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Leiden**  
The Netherlands

## **A regional follow-up study at two years of age in extremely preterm and very preterm infants.**

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### **Citation**

Rijken, M. (2007, November 15). *A regional follow-up study at two years of age in extremely preterm and very preterm infants*. Retrieved from <https://hdl.handle.net/1887/12450>

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**Note:** To cite this publication please use the final published version (if applicable).

CHAPTER 2

Mortality and neurologic, mental and psychomotor development at 2 years in infants born less than 27 weeks' gestation: the Leiden Follow-Up Project on Prematurity

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On behalf of the Leiden Follow-Up Project on Prematurity

## Abstract

**Objective:** To determine the outcome of infants with a gestational age (GA) <27 weeks, born in the mid-1990s.

**Design:** Regional, prospective study; part of the Leiden Follow-Up Project on Prematurity (LFUPP).

**Setting:** Three health regions in the Netherlands.

**Patients:** A total of 266 live born infants (1996/1997) with GA <32 weeks; 46 infants were <27 weeks.

**Main outcome measures:** Neurologic examination (according to Hempel) and assessment of mental and psychomotor development using the Bayley-Scales of Infant Development I, at the corrected age of 2 years.

**Results:** Mortality was 35% (16 of 46) <27 weeks, compared with 6% (14 of 220) in infants with GA 27 to 32 weeks; withdrawal of treatment in 60% and 43%, respectively. Below 27 weeks mortality was higher after extra-uterine transport and pregnancy induction. Neonatal morbidity was higher in infants <27 weeks compared with infants 27 to 32 weeks. Below 27 weeks postnatal use of dexamethasone and being hospitalized at term were associated with abnormal neurologic outcome; there was a higher incidence in (mild) mental developmental delay compared with the older infants ( $p=0.048$ ). Adverse outcome (dead or abnormal neurologic, psychomotor or mental development) in infants 23 to 24, 25, 26, and 27 to 32 weeks GA was, respectively, 92% (11 of 12), 64% (7 of 11), 35% (8 of 23) and 18% (40 of 220).

**Conclusion:** Mortality and neonatal morbidity were higher in infants with GA <27 weeks compared with infants born between 27 and 32 weeks. The high adverse outcome of infants <25 weeks suggests that one should carefully weigh whether or not to aggressively resuscitate and treat these extremely premature infants.

## Introduction

In the 1990s, new techniques have been introduced to increase viability of very premature infants. The use of surfactant, antenatal steroids and better ventilation strategies have resulted in an increased survival of infants of extremely low gestational age (GA) or low birth weight. Some studies report an increase in percentage of severe disabilities<sup>1</sup> with this better survival while others have reported that the handicap-rate has remained the same.<sup>2-5</sup> Finally, with a decreasing mortality and therefore more survivors, the absolute number of infants with handicap has increased.

Worldwide, there is a difference in opinion about the limit of viability: at what GA should one start to resuscitate? Studies from the United States report that resuscitation is indicated from 23 or 24 weeks of gestation, although the chances of intact survival are poor<sup>6-8</sup>; McElrath *et al.*<sup>9</sup> found no survivors, born at 23 weeks' gestation, free from substantial morbidity. Studies from Japan report 18% survival in infants born at 22 to 23 weeks; these survivors, however, have high rates of neurologic sequelae.<sup>10</sup> In Europe (Sweden<sup>11</sup>, United Kingdom<sup>12-14</sup>) high mortality rates (>70%) at 23 and 24 weeks were found. Unfortunately, articles about GA and outcome are relatively scarce. In the past, Verloove *et al.*<sup>15</sup> showed that GA is a more important indicator of maturation than is birth weight.

The aim of this study, which is part of the Leiden Follow-Up Project on Prematurity (LFUPP), was to compare mortality, neonatal morbidity and outcome (neurologic, psychomotor, mental and behavioral) at the corrected age of two years, of infants born with a gestational age of <27 weeks to infants born between 27 and 32 weeks GA. In addition, we looked for intra-group differences among the infants <27 weeks GA. Furthermore, predictors of abnormal outcome at the corrected age of two years were explored.

## Patients and methods

### Patients

The LFUPP, a Dutch regional prospective study, included 92% of eligible live born infants of <32 weeks of gestation, born in 1996/1997 in the health regions The Hague, Leiden and Delft (n=266).

