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Changes in management policies for extremely preterm births and neonatal outcomes from 2003 to 2012: two population-based studies in 10 European regions

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Shortened running title: Changes in management policies for extremely preterm births in Europe

Abstract

Objective: to investigate changes in maternity and neonatal unit policies towards extremely preterm infants (EPTI) between 2003 and 2012 and concurrent trends in their mortality and morbidity in ten European regions.

Design: population-based cohort studies in 2003 (MOSAIC study) and 2011/12 (EPICE study) and questionnaires from hospitals.

Setting: 70 hospitals in ten European regions

Population: infants born at <27 weeks of gestational age (GA) in hospitals participating in both the MOSAIC and EPICE studies (1240 in 2003, 1293 in 2011/2012).

Methods: We used McNemar's Chi2 test, paired t-tests and conditional logistic regression for comparisons over time.

Main outcomes measures: reported policies, mortality and morbidity of EPTI.

Results: The lowest GA at which maternity units reported performing a caesarean section for acute distress of a singleton non-malformed fetus decreased from an average of 24.7 to 24.1 weeks (p<0.01) when parents were in favour of active management and 26.1 to 25.2 (p=0.01) when parents were against. Units reported that neonatologists were called more often for spontaneous deliveries starting at 22 weeks GA in 2012 and more often made decisions about active resuscitation alone, rather than in multidisciplinary teams. In-hospital mortality after live birth for EPTI decreased from 50% to 42% (p<0.01). Units reporting more active management in 2012 than 2003 had higher mortality in 2003 (55% vs. 43%, p<.01) and experienced larger declines (55% to 44%; p<0.001) than units where policies stayed the same (43% to 37%; p=0.1).

Conclusions: European hospitals reporting changes in management policies experienced larger survival gains for EPTI.

Keywords: extremely preterm births, ethics, neonatal intensive care

Tweetable abstract: Changes in reported policies for management of extremely preterm births were related to mortality declines.

Introduction

Extremely preterm infants born before 27 weeks of gestation are at greatly increased risk of mortality and morbidity than infants born at later gestations. Several recent studies have documented declines in their mortality over time, without showing concomitant increases in severe neonatal morbidity.[1-5] However, the prevalence of severe neurological and respiratory morbidity at discharge from hospital remains high – up to 60% in some studies - and appears to be stable over time.[5, 6] About one-quarter of children born before 27 weeks of gestation are estimated to have a severe or moderate impairment in early childhood,[2, 7] with a higher prevalence at the lowest gestational ages.

While the recent trends towards higher survival are consistent across studies in high income countries, survival rates still differ markedly between countries and hospitals. Differences are most marked in the extent of survival gains for babies closest to the limits of viability at 23 and 24 weeks.[2, 5, 8-12] Some of this variation in survival over time and between countries and units may reflect differences in policies and practices of initiating active treatment for these infants or of withholding and withdrawing intensive care for infants with severe neonatal morbidity.[5, 13-16]

The ethical dimension of providing care for infants born at very low gestational ages has been a subject of longstanding debate. National recommendations and guidelines for ethical decision-making differ between countries[14, 17] and studies have shown that the perceptions of viability and impairment of very preterm infants can be different between professionals and hospitals.[16, 18, 19] However, little is known about how changes in laws and national policies related to ethical decision-making at the limits of viability over the past decade have translated into changes in unit policies and clinical practice.[20, 21] Nor has the impact of these changes on the mortality of extremely preterm infants been explored.

Using data from two population-based cohorts in ten regions in Europe in 2003 and 2011/12, we explored changes in reported ethical policies for management of extremely preterm infants in obstetrical and neonatal units over time and investigated concurrent trends in mortality and severe neonatal morbidity of infants born before 27 weeks of gestation in these units.

