A Regional Follow-Up Study at Two Years of Age in Extremely Preterm and Very Preterm Infants

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The Leiden Follow-Up Project on Prematurity 1996-1997

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Aan mijn ouders

Voor Hans, Kyma en Floris

Contents

CHAPTER 1

General introduction

After an increase in the total number of live born infants from 181,294 infants born in 1980 to 202,603 infants in 2001, the total number of live born infants in the Netherlands is decreasing again to 187,910 infants in 2005 (www.CBS.nl). From all registered infants in 2003, 7.9% were born preterm (20 – 37 weeks) and 1.6% very preterm (20 – 32 weeks).[1] So every year, about 3000 very preterm infants are admitted to a Neonatal Intensive Care Unit, unless they are non-viable in case of extremely low gestational age.

New interventions in relation to survival and outcome

During the last decades the survival of very preterm infants has improved due to the introduction of antenatal steroids, the use of surfactant replacement therapy and postnatal steroids. New ventilation strategies (like High Frequency Oscillation Ventilation [HFOV]) did possibly also contribute to the improved survival of these infants. Everybody hoped that these new drugs and techniques would decrease the number of infants with bronchopulmonary dysplasia (BPD) and intracerebral abnormalities, which are the major morbidities of these infants responsible for later developmental problems.

Surfactant therapy did increase the likelihood of survival, even in infants between 23 and 26 weeks: survival increased from 56% in untreated infants to 75% in treated infants.[2] Vohr *et al.*[3] studied the neurodevelopmental outcome of ELBW-infants from 1993 and 1998 and found that administration of antenatal steroids was the only intervention associated with improved neurodevelopmental outcome at 18-22 months corrected age. HFOV was in their study associated with a lower Mental Developmental Index (MDI) on the Bayley Scales of Infant Development. Marlow *et al.* however found no difference in outcome at the corrected age of 2 years in extremely preterm infants who received HFOV compared to conventional ventilation.[4] In the late 1990s the first publications about the adverse effect of postnatal corticosteroids (especially dexamethasone) on neurodevelopmental outcome were reported by Yeh[5], O'Shea[6] and Shinwell.[7] In the study of Vohr *et al.*, postnatal steroids were associated with a higher incidence of cerebral palsy (CP), a lower Mental Developmental Index (MDI) and a lower Psychomotor Developmental Index (PDI).

Increased survival, but what about long term outcome in the post-surfactant area?

This higher survival rate has led to an increased interest in the long-term neurodevelopmental outcome of the preterm infants. Some studies described an increase in percentage of severe disabilities[8] while others found a similar handicap rate.[9-13] An increase in CP among very preterm infants was found by Vincer *et al.*[14] and de Kleine *et al.*[15] Vohr *et al.*, on behalf of the NIHCD Neonatal Research Network[3] showed that from 1993 till 1998 neurodevelopmental outcome of extremely low birth weight (ELBW)-infants was stable in case of CP (18-20% in infants 22-26 weeks, 11-12% in infants born between 27-32 weeks GA) and hearing disorders (2-3%). Outcome improved for blindness (from 6.5% in 1993 to 2.6% in 1998 in infants 22-26 weeks GA, from 3.5% in 1993 to 1.2% in 1998 in infants 27-32 weeks GA). Outcome also improved for Bayley Scales of Infant Development (BSID)-scores: at 18-22 months' corrected age the percentage of infants with a MDI < 70 decreased from 41.8% in 1993 to 37.2% in 1998 in infants 22-26 weeks GA, and from 29.9% in 1993 to 22.8% in 1998 in infants 27-32 weeks GA. Furthermore 31.6% of the infants with GA 22-26 weeks had a PDI < 70 in 1993 compared to 26% in 1998 and numbers for the infants with GA 27-32 weeks were 23.4% in 1993 and 16.9% in 1998 (all changes reached statistical significance). According to Cooke *et al.*[16] the percentage of infants with major neurological disabilities has declined; Foulder-Hughes and Cooke[17] mentioned that above all minor motor disabilities persist in survivors of preterm birth, despite improvements in care and that these disabilities were not confined to the smallest or most preterm infants.