A total of 122 infants (46%) were born in the Leiden University Medical Center (LUMC), 45 (17%) were born in another university hospital with a NICU, 64 (24%) in a regional hospital in The Hague and transported to the NICU of the Juliana Children's Hospital (JCH); another 35 infants (13%) were born in another regional hospital. Infants admitted to one of the hospitals mentioned above but coming from another geographical area were not included in this study. The hospitals contributing to this study had the same clinical protocol for resuscitation, with the exception that other hospitals with a NICU did not resuscitate infants born <25 weeks, in contrast to the LUMC. Seventy percent of the infants were admitted to the LUMC or JCH, 2 hospitals which have the same clinical neonatal care.

Forty-six infants were born < 27 weeks GA. Of these infants, 25 (55%) were born in the NICU of the LUMC, 8 (17%) in another NICU, and 13 (28%) in a regional hospital and immediately after birth transported to a NICU.

Although in the 3 mentioned health regions treatment (full resuscitation in the delivery room without restrictions) was started when an infant had a gestational age of at least 24<sup>+0</sup> weeks, two infants with a GA of 23 weeks were included because the precise GA was uncertain at the time of birth. In general the GA is very well known in the Netherlands because of good antenatal care and early ultrasound assessments. When a GA of 24 weeks is mentioned, a GA of 24<sup>+0</sup> to 24<sup>+6</sup> weeks is meant.

### Data collection

Antenatal and perinatal data were collected including health status and diseases of the mother, socio-economic status (SES), pregnancy induction, reliability of gestational age, diseases and medication during pregnancy, gestational age, birth weight, Apgar score and data about perinatal morbidity and medication. SES was determined by the level of education of each parent individually. A score of 1 was given if the parent's education was low, a score of 2 for an average educational level and a score of 3 for higher levels of education. SES-scores of both

parents were then combined and divided by 2 (range 1-3). Dexamethasone was given in 1996/1997 in an initial dose of 0.5 mg/kg, tapered over 42 days to 0.1 mg/kg. Some infants who remained ventilator-dependent got a second course of dexamethasone but this was not given in a standardized way. The condition at discharge from the hospital was noted and was considered to be normal when there was no neurologic disorder (on clinical examination), no pulmonary problems (need of oxygen and/or diuretics), no cardiac disorder, no feeding problems (tube feeding or regurgitation) and no visual, hearing or psychosocial difficulties. The cause of death was noted and also whether they died naturally or after withdrawal of treatment.

The Medical Ethics Committee of the LUMC approved the study and informed consent of the parents was obtained.

### **Follow-up**

Children were assessed at 2 years of age (corrected for prematurity) by 4 neonatologists experienced in developmental assessment. The examination included a general examination and a neurologic examination according to Hempel<sup>16</sup>, focused on major as well as minor neurologic dysfunctions. The children were considered definitely abnormal (DA) when muscle tone and reflexes were both abnormal (which meant the presence of a cerebral palsy), mildly abnormal (MA) when only part of the reflexes or muscle tone were abnormal, or normal (N).

Mental and psychomotor development were assessed by a developmental psychologist using the Dutch version of the Bayley-Scales of Infant Development I (BSID I).<sup>17,18</sup> During the study period the BSID II was not yet validated for the Dutch population. The BSID I have a mean value of 100 and a standard deviation of 16. A Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI)  $\geq 84$  ( $\geq -1$  SDS) was considered normal (N), MDI or PDI between 68 and 84 was considered as moderate delay (MD) and  $< 68$  ( $< -2$  SDS) as severe delay (SD).

To attain a single outcome measure, neurologic outcome, PDI and MDI were combined. When at least one of these three outcome-measures was DA, children were considered DA and when at least one outcome was MA, children were considered MA.

At 2 years of age behavior was assessed using Achenbach's Child Behavior Checklist<sup>19,20</sup> for 2- to 3-year-old children, completed by the parents. According to this list, behavior could be assessed by using a total problem score: a score

above the 90th percentile was defined as clinical (abnormal), a score from the 85th through 90th percentile as borderline clinical; below the 85th percentile as normal.

### **Statistical analyses**

SPSS10 for Windows was used for statistical analyses. Fischer's Exact test was used to evaluate associations in a 2x2 table/ $\chi^2$ -test. A test on linear association was used in a 2x3 table. Correction for confounding variables was done with binary logistic regression for mortality and the Hempel examination with GA and BPD as confounders. Differences were considered significant with  $P$  values  $< .05$ .

## **Results**

### **Mortality**

Fifteen (33%) of the 46 extremely premature infants ( $<27$  weeks) died in the neonatal period, one girl died at the corrected age of six months, increasing the overall mortality to 16 (35%). In the infants born between 27 – 32 weeks GA ( $n=220$ ), in hospital mortality was 6% (14 infants), which is significantly lower than in the infants of  $<27$  weeks GA ( $p < .001$ ). Mortality decreased with increasing GA.