METHODS

Data sources

This study combines data from the EPICE and MOSAIC studies, which collected population-based information on all stillbirths and live very preterm (VPT) births between 22+0 to 31+6 weeks of gestation during a one year period (6 months in the French region) in the same ten study regions in nine European countries in 2003 (MOSAIC) and 2011/12 (EPICE). [22, 23] Data were also collected from

maternity and neonatal units that provided care for these infants. Participating regions were Flanders in Belgium, the Eastern Region of Denmark, Ile-de-France in France, Hesse in Germany, Lazio in Italy, the Central-Eastern region of the Netherlands, Wielkopolska in Poland, the Northern region of Portugal, and the Northern and former Trent regions in the United Kingdom. Regions were selected to achieve geographic and organizational diversity and for feasibility (on-site infrastructure and expertise for implementing the study protocol) and sample size considerations. The number of total births occurring during the study period in participating regions was 477,805 in 2003 and 499,992 in 2011/12.

Cohort studies

Both studies used pretested structured questionnaires to abstract data on infant characteristics and outcomes from obstetrical and neonatal records until death or discharge home from hospital or into long-term care. Inclusions were cross-checked against birth registers or another external data source in order to verify that all births fulfilling inclusion criteria were identified. All regions obtained ethical authorisations according to national and regional regulations and the European databases were approved by the French National Commission for Data Protection and Liberties (CNIL).

Variables selected for this study were clinical characteristics, including gestational age (based on the best obstetric assessment according to information on ultrasound measures or last menstrual period in completed weeks), birth weight, small for gestational age (defined as the 10th percentile of internal references in each cohort), multiple birth and fetal sex. Medical practices included any administration of antenatal steroids (ANS), mode of onset of labour (spontaneous, induced or caesarean section before labour), and mode of delivery (vaginal or caesarean section (CS)), administration of surfactant, mechanical ventilation and neonatal transfer after birth. Inborn infants were defined as those hospitalised during the first 48 hours after birth in a neonatal unit in the same hospital as the maternity unit. Pregnancy outcomes were stillbirth, including both antepartum and

intrapartum deaths, in-hospital mortality after live birth and survival without major morbidity. Major morbidities included intraventricular haemorrhage (IVH) using Papille grades III and IV, cystic periventricular leukomalacia (PVL) and bronchopulmonary dysplasia (BPD) defined as oxygen dependency or respiratory support at 36 weeks post menstrual age.

Maternity and neonatal unit studies

Questionnaires were sent to heads of maternity and neonatal units. The MOSAIC unit study included all maternity and neonatal units whereas the EPICE study only included hospitals that regularly cared for VPT infants, defined as at least 10 annual VPT admissions to the neonatal unit. Data were collected on the structural characteristics of units (level of specialisation and volume in 2002 and 2011) and on policies related to the management of very preterm infants. In both the maternity unit and neonatal unit questionnaires, there was a section entitled "Ethics" including questions about policies related to active management in obstetric and neonatal units and to withholding and withdrawing care for extremely preterm infants.

To assess the lower limit at which the maternity units began active management of very preterm infants, maternity units were asked: 1) "What is the unit policy regarding the lowest gestational age at which a caesarean section would be performed because of acute fetal distress for a singleton non-malformed fetus?" and 2) "What is the unit policy regarding the lowest gestational age at which a neonatologist would be called in case of spontaneous labour for a singleton non-malformed fetus?". Both questions were asked for situations in which parents wanted everything to be done to save the foetus and those where parents did not want active treatment. In the neonatal unit questionnaire, information was requested about who decided on active resuscitation for births below 25 weeks, as well as the unit's policy for withdrawal or withholding mechanical ventilation for infants who had no chance of survival or those with poor prognosis in case of survival, and about parental involvement in decisions to withhold or withdraw mechanical ventilation (informed, involved or allowed to make the decisions).

