/204 (14)
Survival without major morbidity 23-26 weeks – no. /total no. (%)	31/76 (41)	225/492 (46)
23 weeks – no./total no. (%)	0/1 (0)	9/53 (17)
24 weeks – no./total no. (%)	4/19 (21)	30/96 (31)
25 weeks – no./total no. (%)	10/27 (37)	75/167 (45)
26 weeks – no./total no. (%)	17/29 (59)	111/176 (63)

Comparison to be considered taking into account the limits due to the differences in size and characteristics of the populations studied

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