Outcome studies are increasingly restricted to the extremely preterm infants with GA < 28 weeks (or < 26 weeks) or to the extremely low birth weight infants (ELBW) with birth weight < 1000 grams[18], probably because these infants did not survive in the past and there has been a growing interest in the outcome of these extremely preterm infants. Only a few studies have focussed on neurodevelopmental outcome of low risk preterm infants (GA > 28 weeks and birth weight > 1000 or 1500 grams). Pasman *et al.*[19] showed in a prospective study of 44 low risk preterm infants (i.e. infants with a neonatal risk score indicating a favourable outcome, GA 25–34 weeks) that an unfavourable neurodevelopmental outcome of low risk preterm infants is due to moderate to severe impairment in a few low risk infants, rather than slight impairment in

the majority. Pietz *et al.*[18] studied 70 low risk preterm (i.e. infants born between 28-37 weeks GA, birth weight between 1000-2500 grams and without severe intraventricular haemorrhage, sepsis or prolonged ventilation) and compared them with a matched control group born at term. They found a normal Mean Griffiths Developmental Quotient (102 ± 8) at 20 months in the preterm group. At 7 years of age, reduced mean test results in the range of -0.5 SDS were observed for language and visual-motor abilities in the preterm group. The frequency of children with suboptimal growth at the age of 7 years was increased in the preterm infants (14% < P3). In general, growth lags behind in preterm and very low birth weight infants although different percentages of catch-up growth have been described.[20-24]

Leiden Follow-Up Project on Prematurity (LFUPP)

The Leiden Follow-Up Project on Prematurity (LFUPP), a regionally defined, prospective study, included all live born infants with a gestational age less than 32 weeks, born 1996/1997 in three health regions: Leiden, The Hague and Delft. The purpose of the study was to assess mortality and neonatal morbidity of the very preterm infants and especially of the extremely preterm infants (GA below 27 weeks). We were curious to know if new interventions like antenatal steroids and surfactant replacement therapy had resulted in a higher survival rate and moreover in a higher handicap- and disability-free survival. In the nineteen nineties the Neonatal Intensive Care Unit (NICU) of the Leiden University Medical Center (LUMC) initiated active treatment in infants with a GA of 24 weeks and onwards; most other NICUs in the Netherlands generally started active resuscitation from 25 or 26 weeks GA. To evaluate this limit of viability of 24 weeks, we studied the outcome of the extremely preterm infants (< 27 weeks GA) and compared it with preterm infants born between 27–32 weeks GA and with data from literature.

Antenatal and perinatal data were collected including diseases of the mother, socio-economic status, diseases and medication like antenatal steroids during pregnancy, gestational age, birth weight, Apgar score and data about perinatal morbidity and medication. Severity of respiratory distress syndrome (RDS), incidence of patent ductus arteriosus (PDA), use of surfactant and the number of

days on the ventilator were registered. Bronchopulmonary dysplasia (BPD) was defined as need of oxygen at 36 weeks postmenstrual age (PMA), but need of oxygen at 28 days was also noted. Dexamethasone was given in 1996/1997 in an initial dose of 0.5 mg/kg/day, tapered over 42 days to 0.1 mg/kg/day. Some infants who remained ventilator-dependent received a non-standardised second course of dexamethasone. Ultrasound abnormalities like intraventricular haemorrhage (IVH) and periventricular leucomalacia (PVL) were noted. An ophthalmologist assessed the infants at several times for retinopathy of prematurity (ROP). The condition at discharge from the hospital was considered to be normal when there was no neurological 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.

At term age and at the corrected age of 1 and 2 years paediatricians experienced in neurodevelopmental examination assessed the infants. A complete physical examination was performed and data about length, weight and head circumference were collected. Length was measured in supine position with straight back and knee on a standardised infantometer. Infants were weighed undressed on a calibrated infant balance scale. Head circumference was measured with a standard measuring non-stretch tape taking the largest measurement across the occipito-frontal line. At term age the infants were neurologically examined according to Prechtl[25]: infants were classified as definitely abnormal (DA), which meant the presence of a full-blown neurological syndrome like asymmetry, general hyper/hypotonia, hyper/hypokinesia or hyperirritability/apathy; mildly abnormal (MA) when only part of such a syndrome was present; or normal (N). At one year of age infants were assessed according to Touwen[26] and Hadders-Algra[27] and classified as DA in case of a cerebral palsy; as having a minor neurological dysfunction (MND I in case of an abnormality in one of the four neurodevelopmental clusters (tone/reflexes, gross motor function, fine motor function or cranial nerve function, MND II in case of at least two of these clusters); or normal (N). At 2 years a neurological examination according to Hempel[28] was performed, focused on major as well as minor neurological dysfunctions. The children were considered DA in case of definite neurological dysfunction; MA in the presence of mild deviations in muscle tone regulation, reflexes, fine or gross motor performance; or normal (N). Furthermore, at the corrected ages of 18 and 24 months a Mental Developmental Index (MDI) and