Study Population

In the regions participating in both the MOSAIC and EPICE studies, there were 6,440 VPT between 22+0 to 31+6 weeks of gestation born in 2003 in 379 maternity units and 6,377 infants born in 2011/2012 in 285 maternity units. Out of 93 hospitals with at least 10 VPT neonatal admissions in 2011/12, 70 hospitals with unit questionnaires in both 2003 and 2012 and all infants born before 27 weeks in these hospitals were included (N=1240 in 2003 of which 833 were live born, and 1293 in 2011/12 of which 917 were live births). Hospitals were excluded because they did not respond to both unit questionnaires in the two periods or because they had been restructured, i.e. merged or closed. Infants included in this study therefore represented 83% (1750/2117) of live births <27 weeks in eligible hospitals in both periods. When considered in relation to all live births in participating regions, they represented 71% and 75% in 2003 and 2011/12, respectively. Exclusions are detailed in Figure S1.

Analysis strategy

Structural characteristics of obstetrical and neonatal units were compared over the two periods. Data from the overall cohort of very preterm infants 22+0 to 31+6 weeks of gestation were used to calculate the average annual number of very preterm deliveries and primary admissions to the neonatal intensive care unit (NICU) in each year. Then, reported policies for management of extremely preterm infants in obstetrical and neonatal units in 2003 versus 2011/12 were described. We used McNemar's Chi2 test and paired t-tests for univariate analyses.

Based on these results, units were classified into two groups according to the changes in the lowest gestational age at which CS was considered for fetal reasons. Units were classified as 'more active policy' when gestational age was lower in at least one of the situations (whether parents wanted active or conservative treatment) in 2012 compared to 2003, and as 'no change or less active policy' if gestational age did not change over time or if gestational age was higher in 2012 than in 2003.

Units that declared that they had no policy in 2003, but which had a policy to perform CS before or at 24 weeks in 2011/12 were categorized in the more active policy group. Units were included in the 'no change' group if they had a policy to perform a CS before or at 24 weeks in 2003, but had no policy in 2011/2012. We considered that non-response to this question, despite completion of the other questions in the section (two units in 2003 and one unit in 2012) was equivalent to having no policy.

We compared the characteristics, care and outcomes of infants less than 27 weeks of gestation between the two study periods, overall, and within both groups of units. All infants were assigned to their unit of birth even if they were transported to another hospital after delivery. In the German region of Hesse, ANS use was only recorded for full courses in 2003 and therefore this region was excluded from comparisons of this variable. Conditional logistic regression models were used to study the effect of year of study on in-hospital mortality after live birth in each maternity group overall and by group, while controlling for neonatal characteristics of the infants (gestational age, sex, multiple birth and ANS). Conditional logistic regression models make it possible to match the observations within the same hospitals over time.

Data were analysed using Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

RESULTS

Table 1 describes characteristics of the 70 hospitals included in the analysis. The proportion of level 3 units, the total number of admissions to neonatal units and the services offered in neonatal units did not vary over time. In contrast, the number of deliveries, the caesarean rate among all births, the number of very preterm deliveries and admissions to neonatal care increased. The number of units varied by region: from 11 units in Hesse and 10 units in Lazio to two units in the Dutch Eastern-Central region (Table S1).

Table 2 presents responses to the questions from the ethics section in the maternity and neonatal unit questionnaires. On average, the gestational age (GA) at which a CS would be performed because of acute fetal distress was lower in 2011/2012 than in 2003, and there were fewer units with no policy. These declines were seen when parents wanted everything to be done (from a mean of 24.7 to 24.1, p<.0001) and when they did not want active treatment (26.1 to 25.2, p<.01), although more units had no policy in the latter situation. In both periods, however, there was substantial heterogeneity in responses. In 2011/12, the most common reply was 24 weeks (39%) with 14% of the units reporting they would perform a CS starting at 23 weeks and 10% not until 26 weeks.

