Improvement in perinatal care for extremely premature infants in Denmark from 1994 to 2011

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ABSTRACT

INTRODUCTION: Major advances in perinatal care over the latest decades have increased the survival rate of extremely premature infants. Centralisation of perinatal care was implemented in Denmark from 1995. This study evaluates the effect of organisational changes of perinatal care on survival and morbidity of live-born infants with gestational ages (GA) of 22-28 weeks.

METHODS: Three cohort studies were included from 1994-1995, 2003 and 2011. Data from live-born infants were extracted regarding risk factors, survival, bronchopulmonary dysplasia (BPD), cystic periventricular leukomalacia (cPVL) and intraventricular haemorrhage grade 3-4 (IVH 3-4).

RESULTS: A total of 184, 83 and 127 infants were included from the cohorts. Delivery rates at level 3 Neonatal Intensive Care Unit (NICU) hospitals increased from 69% to 87%. Transfer rates to level 3 NICU almost doubled during the period. Survival rates were stationary, although a trend towards increased survival was observed for infants < 26 weeks. The frequency of infants receiving evidence-based treatment increased from 14% to 46%. IVH 3-4 rates were reduced from 21% to 12%, whereas BPD and cPVL rates did not change. Survival odds increased with higher gestational age and administration of surfactant.

CONCLUSIONS: Centralisation of treatment of extremely premature infants has been implemented because more children are being born at highly specialised perinatal centres. Care improved as more infants received evidence-based treatment. IVH 3-4 rates declined. A trend towards increased survival was observed for infants with a GA < 26 weeks.

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The survival rate of extremely premature infants has gradually increased owing to major advances in perinatal care with antenatal administration of steroids to mothers [1], instillation of exogenous surfactant and use of mechanical ventilation for respiratory distress syndrome [2]. As a consequence, technical and personnel resources have been upgraded and organisational changes introduced to ensure the optimal treatment of high-risk infants at highly specialised centres. This centralisation is based on the paradigm that large units with adequate technical and personnel resources can treat a larger number of infants with complex diseases, thereby achieving an improved care and a lower mortality and morbidity. Recent studies support the benefit of centralisation [3-6], but larger units with intense resource utilisation may increase the odds of a composite adverse outcome in very preterm infants [7, 8].

Centralisation of perinatal care has been implemented in Denmark during the past two decades; and in that period, three prospective cohort studies were conducted. Based on the data from these cohorts, this study evaluated the effect of organisational changes of perinatal care on survival and morbidity of live-born infants with gestational ages (GA) between 22 and 28 weeks.

METHODS

A total of three cohort studies were included: The Danish national study of infants with extremely low gestational age and birthweight (ETFOL) [9], Models of OrganiSing Access to Intensive Care for very preterm births (MOSAIC) study [10] and The Effective Perinatal Intensive Care in Europe (EPICE) study [11]. Data from all live-born infants (22-28 weeks) delivered at hospitals in Eastern Denmark were extracted for this analysis.

In brief

ETFOL (1994-1995) recorded data on all infants delivered at hospitals in Denmark with a GA < 28 weeks or a birthweight (BW) < 1,000 g. The reported number of infants was cross-checked with that of the Danish Birth Registry [9]. MOSAIC (2003) included data on all infants delivered with GA < 32 weeks in the eastern region of Denmark (Funen, Zealand, Lolland and Falster). Identifications were checked against the records of the Danish Birth Registry [10].

EPICE (May 2011-April 2012) included data on all infants delivered with a GA < 32 weeks in the eastern region of Denmark (Funen, Zealand, Lolland and Falster). Identifications were checked against the records of the Danish Birth Registry [11].

Infants

Live-born infants with a GA between 22 and 28 weeks (22 ≤ GA < 28) who had been delivered at hospitals in the eastern region of Denmark were identified from the three data sets. During the period, eight hospitals had a

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TABLE 1

Definitions of data extracted from each of the three cohorts.