a Psychomotor Developmental Index (PDI) according to the Bayley Scales of Infant Development I[29;30] were determined. 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) ≥ 84 (≥ -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). At two years of age behaviour was assessed using Achenbach's Child Behavior Checklist for 2-3 year old children, completed by the parents. According to this list, behaviour could be assessed by using a total problem score: a score above the 90th percentile was defined as clinically abnormal; a score between the 85th and 90th percentile as borderline clinical; below the 85th percentile as normal.[31-33]

Another purpose of the study was to compare mortality and perinatal morbidity of very preterm infants born in the nineteen nineties (LFUPP) with results from the Project on Preterm and Small for gestational age infants (POPS), a cohort from the nineteen eighties. In the POPS, all live born infants born in 1983 with a gestational age < 32 weeks and/or a birth weight <1500 grams were included. The total cohort existed of 1338 infants; in-hospital mortality was 25.4%. Gestational age was a better predictor of neonatal mortality than birth weight.[34] In-hospital mortality in infants < 27 weeks of gestation was 76%; total handicap rate in the surviving children at two years of age was 21% (9% major handicap, defined as presence of retardation (DQ < 80) and/or at least one of the following: a severe neurological disorder, sever visual or hearing defects or serious psychosocial problems). In contrast to mortality, handicap was apparently unrelated to gestational age or birth weight.[35;36] Compared with the handicap rate of the same cohort at 2 years of age, a more favourable outcome at 5 years was seen in 10% and a less favourable outcome in 7% of the children.[37]
Children from this cohort are assessed at later ages; the 19-year follow-up program is still ongoing and incorporated in a large collaborative study in the Netherlands. Various investigators are looking at the long-term effect of prematurity and being small for gestational age on various medical, psychological and social parameters.[38;39]

Outline of the thesis

This thesis describes the results of the Leiden Follow-Up Project on Prematurity. The first part of the thesis is focussed on extremely preterm infants (gestational age < 27 weeks), the second part on very preterm infants (gestational age < 32 weeks).

In **chapter 2** the mortality and neurological, mental and psychomotor development at 2 years of age of the infants born with a gestational age below 27 weeks are analysed and compared with the results of the infants born with a gestational age between 27 – 32 weeks. Ethical considerations about maintaining these extremely preterm infants are described in **chapter 3**, where an overview is presented of the results and opinions of the limits of viability in most European countries along with some examples from the United States of America and Australia.

In **chapter 4** growth of the preterm born infants until the corrected age of 2 years is presented: length, weight, weight for length and head circumference measurements were expressed as standard deviation scores (SDS) compared to Dutch references. The association between perinatal risk factors (especially dexamethasone) and growth was also analysed. **Chapter 5** was designed to study the effect on later growth and development of intra-uterine growth restriction in comparison to extra-uterine growth restriction in preterm infants. Preterm growth restraint, which means extra-uterine growth restriction, was defined as length or weight at term age < -1.3 SD.

Chapter 6 describes major risk factors in preterm infants for neurological morbidity at term age, especially hypotension, next to bronchopulmonary dysplasia and cystic periventricular leucomalacia. Because bronchopulmonary dysplasia is an important complication of prematurity despite new interventions, the aim of **chapter 7** was to analyse the respiratory and neurodevelopmental outcome at 2 years of age, in children born with bronchopulmonary dysplasia (BPD). BPD was defined as need of supplemental oxygen at 36 weeks post menstrual age. In **chapter 8** the developmental outcomes of the study group (according to the BSID I) at 18 and 24 months corrected age are presented. Both Mental and Psychomotor Developmental Indices of the children were assessed. Risk factors for delayed development at 18 or 24 months were also determined. The aim of **chapter 9** was to compare the results of two cohorts of very preterm infants born in the Netherlands: the POPS-infants, born in 1983

and the LFUPP-infants, born in 1996-1997. For this purpose, only infants from the POPS-cohort with a gestational age < 32 weeks and from the same health regions (selection by postal code) as the infants from the LFUPP-cohort were included in the analyses.