More units called a neonatologist in case of a spontaneous preterm delivery starting at 22 weeks in 2012 than in 2003 and there were fewer units without a policy (Table 2). However, there was not a significant change in the average GA at which a neonatologist was called. There was less difference in this policy in relation to parental preferences about active management. Responses from the neonatal unit confirmed the larger role of the neonatologist at early gestational ages, as more units responded that the neonatologist alone made decisions about active resuscitation for infants < 25 weeks GA. In contrast, there was no change in the proportion of units that reported that they made decisions to withhold or withdraw mechanical ventilation either when the baby had a poor chance of survival or in cases with a poor prognosis. More units reported that parents were involved in the decision-making process, but the change was not significant.

Table 3 shows characteristics, care and outcomes of infants born before 27 weeks overall and by group ('more active policy in 2011/2012' or 'no change or less active policy in 2011/2012'). Of the 70 units, 43 were classified as having a more active policy and 27 as having the same or less active policy. Most regions had units in both groups except for Denmark and the Netherlands where all units had more active policies in 2012 (Table S2). Over the two periods, stillbirths declined

significantly (from 32.8% to 29.1%), but there were no significant differences for mean gestational age or mean birth weight among all births or among live births (Table 3). Overall more infants received ANS in 2011/12 (80.7% versus 74.9%) and surfactant (87.6% vs 80.1%), but rates of caesarean and the use of mechanical ventilation remained the same. The proportion of caesarean deliveries did not change across the two groups, however caesarean deliveries were more frequent in 2011/2012 in units where policies became more active (comparison between groups in 2011/2012, p=0.02). In this group, more infants received ANS and surfactant in 2011/2012 compared to 2003. Use of ANS, surfactant and mechanical ventilation was already higher in 2003 in units where policies stayed the same (comparison between groups in 2003, p<.001), and practice variation over time was less significant.

In-hospital mortality after live birth <27 weeks of GA decreased from 50.3% to 41.8%. Units where policies became more active had higher mortality in 2003 (comparison between groups in 2003, p<.01), and experienced steeper decreases (54.7% to 44.0%) than units where policies stayed the same (43.2% to 36.7%). However, mortality rates remained higher in units where policy changed to more active. There were some differences according to gestational age groups: mortality decreased for infants born at $25^{+0 \text{ to } +6}$ in both groups, and for infants born at $26^{+0 \text{ to } +6}$ in the more active group. Rates of severe neonatal morbidity stayed the same. After adjustment for patient characteristics, the decline over time in mortality was more pronounced in the more active policy group (aOR= 0.44 95%CI 0.33-0.59) when compared to the no-change or less active policy group (aOR=0.69; 95% CI 0.46-1.04) (Table 4).

Discussion

Main findings

Reported maternity and neonatal unit policies for the management of extremely preterm infants changed in maternity and neonatal units in 10 European regions between 2003 and 2012. Maternity units reported more active obstetrical management, characterized by the willingness to perform caesarean sections at earlier gestational ages in case of fetal distress. The role of neonatologists increased over time, as witnessed by their reported presence in the delivery room at earlier gestations and more frequent involvement in resuscitation decisions. Nonetheless, significant heterogeneity was evident across units in both time periods. These changes were accompanied by an increase in survival for infants born at less than 27 weeks, particularly in units where policies shifted towards more active management, although these were also the units where mortality was higher in 2003. Survival gains were not accompanied by an increase in major neonatal morbidities.

Strengths and limitations

A strength of our study is its unique design that makes it possible to compare policies and outcomes using population-based cohort studies from 10 European regions. We used data from the same hospitals collected using similar protocols, including identically worded questions about the management of extremely preterm births. In both studies, inclusions were cross-checked with other sources to verify completeness. The study was restricted to hospitals with at least 10 VPT annual admissions which were more likely to have unit policies concerning very preterm infants. We were not able to include all of these hospitals because of restructuring or non-response to one of the questionnaires, resulting in the exclusion of about 17% of infants. Also, because we did not include smaller hospitals, our results cannot be generalized to infants born in these hospitals. Another limitation is that responses may be sensitive to the person who completed the questionnaire; it is possible that practices in the units were more heterogeneous than the reported institutional policies.