Term	Definition
Gestational age	Postmenstrual age assessed by the following in prioritised order: 1st, 2nd or 3rd trimester ultrasound Last menstrual period
Birth weight	Weight in g measured at birth
Antenatal steroids	Any steroids administered to mother before birth for foetal maturation
Caesarean section	Birth during caesarean section
Delivery	Vaginal or by caesarean section
Transfer	Postnatal transportation within the first 24 h of life to level 3 NICU
Administration of surfactant	Administration of any surfactant to the infant (Curosurf in all cases)
Intermittent positive pressure ventilation	Use of any mechanical ventilation (nCPAP not included)
Survival	Survival to discharge
Level of NICU	According to levels of neonatal care classification
Bronchopulmonary dysplasia	Need for any oxygen supplement at postnatal age corresponding to a gestational age of 36 weeks
Intraventricular haemorrhage grade	According to Papile classification [13]
Cystic periventricular leukomalacia	Cystic abnormalities are detected using ultrasound or computed tomography

nCPAP = nasal continuous positive airway pressure; NICU = Neonatal Intensive Care Units.

delivery service and neonatal support: two university hospitals (level-3 Neonatal Intensive Care Units (NICU)): Rigshospitalet and Odense University Hospital and six regional hospitals (level 2 NICUs): Hvidovre, Glostrup/Herlev (In 2010, the delivery service and neonatal support were moved from Glostrup Hospital to Herlev Hospital), Hillerød, Roskilde, Holbæk and Næstved [12].

The following data were extracted: gender, GA, BW, administration of antenatal steroids to the mother, mode of delivery, administration of surfactant, use of intermittent positive pressure ventilation (IPPV), survival to discharge and morbidities discovered during hospitalisation (i.e. bronchopulmonary dysplasia (BPD), intraventricular haemorrhage grade 3-4 (IVH 3-4) and cystic periventricular leukomalacia (cPVL)). Definitions are provided in **Table 1**.

Organisation of perinatal care

A national plan was developed in 1994 to improve the treatment of extremely preterm infants, and recommendations were gradually implemented during the 1995-1999 period [14]. Extremely preterm delivery should occur at high-level hospitals with in-utero transfer in case of imminent birth; and highly specialised teams were created for safer transport of infants born outside specialised units. In the eastern part of Denmark, perinatal care of extremely premature infants, i.e. GA below 28 weeks, was centralised in two level-3 NICUs, while the region has another six level-2 NICUs for basic care [12]. This strategy was confirmed in the Danish specialty plans of 2001 and 2010 [15, 16].

Ethics and permissions

Permission to use data from the three cohorts was obtained from the regional EPICE and MOSAIC research coordinators. Our use of ETFOL data was approved by the Danish Paediatric Society. The present study is a register-based and ethical approval is therefore not required according to the Danish Ethical Committee System [17].

Statistics

Data are presented as numbers and group mean values with standard deviations. Between-group quantitative data were compared by analysis of variance (ANOVA). Dichotomous data were tested using the chi-squared test.

Possible predictors of survival to discharge from hospital were tested by logistic regression: GA, study period (cohorts approximately ten years apart), level of NICU (2 or 3) at delivery hospital, administration of antenatal steroid, mode of delivery, administration of surfactant and use of IPPV.

The level of significance was set to $p < 0.05$ (SPSS Statistics, version 20.0, Chicago, IL, USA).

Trial registration: not relevant.

RESULTS

In total, 184, 83 and 127 live-born infants with a GA below 28 weeks were included from the ETFOL (1994-1995), MOSAIC (2003) and EPICE (2010) studies, respectively. A significant increase in the live birth rate of extremely preterm infants from 2.4 to 3.8 per 1,000 births was observed from 2003 to 2010 (**Table 2**). GAs and BWs were slightly different with the smallest infants born in 2003 (Table 2).

The ratio of infants born at hospitals with level-3 NICUs increased markedly over time from 69% to 87%, while the number of deliveries at hospitals with level-2 NICUs decreased concordantly. In case of delivery at hospitals with level-2 NICUs, the ratio of infants who were transferred to level-3 NICUs almost doubled during the period.

Overall, survival increased from 59% to 69%; yet, the increase was insignificant ($p = 0.16$). The trend was more pronounced for infants below 26 weeks in whom survival increased from 37% to 57% ($p = 0.07$).

The use of evidence-based therapies became more frequent over the period. Thus, in 2011, antenatal administration of one dose of steroids was administered to 97% of mothers, whereas infant treatment with surfactant increased significantly (Table 2). The frequency

of infants receiving all evidence-based practices extracted in this study (antenatal steroids, administration of surfactant and delivery in hospital with level-3 NICU) increased significantly from 14% to 46% (p < 0.0001).

Delivery by caesarean section tended to increase from 1994 to 2011 (p = 0.05).