#### *Infants born $<27$ weeks GA*

Seventy percent of the infants born  $<27$  weeks had a birth weight  $<1000$  grams. Mortality was 50% when birth weight was  $<750$  grams. Mortality decreased with increasing birth weight.

Neonatal mortality was higher in infants born in peripheral hospitals and then immediately afterwards transported to a NICU, compared with infants born in a hospital with a NICU: 10 of 13 (77%) versus 6 of 33 (18%); odds ratio (OR) 15 (95% confidence interval [CI]: 3.1 – 71.7),  $p < .001$ . After correction for GA the OR remained about the same: 13.4 (95% CI: 2.4 – 75.1;  $p = .003$ ). Mortality was higher when pregnancy was induced: 5/7 (71%) in IVF (4) /ICSI (1) compared with 11/39 (28%) in spontaneous pregnancies (OR 6.4, 95% CI: 1.1 – 37.8;  $p = .04$ ). After correction for GA the OR remained at the same level of 6.1 (95% CI: 0.8 – 45.0;  $p = .08$ ), hence little confounding in the data. Although multiple birth occurred more often in case of pregnancy induction ( $p = .001$ ), multiple

birth itself was not associated with higher mortality: 25% in multiple pregnancy compared with 37% in singleton pregnancy, this was not statistically significant. Withdrawal of treatment (when further treatment was considered futile) occurred in 60% of cases (n=9). Two infants died the first day; 8 infants (53%) died in the first week, mainly because of pulmonary or intracerebral problems; withdrawal of treatment occurred in 63% of them. Another 7 infants died before the fourth week because of various problems. One infant died at the age of six months secondary to BPD.<sup>21</sup> In the 14 infants born between 27-32 weeks gestation that died, treatment was withdrawn in 43%.

For a more detailed study of the extremely premature infants we divided the group into infants with a gestational age of 23-25 weeks (n=23) and of 26 weeks (n=23). In the first group 12 infants died (52%), in the second group 4 infants (17%): OR 5.1, 95% CI: 1.3-20.1; p = .03.

### **Perinatal morbidity**

#### *Comparison of infants <27 weeks GA to infants of 27 to 32 weeks GA*

The mean GA in the group <27 weeks GA was 25.7 weeks, compared with 30.0 weeks in the group 27 to 32 weeks GA; mean birth weight was 843 grams and 1335 grams, respectively. The incidence of perinatal problems in infants with a GA <27 weeks was compared with the incidence in infants born between 27 and 32 weeks. The incidence of pregnancy-induction, male gender, percentage of twin or triplet, use of antenatal steroids, and the number of infants with intrauterine growth failure did not vary between the 2 groups; the percentage of delivery by Cesarean section was higher (p < .001) in the infants born between 27 and 32 weeks of gestation (Table 1). Neonatal morbidity was much higher in the more premature group (Table 2).

The condition at discharge is summarized in Table 3: the extremely premature infants were more frequently considered abnormal at discharge and more frequently discharged with oxygen or a home monitor.

#### *Comparison of infants born at 23 to 25 weeks GA to infants born at 26 weeks GA*

No differences existed between the groups in the incidence of pregnancy-induction, gender, singleton versus twin/triplet and antenatal use of glucocorticosteroids. The mean birth weight in the group 23 to 25 weeks GA was lower than in infants born at 26 weeks of gestation (739 grams compared with 948 grams, p<.001). The incidence of respiratory distress syndrome<sup>22</sup>, hypotension,



**Table 1.** Prenatal factors in infants < 27 weeks versus 27 to 32 weeks GA

<b>Gestational age</b>	<b>&lt; 27 weeks N (%)</b>	<b>27 – 32 weeks N (%)</b>
Pregnancy induction		
- none	39/46 (85)	190/219 (87)
- IVF	6/46 (13)	16/219 (7)
- ICSI	1/46 (2)	1/219 (1)
- medication	-	12/219 (5)
Gender: male	25/46 (54)	122/220 (56)
Multiple birth		
- singleton	30/46 (65)	151/220 (69)
- twins	13/46 (28)	60/220 (27)
- triplets	3/46 (7)	9/220 (4)
Reliability GA		
- sure	44/46 (96)	215/217 (99)
- unsure	2/46 (4)	2/217 (1)
Antenatal steroids		
- none	8/42 (19)	59/207 (29)
- 1 gift	18/42 (43)	42/207 (20)
- 2 gifts (= 1 course)	16/42 (38)	106/207 (51)
Intra uterine growth retardation (<P <sub>10</sub> )	2/46 (4)	31/219 (14)
Cesarean section	6/46 (6)	40/160 (25)
SES (mean, range 1-3)	2.10	1.93