Finally, we did not investigate longer term neurodevelopmental or other health outcomes after hospital discharge.

Interpretation

Several countries in our study issued new laws or professional guidelines related to ethical decision-making at the limits of viability between 2003 and 2012 and this likely contributed to the changes in policies and practices. These supported more active management for infants at 24-25 weeks of gestation in France,[24] Germany,[25] Italy,[26] the Netherlands[2, 27] and the UK.[28] In general, these documents align with other national or international guidelines[13, 15, 29, 30] not to offer active treatment to the mother (caesarean section, antenatal steroids) aimed to protect the fetus or to the newborn before 23 weeks of gestation and to offer active treatment starting at 24^{+0} or $25+^{0}$ weeks of gestation.

We used changes in the lower GA at which obstetrical teams would be willing to perform a caesarean for fetal distress to measure whether management became more active over time. Willingness to perform CS for fetal indications has been used by others to evaluate more active obstetrical management.[31, 32] Other interventions have also been considered as active obstetrical management, including in-utero-transfer, antenatal steroids, tocolysis, magnesium sulphate for neuroprotection, antibiotics or induction for preterm prelabour rupture of membranes (PPROM),[31, 33, 34] but information on policies for these interventions was not collected in both of our studies. Other observational studies have also shown that the willingness to perform a caesarean section for fetal distress positively influenced neonatal survival independently of the actual method of delivery.[31, 32] We selected this variable to identify changes in units' policies instead of the presence of a neonatologist in the delivery room, although this also evolved over this period, and might influence neonatal management as shown by others.[35] More neonatologists were reported to be

present in the delivery room at earlier gestational ages and made decisions about the resuscitation of extremely preterm infants alone. However, we did not have information on delivery room interventions to investigate to what extent neonatologists were providing resuscitation or comfort care.

We observed significant improvements in neonatal survival over the two periods which were not explained by differences in the characteristics of the infants. Our results support those of recent studies showing a decline in mortality without concurrent increases in morbidity.[2, 5, 8, 36] Our study adds to this knowledge by showing that the most pronounced decreases in mortality occurred in units where policies for initiating active management shifted to earlier gestations in 2011/12. These units were also those that had the highest mortality and where use of ANS and surfactant was lower in 2003. In units that did not report an increase in active management policies over the period, and where use of ANS, surfactant and mechanical ventilation was already high in 2003, mortality decreased, but more moderately. The heterogeneity of the results among units and the differences between groups, according to reported changes in management policies, suggests that more active management of extremely preterm deliveries was a key contributor, in tandem with advances in neonatal and obstetric care, to declines in extremely preterm mortality.

Conclusion

We documented changes in policies for active management of extremely preterm births in European hospitals over the past decade along with significant decreases in mortality among infants born before 27 weeks of gestational age. Our results suggest that evolutions in policies regarding active management have contributed to increased survival in this population without increases in morbidity at discharge from hospital. When evaluating improvements in the quality and efficacy of

medical care for this high risk population over time, changes in practices related to active management need to be considered. The effects of increased survival on longer term morbidity also need further evaluation.

Conflict of interest

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. The ICMJE disclosure forms are available as online supporting information.