The proportion of infants with severe intracranial haemorrhage (IVH 3-4) decreased significantly from 21% to 12%, whereas BPD and cPVL rates remained unchanged.

Predictor variables for survival to discharge

Odds for survival increased significantly with higher gestational age and with administration of surfactant, and the changes over the approximate 20-year study period almost reached significance for improved survival. This being examined by the impact of the three cohorts being approximately ten years apart. In contrast, neither gender, level of unit, administration of antenatal steroids, mode of delivery, nor use of mechanical ventilation were statistically associated with survival (**Table 3**).

DISCUSSION

This study demonstrates that the national plan with centralisation of perinatal care of extremely preterm infants has become established in Eastern Denmark during the 1994-2011 period. Over time, significantly more infants were delivered at hospitals with level-3 NICUs, and approximately 85% had been transported in-utero. Of the remaining infants, the majority were transferred to level-3 NICUs within their first day of life. Transportation of compromised preterm infants may be a very hazardous procedure and specialised teams were available in 2011.

Early admission to the hospitals with level-3 NICUs may stabilise the sick mother and prepare the foetus for the imminent birth. Steroids to the mother 24 hours before delivery halves the risk that the infant develops re-

TABLE 2

Descriptive data, risk factors and outcome data for mortality and morbidity from the three cohorts 1994-1995 (ETFOL), 2003 (MOSAIC) and 2011 (EPICE).

	Study			
	ETFOL	MOSAIC	EPICE	p-value
Year	1994-1995	2003	2011	-
Months, n	24	12	12	-
Incidence				
Births in the period, n	72,846	34,637	33,585	
Liveborn, GA (22 + 0)-(27 + 6) weeks, n (per 1,000 births)	184 (2.5)	83 (2.4)	127 (3.8)	0.0004
Risk factors:				
Gestational age, days, mean (± SD)	26.1 (± 1.2)	25.8 (± 1.1)	26.2 (± 1.3)	0.043
Birthweight, g, mean (± SD)	862 (± 211)	788 (± 173)	832 (± 201)	0.014
Gender, M/F (% M)	103/81 (56)	40/43 (48)	61/66 (48)	0.295
Antenatal steroids, n (%)	108 (59)	64 (96)	119 (97)	< 0.0001
Caesarian section, n (%)	99 (54)	54 (69)	84 (66)	0.05
Administration of surfactant, n (%)	92 (50)	45 (57)	85 (69)	0.003
Intermittent positive pressure ventilation, n (%)	98 (53)	49 (62)	81 (66)	0.07
All evidence-based practices (antenatal steroids, administration of surfactant, delivery at hospital with level 3 NICU), n (%)	26 (14)	33 (40)	58 (46)	< 0.0001
NICU, n (%):				
Delivery at hospital with level 2	57 (31)	12 (14)	17 (13)	0.0002
Postnatal transfer to level 3	19 (33)	7 (58)	11 (65)	0.037
Delivery at hospital with level 3	127 (69)	71 (86)	110 (87)	0.0002
Outcome, n (%)				
Overall survival to discharge:	109 (59)	57 (69)	87 (69)	0.16
Survival, delivery at hospital with level 2 NICU	32 (56)	10 (83)	10 (59)	0.21
Survival, delivery at hospital with level 3 NICU	77 (61)	47 (66)	77 (70)	0.31
Survival, GA < 26	29 (37)	18 (53)	26 (57)	0.07
Survival, GA 26-27 weeks	80 (76)	39 (80)	61 (75)	0.85
Bronchopulmonary dysplasia, n +/-/unknown (%)[a]	12/98/74 (11)	9/43/31 (17)	15/62/50 (19)	0.24
Intraventricular haemorrhage 3-4, n +/-/unknown (%)[a]	27/101/56 (21)	7/72/4 (9)	15/107/5 (12)	0.03
Cystic periventricular leukomalacia, n +/-/unknown (%)[a]	7/104/73 (6)	2/77/4 (3)	2/111/14 (2)	0.16

ETFOL = The Danish national study in infants with extremely low gestational age and birthweight; EPICE = Effective Perinatal Intensive Care in Europe; F = female; GA = gestational age; M = male; MOSAIC = Models of OrganiSing Access to Intensive Care for very preterm births; NICU = Neonatal Intensive Care Units; SD = standard deviation.

a) Number of infants with/without/missing data, infants with missing data are omitted in the calculations.

TABLE 3

Results of survival to discharge logistic regression with risk factors including all three cohorts.