IVF indicates in vitro fertilization; ICSI, intracytoplasmic sperm injection. Antenatal steroids: 6 mg Bethamethasone, second gift after 24 hours.

patent ductus arteriosus, need for oxygen at 28 days, BPD, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP)<sup>23</sup>, intra-ventricular hemorrhage (IVH), or cystic periventricular leucomalacia (PVL) was the same in the 2 groups. The younger group tended to be more frequently treated with diuretics (92% versus 56%,  $p = .05$ ) and with dexamethasone postnatally (83% versus 50%,  $p = .06$ ) than the older group. Condition at discharge was abnormal in 91% of the infants born at 23 to 25 weeks gestation compared with 61% in infants born at 26 weeks gestation (Table 3).

**Table 2.** Neonatal factors in infants < 27 weeks versus 27 to 32 weeks GA

	23–25 wks N (%)*	26 wks N (%)*	< 27 wks N (%)*	27 – 32 wks N (%)*	p- value†
No RDS	3/23 (13)	4/23 (17)	7/46 (15)	98/215 (46)	<.001
RDS grade I/II	9/23 (39)	7/23 (30)	16/46 (35)	60/215 (28)	
RDS grade III/IV	11/23 (48)	12/23 (53)	23/46 (50)	57/215 (26)	
Use of surfactant	14/23 (61)	14/22 (64)	28/45 (62)	84/220 (38)	.004
Hypotension	19/22 (86)	16/23 (70)	35/45 (78)	55/215 (25)	<.001
PDA	15/23 (65)	17/23 (74)	32/46 (69)	38/219 (18)	<.001
NEC	4/23 (17)	3/23 (13)	7/46 (15)	18/219 (8)	.003
No IVH	13/23 (57)	14/23 (61)	27/46 (59)	171/220 (78)	.007
IVH Grade I / II	6/23 (26)	6/23 (26)	12/46 (26)	37/220 (17)	
IVH Grade III / IV	4/23 (17)	3/23 (13)	7/46 (15)	12/220 (5)	
Cystic PVL	2/23 (9)	3/23 (13)	5/46 (11)	8/212 (4)	.06
No ROP	15/23 (65)	14/22 (64)	29/45 (65)	172/182 (95)	<.001
mild ROP (grade 1/2)	7/23 (31)	8/22 (36)	15/45 (33)	9/182 (5)	
severe ROP (> grade 2)	1/23 (4)	-	1/45 (2)	-	
No dexamethasone postnat.	8/23 (35)	10/22 (45)	18/45 (40)	201/219 (92)	<.001
one course dexameth.	11/23 (48)	11/22 (50)	22/45 (49)	16/219 (7)	
two courses dexameth.	4/23 (17)	1/22 (5)	5/45 (11)	2/219 (1)	
Oxygen for 28 d	12/23 (52)	18/23 (78)	30/46 (65)	36/214 (17)	<.001
BPD (Oxygen at 36 wk)	8/23 (35)	15/23 (65)	23/46 (50)	26/216 (12)	<.001

\* % of liveborn ; † p-value GA < 27 wks versus 27 to 32 wks. RDS indicates respiratory distress syndrome; PDA, patent ductus arteriosus.

### Neurologic outcome at 2 years

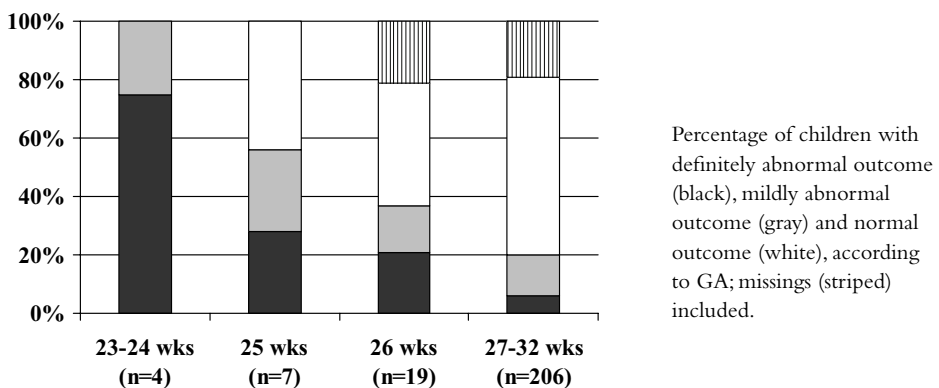
At 2 years, 23 of the 30 survivors (87%) with GA <27 weeks were examined according to Hempel; 1 child was examined by another pediatrician and considered normal, 2 children were considered completely normal according to another pediatrician at the age of 18 months corrected age and they were not followed any further because they were doing so well. The results of these 26 children are shown in Figure 1.