Author Contributions

MB and JZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They act as guarantors of the study.
Study concept and design: JZ, MB, AP, MC, EMB, PHJ, LK, RFM, DWAM, PVR, TW, HB, JG, ESD; Acquisition, analysis, or interpretation of data: JZ, MB, AP, MC, EMB, PHJ, LK, RFM, DWAM, PVR, TW, HB, JG, ESD and all authors in Mosaic and Epice Research Groups; Drafting of the manuscript: JZ, MB, AP, MC, EMB, PHJ, LK, RFM, DWAM, PVR, TW, HB, JG, ESD; Critical revision of the manuscript for important intellectual content and approval of final version of the manuscript: All authors (including investigators listed in MOSAIC EPICE Research Group); Statistical analysis: JZ, AP, MB; Study supervision: JZ, ESD;

Details of ethics approvals

The two European studies were approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS, N° 02.345 on 14/11/2002 for MOSAIC and N° 13.020 on 24/01/2013 for EPICE) and the French National Commission for Data Protection and Liberties (CNIL, N° 03-1052 on 07/03/2003 for MOSAIC and DR-2013-194, on 10/04/2013 for EPICE). The EPICE study authorizations covered analyses combining data from both studies.

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Table 1. Characteristics of 70 hospitals providing care for very preterm infants in 10 European regions in 2003 and 2011/12

	MOSAIC 2003		EPICE 2011/2012		p*
Characteristics of units	**n/median**	**%/IQR**	**n/median**	**%/IQR**	
Maternity units:					
Level 3 units (%)**	54	77.1	53	75.7	>.99
Number of total deliveries (median/IQR)	2271	[1453-3015]	2516	[1627-3530]	<0.01
Caesarean section rate for all deliveries (median/IQR)	23.7	[19.6-30.5]	27.7	[22.3-37.3]	<0.01
Number of very preterm deliveries (median/IQR) ***	53.3	[33-81]	62.5	[40-84]	0.01
Percent VPT deliveries <27 weeks GA (median/IQR)	41.6	[34.5-47.3]	40.2	[35.0-47.2]	0.40
Neonatal units:					
Number of total admissions (median/IQR)	464	[321-602]	463	[306-677]	0.60
Number of very preterm admissions**** (median/IQR)	35.0	[23-64]	48.5	[28-67]	<0.01
Percent of VPT admissions < 27 weeks GA (median/IQR)	27.6	[20.0-35.3]	30.8	[23.0-36.8]	0.7
Units with service/facility on-site (n/%)					
Mechanical ventilation for more than 24h	65	92.9	64	91.4	>.99

Parenteral nutrition through central venous catheter	69	98.6	67	95.7	>.99
Neonatal surgery	32	45.7	35	50.0	0.30

IQR: interquartile range * McNemar's test or Wilcoxon signed-rank test, Wilcoxon rank-sum test; **highest level of care according to local definitions; ***calculated from observed very preterm births in the cohorts; **** very preterm admissions for the first consecutive 48 hours after birth or death when it occurred in the first 48 hours calculated from observed admissions in the cohorts.

Table 2. Reported policies regarding active treatment and withholding or withdrawing treatment for extremely preterm infants in 70 European hospitals in 2003 and 2011/12

	2003		2011/2012		
	n	**%**	**n**	**%**	**p***
Maternity unit questionnaire	**70**		**70**		
The earliest gestational age at which caesarean would be performed because of acute fetal distress for a singleton non-malformed fetus					
Parents want to have everything done					
No policy	15	21.4	11	15.7	
Starting at 22 weeks	1	1.4	3	4.3	
Starting at 23 weeks	5	7.1	10	14.3	
Starting at 24 weeks	24	34.3	27	38.6	
Starting at 25 weeks	11	15.7	12	17.1	
Starting at 26 weeks	12	17.1	7	10.0	
Starting at 27 + weeks	2	3.0	0	0.0	
Mean GA** (50 units)	24.7 (1.2)		24.1 (1.0)		<0.0001
Parents don´t want active management					
No policy	27	38.6	24	34.3	
Starting at 22 weeks	1	1.4	1	1.4	
Starting at 23 weeks	2	2.9	2	2.9	
Starting at 24 weeks	10	14.3	16	22.9	
Starting at 25 weeks	2	2.9	6	8.6	
Starting at 26 weeks	16	22.9	15	21.4	
Starting at 27 + weeks	12	17.0	6	8.5	
Mean GA** (29 units)	26.1 (1.7)		25.2 (1.2)		0.01
The earliest gestational age a neonatologist would be called in case of spontaneous labour for a singleton non-malformed fœtus					
Parents want to have everything done					
No policy	12	17.1	5	7.1	