In **chapter 10** the main findings of the thesis are discussed, together with some perspectives in relation to ongoing changes in neonatology. A summary is presented in **chapter 11** (in Dutch in **chapter 12**).

References

1. Stichting Perinatale Registratie Nederland. Perinatale Zorg in Nederland 2003. 2006. Bilthoven.
2. Hoekstra RE, Ferrara TB, Payne NR. Effects of surfactant therapy on outcome of extremely premature infants. Eur.J.Pediatr. 1994;153:S12-S16.
3. Vohr BR, Wright LL, Poole WK, McDonald SA, for the NICHD Neonatal Research Network Follow-up Study. Neurodevelopmental Outcomes of Extremely Low Birth Weight Infants <32 Weeks' Gestation Between 1993 and 1998. Pediatrics 2005;116:635-43.
4. Marlow N, Greenough A, Peacock JL, Marston L, Limb ES, Johnson AH et al. Randomised trial of high frequency oscillatory ventilation or conventional ventilation in babies of gestational age 28 weeks or less: respiratory and neurological outcomes at 2 years. Arch.Dis.Child.Fetal Neonatal Ed. 2006;91:F320-F326.
5. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC *et al*. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics 1998;101:E7.
6. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG. Randomized Placebo-controlled Trial of a 42-Day Tapering Course of Dexamethasone to Reduce the Duration of Ventilator Dependency in Very Low Birth Weight Infants: Outcome of Study Participants at 1-Year Adjusted Age. Pediatrics 1999;104:15-21.
7. Shinwell ES, Karplus M, Reich D, Weintraub Z, Blazer S, Bader D *et al*. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. Arch.Dis.Child Fetal Neonatal Ed 2000;83:F177-F181.
8. Emsley HCA, Wardle SP, Sims DG, Chiswick ML, D'Souza SW. Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants, 1990-4 compared with 1984-9. Arch Dis Child Fetal & Neonatal Ed 1998;78:F99-F104.
9. Battin M, Ling EW, Whitfield MF, Mackinnon M, Effer SB. Has the outcome for extremely low gestational age (ELGA) infants improved following recent advances in neonatal intensive care? Am.J.Perinatol. 1998;15:469-77.
10. Ferrara TB, Hoekstra RE, Couser RJ, Gaziano EP, Calvin SE, Payne NR *et al*. Survival and follow-up of infants born at 23 to 26 weeks of gestational age: effects of surfactant therapy. J.Pediatr. 1994;124:119-24.
11. Hack M, Friedman H, Fanaroff AA. Outcomes of extremely low birth weight infants. Pediatrics 1996;98:931-7.
12. Johnson S, Marlow N. Developmental screen or developmental testing? Early Hum.Dev. 2006;82:173-83.