Infants with a GA <27 weeks were more often classified as DA than infants

**Table 3.** Condition at discharge according to GA

	23 – 25 wks N (%)	26 wks N (%)	27 – 32 wks N (%)	p-value
Condition abnormal:	10/11 (91)	11/18 (61)	67/218 (31)	<.001
- neurologic disorder	4/11 (36)	2/18 (11)	17/217 (8)	.007
- respiratory disorder	9/11 (82)	7/18 (39)	23/217 (11)	<.001
- feeding problems	6/11 (55)	4/18 (22)	13/217 (6)	<.001
- ROP (any grade)	5/11 (46)	3/17 (18)	4/205 (2)	<.001
Home monitor	6/11 (55)	4/19 (21)	10/217 (5)	<.001
Supplemental O <sub>2</sub>	4/11 (36)	3/19 (16)	3/218 (1)	<.001
Still admitted at term	7/11 (64)	4/18 (22)	39/213 (18)	.003

born between 27–32 weeks GA (35% compared with 9%;  $p < .001$ ); in the older group, 73% had a normal neurologic examination compared with 42% in the youngest group. Because of small numbers, infants with a normal outcome were compared with infants with a MA or DA outcome. In the infants born <27 weeks none of the antenatal or neonatal factors was associated with an abnormal neurologic outcome, neither was gender, GA or SES. Still hospitalized at term was associated with an abnormal neurologic outcome: OR 20, 95% CI: 2.0–203.3;  $p = .004$  (from the 11 infants still admitted, 10 had an abnormal neurologic out-

**Figure 1.** Neurologic outcome at 2 years corrected age

come compared with 5 infants of the 14 discharged infants). After correction for GA this difference remained significant: OR 17 (95% CI: 1.5 – 194.4;  $p = .02$ ). With respect to the use of postnatal steroids, 67% (6 of 9) of the infants who were not treated with postnatal steroids were classified as normal, compared with 25% (4 of 16) of the infants who did receive postnatal steroids (OR 6.0, 95% CI: 1.0 – 35.9;  $p = .05$ ). After correction for GA the OR was 4.8, after correction for just BPD the OR remained 6.0. After correction for GA and BPD the OR was 4.1 (95% CI: 0.5 – 33.4;  $p = .2$ ), so there was some confounding by GA but there still remains an association between the postnatal use of dexamethasone and abnormal outcome. A normal condition at discharge from the hospital was associated with a normal neurologic examination at 2 years (OR 11.7, 95% CI: 1.1 – 122.4;  $p = .03$ ): 5 of 6 infants who were normal at discharge had a normal neurologic examination at 2 years, compared with 6 of 20 infants who were not normal at discharge. Especially infants with pulmonary problems at discharge were more frequently neurologically abnormal: 12 infants were abnormal of the 16 infants with lung problems compared with 3 of 10 infants who had no lung problems at discharge (OR 7.0, 95% CI: 1.2 – 40.8;  $p = .03$ ). No association existed between feeding difficulties or neurologic problems at discharge and abnormal outcome at 2 years.

Although 27% of the infants born between 23 and 25 weeks GA had a normal neurologic examination at 2 years, compared with 53% of the infants born at 26 weeks GA, this difference did not reach significance ( $p = .4$ ).

### **Bayley-scales at 2 years**

The developmental psychologist tested two-third of the survivors born <27 weeks: in 21 children a MDI was measured, in 22 children a PDI. Children were lost because of different reasons: in 1 case removal to another country, 1 child was blind, 1 was in the hospital for a long time for pulmonary problems, 2 were seen by another pediatrician, 1 couple of parents did not want any contact with the hospital anymore and 2 children were tested by the Stutsman Intelligence Test instead of the BSID I. The lost group did not differ from the tested group in GA, gender, neonatal morbidity or SES.

In the immature group (<27 weeks) more (mild) mental delay occurred compared with the older premature infants (27 to 32 weeks;  $p = .048$ ); psychomotor delay occurred also more frequently (45% compared with 30%) but this difference did not reach significance (Fig 2). No association was found between any

of the perinatal factors (SES, RDS, hypotension, patent ductus arteriosus, NEC, PVL, IVH etc, as summarized in Table 2) and the developmental delay.