Predictor	OR (95% CI)	p-value
Gestational age, per week	2.14 (1.71-2.66)	0.000
Study period, cohorts approx. 10 yrs apart	1.36 (1.00-1.86)	0.054
Delivery at level 3 NICU	0.88 (0.49-1.59)	0.673
Antenatal steroid	0.91(0.49-1.68)	0.760
Caesarean section	1.10 (0.66-1.83)	0.712
Surfactant	1.88 (1.07-3.29)	0.028
Intermittent positive pressure ventilation	1.03 (0.60-1.79)	0.905
Gender, female	0.95 (0.59-1.54)	0.832

CI = confidence interval; NICU = Neonatal Intensive Care Units; OR = odds ratio.

spiratory distress syndrome [1], and this effect is enhanced by administration of an exogenous surfactant [2]. Special skills in resuscitation and provision of intensive care are essential for a good outcome, i.e. tracheal intubation for surfactant instillation. The significant increase in infants receiving all evidence-based treatments can be seen as a rise in the quality of care over the decades [18].

Perinatal care was improved from 1994 to 2011. More infants were delivered and treated at hospitals with a level-3 NICU with highly specialised personnel and technical resources. Specialised teams transferred out-born infants, and more infants received evidence-based treatments with antenatal steroids and surfactant administration. During this period, no apparent effect on survival rates was observed; however, a trend towards increased survival in infants below 26 weeks was seen. Certainly, the tiniest infants are the most vulnerable ones and they are in need of special care, whereas this may not be the case for infants of 26 gestational weeks and above. BW and GA differed slightly between the cohorts, and the lowest mean values were seen in 2003. We are unable to explain this variation over time.

Skin to skin care for a very preterm infant.

Centralisation itself may be responsible for improved care, but the improved outcome may also be owed to the establishment of successful interventions. In 2011, more infants were dependent on oxygen at a GA of 36 weeks, but this may reflect the more extended use of mechanical ventilation in that period. The proportion of infants with BPD actually remained constant through the decades.

Data regarding BPD, IVH 3-4 and cPVL should be interpreted with caution as the proportion of examined infants varied between the different NICUs and cohorts (Table 2).

The proportion of infants with major intracranial haemorrhage grades 3-4 was halved in 2011, probably owing to a higher use of antenatal steroids. However, it is unknown whether an improved neurological outcome was achieved as follow-up data are very limited. The ETFOL study documented an intellectual disability rate of approximately 19% at five-year follow-up [19]. The results of the systematic two-year follow-up of the EPICE cohort will be presented in the near future.

Some words of caution should be noted: First, centralisation may move trained personnel towards highly specialised centres, thereby leaving the 13% of infants born at smaller hospitals at risk of a poorer immediate care. Second, the apparent rise in survival rate may be underestimated. In 1994, the definition of live birth in Denmark was subjective, why attitudes towards outcome and possibilities for care may have influenced the initial support and decision. The attitude became more optimistic over the years, and WHO criteria for stillbirth were confirmed in 2004 [20].

Limitation and strengths

This study is limited by the size of the Eastern Denmark population. The size of the region may be a strength with respect to centralisation as the region is serviced by only two level-3 NICUs, which are easily accessible as the transport transfer times are short from anywhere in the region and therefore a high proportion of transfers occur according to guidelines and protocols.

Data analysed are from three different data collections. Data entries are fully comparable between the cohorts, but over a period of 20 years, definitions of disease, definitions of live births and treatment regimens have changed thereby interfering with the present analysis.

CONCLUSIONS

Centralisation of treatment of extremely premature infants has been implemented and a larger fraction of premature infants are now being born at highly specialised perinatal centres, whereas deliveries in lower level hospitals are minimised. Survival rates increased for infants with a GA below 26 weeks without changes in BPD or

cPVL, whereas the IVH grade 3-4 was halved. A significant increase in the use of evidence-based practices, i.e. administration of surfactant, antenatal steroids and delivery at hospital with level 3 NICU, was identified over the decades.

This study examines outcome until discharge. The number of patients who survive has increased; but so has the number of patients who survive with possible long-term neurological impairment that may require assistance further on in life such as health services, educational special needs and social assistance. Further research is needed to identify infants who are more susceptible to severe morbidities and long-term challenges and to prevent these adverse outcomes. At the moment, we are processing two-year follow-up results, and five-year follow-up is planned in order to examine which long-term effects extremely premature birth may have.

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