13. La Pine TR, Jackson JC, Bennett FC. Outcome of infants weighing less than 800 grams at birth: 15 years' experience. Pediatrics 1995;96:479-83.
14. Vincer MJ, Allen AC, Joseph KS, Stinson DA, Scott H, Wood E. Increasing prevalence of cerebral palsy among very preterm infants: a population-based study. Pediatrics 2006;118:e1621-e1626.
15. De Kleine MJ, den Ouden AL, Kollee LA, van Baar A, Nijhuis-Van Der Sanden MW, Ilsen A *et al.* Outcome of perinatal care for very preterm infants at 5 years of age: a comparison between 1983 and 1993. Paediatr.Perinat.Epidemiol. 2007;21:26-33.
16. Cooke RWI. Trends in incidence of cranial ultrasound lesions and cerebral palsy in very low birthweight infants 1982-93. Arch.Dis.Child.Fetal Neonatal Ed. 1999;80:F115-F117.
17. Foulder-Hughes LA, Cooke RWI. Motor, cognitive, and behavioural disorders in children born very preterm. Dev.Med.Child Neurol. 2003;45:97-103.
18. Pietz J, Peter J, Graf R, Rauterberg-Ruland I, Rupp A, Sontheimer D *et al.* Physical growth and neurodevelopmental outcome of nonhandicapped low-risk children born preterm. Early Human Development 2004;79:131-43.
19. Pasman JW, Rotteveel JJ, Maassen B. Neurodevelopmental profile in low-risk preterm infants at 5 years of age. Eur J Paediatr Neurol 1998;2:7-17.
20. Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. J.Pediatr. 2003;142:463-8.
21. Casey PH, Kraemer HC, Bernbaum J, Yogman MW, Sells JC. Growth status and growth rates of a varied sample of low birth weight, preterm infants: a longitudinal cohort from birth to three years of age. J.Pediatr. 1991;119:599-605.
22. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics 2006;118:1078-86.
23. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? Semin. Perinatol. 2003;27:302-10.
24. Ford GW, Doyle LW, Davis NM, Callanan C. Very low birth weight and growth into adolescence. Arch.Pediatr.Adolesc.Med. 2000;154:778-84.
25. Prechtl HF. The neurological examination of the fullterm newborn infant. Clin Dev Med 63. London, Heinemann. 1977.
26. Touwen BCL. Neurological development in infancy. London: Heinemann, 1976.
27. Hadders-Algra M. The clumsy child, at the border of cerebral palsy? In Velickovic Perat M, Perat M, eds. Cerebral palsy, Amsterdam: Elsevier Science, 2001.
28. Hempel MS. The neurological examination technique for toddler-age. Thesis. University of Groningen. 1993.
29. Bayley N. Bayley Scales of Infant Development. New York: Psychological Corporation, 1969.
30. Meulen van der SF, Smrkovsky M. Bayley ontwikkelingsschalen handleiding. Lisse: Swets & Zetlinger BV, 1983.
31. Achenbach TM. Manual for the Child Behavior Checklist/2-3 and 1992 profile. Burlington, Univerity of Vermont, department of psychiatry. 1992.
32. Achenbach TM, Edelbrock C, Howell CT. Empirically based assessment of the behavioral/emotional problems of 2- and 3- year-old children. J.Abnorm.Child Psychol. 1987;15:629-50.
33. Stoelhorst GMSJ, Martens SE, Rijken M, Zwieten PHT, Zwinderman AH, Wit JM *et al.* Behaviour at 2 years of age in very preterm infants (gestational age >32 weeks). Acta Paediatr. 2003;92:595-601.
34. Verloove-Vanhorick SP, Verwey RA, Brand R, Bennebroek Gravenhorst J, Keirse MJNC, Ruys JH. Neonatal mortality risk in relation to gestational age and birthweight: Results of a

National Survey of Preterm and Very-low-birthweight Infants in the Netherlands. The Lancet 1986;327:55-7.

35. van Zeben-van der AA T, Verloove-Vanhorick SP, Brand R, Ruys J. Morbidity of Very Low Birthweight Infants at corrected age of two years in a geographically defined population: Report from Project On Preterm and Small for Gestational Age Infants in the Netherlands. The Lancet 1989;333:253-5.
36. Van Zeben-van der AA, DMCB. Outcome at two years of age in very preterm and very low birthweight infants in the Netherlands. Thesis. Leiden University. 1989.
37. Veen S, Ens-Dokkum MH, Schreuder AM, Verloove-Vanhorick SP, Brand R, Ruys JH. Impairments, disabilities, and handicaps of very preterm and very-low-birthweight infants at five years of age. The Collaborative Project on Preterm and Small for Gestational Age Infants (POPS) in The Netherlands. Lancet 1991;338:33-6.
38. Hille ETM, den Ouden AL, Stuifbergen MC, Verrips GHW, Vogels AGC, Brand R *et al*. Is attrition bias a problem in neonatal follow-up? Early Human Development 2005;81:901-8.
39. Hille E, Weisglas-Kuperus N, van Goudoever JB, Jacobusse GW, Ens-Dokkum MH, de Groot L *et al*. Functional outcomes and participation in young adulthood for very premature and very low birth weight infants: the Dutch POPS-study at 19 years of age. Pediatrics 2007;120:e587-95.

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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Pediatrics 2003; 112: 351-358

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[1] with this better survival while others have reported that the handicap-rate has remained the same.[2-5] 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[6-8]; McElrath *et al.*[9] 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.[10] In Europe (Sweden[11], United Kingdom[12-14]) 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.*[15] 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^{+0} 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^{+0} to 24^{+6} 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[16], 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).[17,18] 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) ≥ 84 (≥ -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[19,20] 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/X^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.[21] 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 Cesarian 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[22], hypotension,