### **Behavior at 2 years**

Parents of 23 children (23 of 30 = 77%) returned the Child Behavior Checklist: 20 children (87%) had normal behavior and 3 children (13%) abnormal (clinical) behavior (2 born at 25 weeks, 1 born at 26 weeks). These percentages did not differ from the infants born between 27 and 32 weeks GA. Two of these 3 children with abnormal behavior had a complete normal neurologic examination and normal Bayley-scores, 1 child was classified as MA according to Hempel and the Bayley-scores.

### **Combining neurologic development, MDI and PDI at 2 years in a total outcome score**

Twenty-six of the 30 survivors were neurologically examined. Of the 4 children without a neurologic examination, in 2 cases an intelligence test according to Stutsman was done: one child had a normal IQ, the other a mildly abnormal IQ. For the total-score (neurologic, psychomotor and mental development) these 2 children were included. So finally the loss in the immature group was 2 of 30 (7%) for this total outcome score.

Thirty-six percent (10 of 28) of the assessed survivors born <27 weeks had a DA outcome compared with 16% (26 of 167) of the assessed survivors born between 27 and 32 weeks GA (OR 3.0, 95% CI: 1.3 – 7.3;  $p = .02$ ). Infants born at 23 to 25 weeks were classified as DA in 55% (6 of 11), infants born at 26 weeks GA in 21% (4 of 17); this difference did not reach significance.

When we add behavior to this total outcome-score, 46% (13 of 28) of the assessed survivors born <27 weeks had a DA outcome (compared with 21% of the infants born between 27 and 32 weeks,  $p < .001$ ).

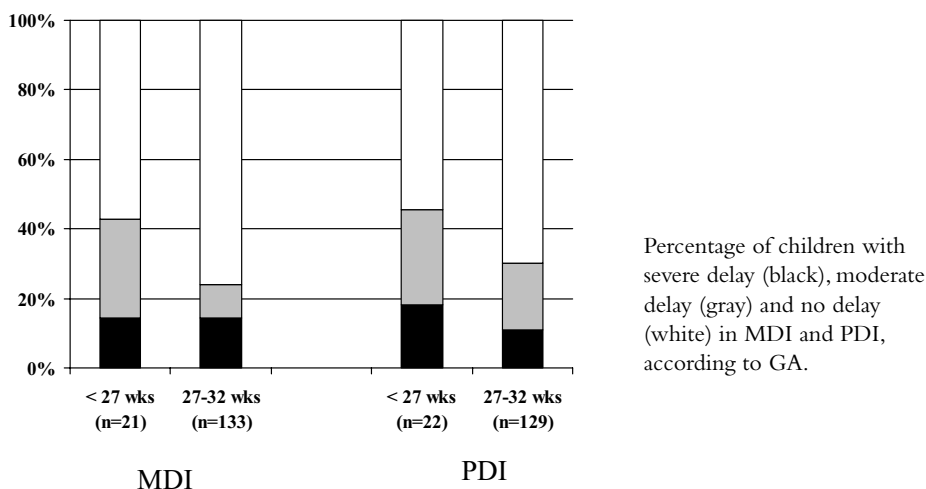
One of the infants born <27 weeks was blind, and 2 infants were deaf at the age of 2 years (all 3 neurologically abnormal).

Neurologic examination as well as both the Bayley tests and the Child Behavior Checklist, were available from 21 of the 30 survivors born <27 weeks gestation; of these 21 children only 3 had a normal outcome at all tests (2 born at 25 weeks, 1 born at 26 weeks).

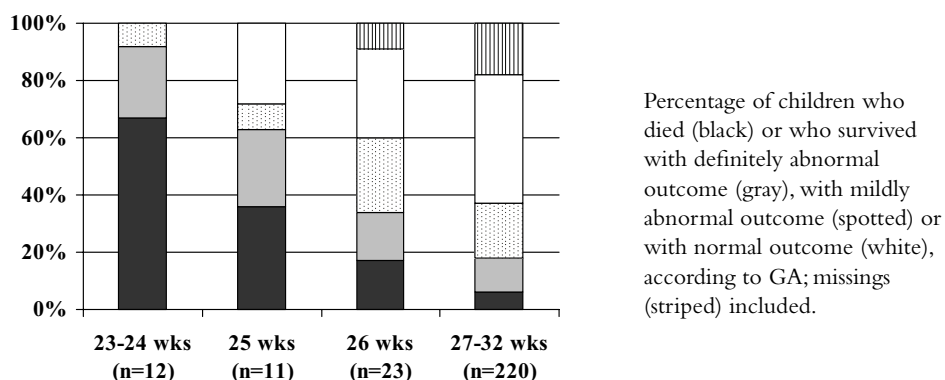
**Adverse outcome**

Overall, adverse outcome (defined as dead or at least 1 conclusion DA in neurologic, mental or psychomotor development) was 57% in infants born <27 weeks gestation compared with 18% in infants born between 27 and 32 weeks. Adverse outcome in infants born at 23 to 24, 25, and 26 weeks gestation was, respectively, 92%, 64%, and 35% (Fig 3).