Starting at 22 weeks	11	15.7	22	31.4	
Starting at 23 weeks	16	22.9	13	18.6	
Starting at 24 weeks	24	34.3	27	38.6	
Starting at 25 weeks	6	8.6	3	4.3	
Starting at 26 weeks	1	1.4	0	0.0	
Starting at 27 + weeks	0	0.0	0	0.0	
Mean GA** (57 units)	23.5 (1.0)		23.3 (0.9)		0.2
Parents don´t want active management					
No policy	19	27.2	8	11.4	
Starting at 22 weeks	8	11.4	19	27.1	
Starting at 23 weeks	11	15.7	7	10.0	
Starting at 24 weeks	20	28.6	29	41.4	
Starting at 25 weeks	8	11.4	4	5.7	
Starting at 26 weeks	4	5.7	3	4.4	
Starting at 27 + weeks	0	0.0	0	0.0	
Mean GA** (49 units)	23.8 (1.1)		23.6 (1.1)		0.3
Neonatal unit questionnaire					
Who usually decides about active resuscitation for an infant < 25 weeks GA					
Obstetrician	0	0.0	1	1.4	0.03***
Neonatologist	20	28.6	34	48.6	
Multidisciplinary team	48	68.6	35	50.0	
No Response	2	2.8	0	0.0	
Decisions were ever taken to withhold or withdraw mechanical ventilation					
Because a baby has no chance of survival (yes)	57	83.8	60	87.0	0.3
Because poor prognosis in case of survival (yes)	49	73.1	49	72.1	0.8
Role of parents in decisions to withhold or withdraw mechanical ventilation					
Parents informed about decisions	14	20.0	7	10.0	0.4***
Parents involved in the decision process	38	54.3	48	68.6	

Parents allowed to make the decision	8	11.4	7	10.0
No response	10	14.3	8	11.3

* Significance tests: McNemar 's chi² test for proportions; paired t-tests for means ; **Exact McNemar's chi² test for units with a policy with gestational age limits; ***test of symmetry

Table 3. Characteristics, outcomes and care of infants born at less than 27 weeks GA overall and by changes in maternity unit policies from 2003 to 2011/12

	All units (N=70)			More active policies* in 2012 (N=43)			Less active or no change in policies** in 2012 (N=27)		
	2003	**2011/2012**	**p**	**2003**	**2011/2012**	**p**	**2003**	**2011/2012**	**p**
	n / %	**n / %**		**n / %**	**n / %**		**n / %**	**n / %**	
Live and still births (N)	1240	1293		759	892		481	401	
Stillbirths*** (%)	32.8	29.1	0.04	32.0	28.7	0.14	34.1	29.9	0.19
Gestational age- mean (sd)	24.4 (1.4)	24.4 (1.4)	0.48	24.3 (1.4)	24.3 (1.4)	0.69	24.5 (1.4)	24.5 (1.3)	0.80
Birth weight –mean(sd)	672 (210)	688 (221)	0.07	671 (221)	684 (228)	0.22	675 (208)	696 (205)	0.13
Live births (N)	833	917		516	636		317	281	
Gestational age in weeks – mean(sd)	24.8 (1.2)	24.7 (1.2)	0.06	24.8 (1.2)	24.7 (1.2)	0.22	24.9 (1.1)	24.8 (1.2)	0.23
Birth weight in grams– mean(sd)	740 (181)	737 (181)	0.70	739 (183)	734 (185)	0.66	742 (178)	743 (171)	0.95
Small for gestational age**** (%)	9.7	10.3	0.67	9.1	11.1	0.30	10.6	8.6	0.43
Male (%)	52.7	52.6	0.97	54.0	50.7	0.27	50.5	56.8	0.12
Multiples (%)	27.5	31.8	0.05	27.1	33.0	0.03	28.1	29.2	0.77