**Figure 2.** MDI and PDI of infants < 27 wks GA and of infants 27 – 32 weeks GA at two years corrected age



**Figure 3.** Adverse outcome at two years corrected age



## Discussion

### Mortality

Reports about an increase in survival come from all over the world (United States, Canada, Australia and Japan), but, as already noticed by Hack and Fanaroff<sup>24</sup>, there are very few reports from Europe: only a few from the United Kingdom (12–14), Sweden<sup>11</sup> and Finland.<sup>25</sup> It is difficult to compare survival rates in different studies because of several reasons: some groups present survival rates according to GA, but most of them to birth weight which is not always a reliable marker for maturation. Furthermore, the definition of survival often differs: some report survival from the resuscitation room, some from the NICU or in-hospital period and some report about the survival at 1 year.

In the health regions in the Netherlands in which this study was performed, treatment was started at 24<sup>+0</sup> weeks. In-hospital survival in infants with a GA of 24 weeks was 40%, at the age of two years survival was 30% which is comparable with studies from the United Kingdom<sup>12, 13, 26</sup>, Sweden<sup>11</sup> and Canada.<sup>27,28</sup> Most studies from the United States found higher survival rates: survival at discharge and in the first year 48–62%.<sup>6-8, 24, 26</sup> Survival in the infants born at 25 weeks GA was 64% in our study, comparable to various results from Sweden<sup>11</sup> and Canada<sup>27,28</sup>; somewhat higher than in the United Kingdom<sup>12-14,29</sup> but lower than in the United States.<sup>3,7,8,24,26,30-32</sup> Survival in infants of 26 weeks GA was 83%, rather high compared with literature.<sup>8,13,28,31,32</sup> Jacobs *et al.*<sup>33</sup> found exactly the same mortality-rate (35%) as we did in infants born between 23–26 weeks, born between 1990–1994. Because mortality was higher in the group infants transported postnatally compared with infants born in a center with a NICU (77% vs. 18%, independent of GA), we expect that mortality would be lower when all infants would have been born in a neonatal center. It is also concerning that mortality was higher in infants born after pregnancy induction, irrespective of multiple pregnancy.

### Neonatal morbidity

With respect to literature, we found a comparable incidence of grade III / IV IVH (18%) and cystic PVL (11%) in infants <27 weeks GA. Gibson<sup>34</sup> reported incidences of 25–32% for the combination of serious IVH and PVL; Hack and Fanaroff<sup>24</sup> in a recent review found a range of 10–83% for infants born at 23 to 24 weeks GA and of 10–22% for infants born at 25 weeks GA for severe cranial

ultrasound-abnormalities. The incidence of NEC (15%) was comparable with literature, the incidence of severe retinopathy of prematurity (2%) somewhat lower. Gibson<sup>34</sup> reports that the need of oxygen at the age of 28 days is almost universal, like in this study (97%). We found a rather high percentage of infants with BPD (50%) compared with for example Kilpatrick (15%)<sup>7</sup>, but Hack and Fanaroff<sup>24</sup> report a wide range in BPD: 57-70%, 23-89% and 16-71% for infants born at respectively, 23, 24, and 25 weeks of gestation. The reason could be a difference in oxygen saturation monitoring practices with varying criteria for the administration and weaning of oxygen.<sup>24</sup>

### **Outcome at 2 years**

Perhaps even more important than survival itself is intact survival. Hack and Fanaroff<sup>24</sup> report that there is a wide variety in outcome among survivors of extremely premature infants: they found severe disabilities in 30%, 17-45% and 12-35% for infants of 23, 24, and 25 weeks of GA, respectively. There are many explanations for these wide ranges but the most important ones are differences in definition of disabilities and handicaps and in the length of follow-up. For example, Holtrop<sup>35</sup> found a good short-term outcome in 90% of the survivors of 23-25 weeks GA, this just being defined as the absence of PVL or IVH, while Piecuch<sup>36</sup> demonstrated that in extremely premature infants PVL and IVH do not account for all of the neurologic abnormalities. However, in our study an IVH grade III or IV or cystic PVL were not associated with abnormal neurologic outcome at the age of two years, maybe because of small numbers. In general, Cooke<sup>29</sup> found in a 10-year cohort of premature infants with a GA <26 weeks 74% free of serious handicaps; Tin<sup>14</sup> also reported 75% of the survivors with a GA <26 weeks free from a severe disability. In our study 55% of the survivors born <26 weeks had a normal or MA outcome at the age of 2 years.

At 2 years, the percentage of children with a completely normal neurologic examination remained about the same as at term age (48% at term – data not shown – and 42% at 2 years), but the percentage of children with a MA examination decreased (from 33% to 19%) at the cost of an increase in the number of children with a DA neurologic examination (16% to 39%). We know that a lot of problems concerning speech and language development, concentration, and behavior appear later and are not noticed yet at the age of 2 years.<sup>37</sup> It is alarming that 36% (10/28) of the assessed survivors born <27 weeks gestation had a DA total outcome score at this age; 46% (13/28) when behavior was added to this score.



### Starting active treatment

Worldwide, people do not agree about the limit of viability: Kramer<sup>8</sup> from the USA suggests an active approach from 24 completed weeks, Kilpatrick<sup>7</sup> advises not to resuscitate infants born at 23 and 24 weeks GA (only if the parents insist) and to resuscitate infants from 25 weeks GA only when birth weight is >600 gram; Sanders (USA)<sup>38</sup> and Battin (Canada)<sup>2</sup> agree that 22 weeks is not acceptable, 23 to 24 weeks a sort of limit with high morbidity and they suggest starting at 25 weeks. Piecuch<sup>36</sup> remarks that in infants born at 24 and 25 weeks the high rate of cognitive problems is concerning. Recently, Wood<sup>39</sup> from the EPICure Study Group showed that severe disability is common among children born <26 weeks GA (half of the infants had any disability; 23% a severe disability) and remains a major challenge in this group of infants. The question remains if one should start to resuscitate these infants when there is 25, 50 or 75% chance on intact survival? There will always be differences in opinion on what is ethical. Maybe one can start resuscitation (at 24 or 25 weeks) but after having started one should not be negative towards withdrawal of treatment in cases of very poor prognosis. However, not starting treatment always seems easier than withdrawing treatment.<sup>40</sup> Recently Lorenz *et al.*<sup>41</sup> reported about the differences in management strategies for extreme prematurity in the United States and some countries in Europe like the Netherlands. They explain that in the United States (offering intensive care to all infants), there will be more survivors at the cost of a higher percentage of disabling cerebral palsy, while in the Netherlands (more selective treatment) some infants will die who might have survived without disability. This is a moral dilemma without a definitive answer, depending on the personal view of parents and doctors.

It would be helpful if there were some risk factors associated with adverse outcome. In this study, the postnatal use of dexamethasone and still being admitted at term seem to be associated with an abnormal neurologic outcome. Both factors could be taken into consideration in the communication with the parents. An explanation for the lack of association between other perinatal factors and outcome could be the small numbers in this study.

The set up of our study was prospective and regional. Not only a standardized neurologic examination was performed, but also mental and psychomotor development and behavior were assessed. In the Netherlands, the GA is in general precisely known in pregnant women, so this makes it possible to associate outcome with gestational age instead of birth weight. The endpoint was the corrected

age of 2 years, which is not so frequently described in a cohort infants born in the 1990s. The flaws of this study are the small numbers and the rather high loss (about 30%) in the BSID, but the parameters of the lost group and the assessed group did not differ and the conclusions point in the same direction as found in literature: higher mortality and morbidity with decreasing GA. We also found higher mortality in extremely premature infants born after pregnancy induction ( $p = .04$ ) and when transported extra-uterinely ( $p < .001$ ); the association between abnormal neurologic outcome and the postnatal use of dexamethasone is compatible with literature. The high percentage (74%) of adverse outcome in infants born <26 weeks' gestation is reason for concern and needs to be kept in mind when counseling the parents. The even higher percentage of adverse outcome in infants < 25 weeks (92%) suggests that one should carefully weigh whether or not to aggressively resuscitate and treat these extremely premature infants.

## Acknowledgements

The authors like to thank Carmen IJE van Vianen, former nurse at the high-risk follow-up clinic, for her participation in this project and J Feenstra, developmental psychologist for the Bayley-assessments. They also would like to thank Frans J Walther, MD, PhD, and head of the neonatal center of the LUMC, for his criticism on earlier versions of the manuscript.

Other participants of the LFUPP include the pediatric staff of 't Lange Land Hospital Zoetermeer (Irene Hofmeier; Harriet CJ Roggeveen), Rijnland Hospital Leiderdorp (Nel EC Mourad-Baars), Diaconessen Hospital Leiden (Adele C Engelberts), Reinier de Graaf Hospital Delft (Piet JC van der Straaten) and Antoniushove Hospital Leidschendam (Theo A Nijenhuis), the Netherlands.

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