Inborn (%)	93.6	91.7	0.15	95.9	92.3	0.02	89.9	90.2	0.90
Antenatal steroids (%)*****	74.9	80.7	0.009	71.3	77.9	0.02	80.5	87.2	0.05
Spontaneous onset of labour	69.6	76.2	0.002	67.8	74.4	0.013	72.6	80.1	0.034
Caesarean delivery (%)	42.6	44.7	0.38	43.1	47.2	0.16	41.8	38.9	0.48
Any mechanical ventilation (%)	89.8	90.1	0.78	85.4	87.8	0.28	96.8	95.7	0.48
Any surfactant (%)	80.1	87.6	<0.001	72.3	84.2	<0.001	92.6	94.5	0.38
In-hospital mortality (%)	50.3	41.8	<0.001	54.7	44.0	<0.001	43.2	36.7	0.10
In-hospital mortality by gestational age									
22 weeks (n) %	(41) 100	(45) 100		(30)100	(32) 100		(11) 100	(13) 100	
23 weeks (n) %	(80) 90.9	(87) 85.3	0.24	(53) 94.6	(67) 87.0	0.14	(27) 84.4	(20) 80.0	0.67
24 weeks (n) %	(91) 60.1	(113) 50.7	0.05	(59) 66.3	(81) 52.3	0.03	(32) 53.3	(32) 47.1	0.48
25 weeks (n) %	(121) 47.1	(76) 30.9	<0.001	(81) 47.9	(55) 32.5	0.004	(40) 45.5	(21) 27.3	0.02
26 weeks (n) %	(86) 28.9	(62) 20.6	0.02	(59) 34.3	(45) 22.2	0.009	(27) 21.4	(17) 17.4	0.45
Survivors to discharge (N)	414	534		228	206		107	81	
PVL/IVH (%)	16.7	16.1	0.80	16.9	15.3	0.62	16.4	17.5	0.77
BPD (%)	50.3	44.5	0.09	46.6	40.9	0.18	55.1	51.7	0.53

PVL/IVH: periventricular leukomalacia/intraventricular hemorrhage; BPD: bronchopulmonary dysplasia; *reported decrease in threshold for lower GA for performing CS for cases of acute fetal distress in singleton non-malformed fetuses in 2012 compared to 2003 ; **GA threshold stayed the same or increased; ***antepartum or intrapartum stillbirths; ****<10th percentile of birthweight standards from the MOSAIC and EPICE cohorts; *****excluding Germany.

Table 4. Changes in in-hospital mortality of extremely preterm infants born less than 27 weeks of gestation according to changes in maternity unit policies between 2003 and 2011/12 - Conditional logistic regressions

In-hospital mortality	All units (N=70)		More active policies* in 2012 (N=43)		Less active or no changes in policies† in 2012 (N=27)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Crude OR	0.68	(0.55-0.83)	0.62	(0.49-0.80)	0.80	(0.56-1.14)
Adjusted OR for gestational age (GA)	0.52	(0.41-0.65)	0.44	(0.33-0.59)	0.70	(0.47-1.05)
Adjusted OR for GA, sex,multiple	0.51	(0.40-0.65)	0.44	(0.33-0.59)	0.69	(0.46-1.04)
Adjusted OR for GA, sex,multiple, antenatal steroids‡	0.48	(0.37-0.62)	0.38	(0.27-0.53)	0.77	(0.49-1.21)

* reported decrease in threshold for lower GA for performing CS for cases of acute fetal distress in singleton non-malformed fetuses in 2012 compared to 2003 ; † GA threshold stayed the same or increased; ‡excluding Germany.