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

Gestational age	**< 27 weeks N (%)**	**27 – 32 weeks N (%)**
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 ($<P_{10}$)	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, intracytoplasmatic 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)[23], 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 RDS grade I/II RDS grade III/IV	3/23 (13) 9/23 (39) 11/23 (48)	4/23 (17) 7/23 (30) 12/23 (53)	7/46 (15) 16/46 (35) 23/46 (50)	98/215 (46) 60/215 (28) 57/215 (26)	<.001
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 IVH Grade I / II IVH Grade III / IV	13/23 (57) 6/23 (26) 4/23 (17)	14/23 (61) 6/23 (26) 3/23 (13)	27/46 (59) 12/46 (26) 7/46 (15)	171/220 (78) 37/220 (17) 12/220 (5)	.007
Cystic PVL	2/23 (9)	3/23 (13)	5/46 (11)	8/212 (4)	.06
No ROP mild ROP (grade 1/2) severe ROP (> grade 2)	15/23 (65) 7/23 (31) 1/23 (4)	14/22 (64) 8/22 (36) -	29/45 (65) 15/45 (33) 1/45 (2)	172/182 (95) 9/182 (5) -	<.001
No dexamethasone postnat. one course dexameth. two courses dexameth.	8/23 (35) 11/23 (48) 4/23 (17)	10/22 (45) 11/22 (50) 1/22 (5)	18/45 (40) 22/45 (49) 5/45 (11)	201/219 (92) 16/219 (7) 2/219 (1)	<.001
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.

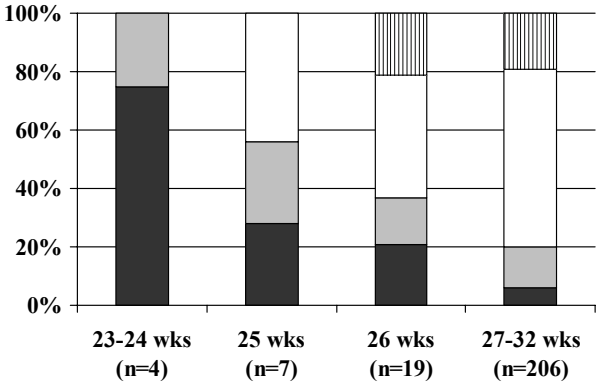
Infants with a GA <27 weeks were more often classified as DA than infants

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_2	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



Percentage of children with definitely abnormal outcome (black), mildly abnormal outcome (gray) and normal outcome (white), according to GA; missings (striped) included.

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, $p < .001$).

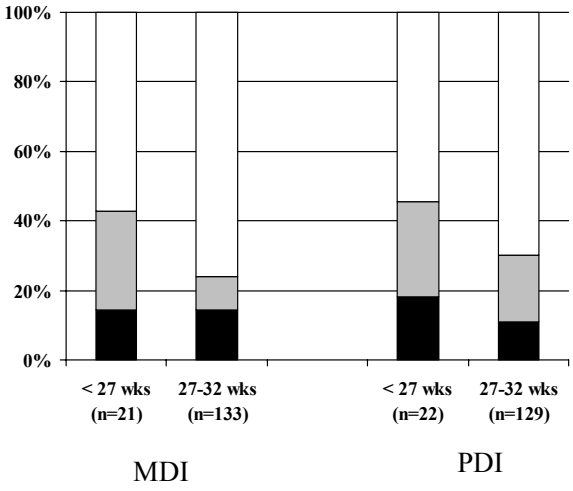
One of the infants born <27 weeks was blind, and 2 infants were deaf at the age of 2 years (all 3 neurologically abnormal).

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

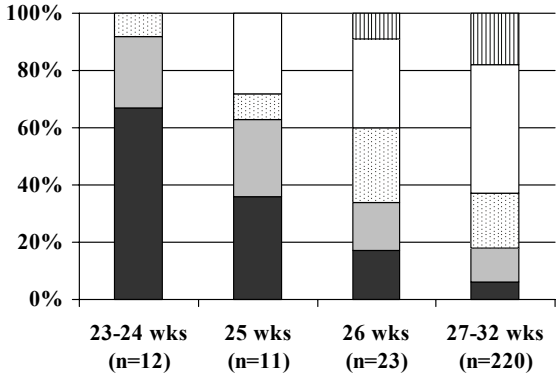
Overall, adverse outcome (defined as dead or at least 1 conclusion DA in neurologic, mental or psychomotor development) was 57% in infants born <27 weeks gestation compared with 18% in infants born between 27 and 32 weeks. Adverse outcome in infants born at 23 to 24, 25, and 26 weeks gestation was, respectively,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



Percentage of children with severe delay (black), moderate delay (gray) and no delay (white) in MDI and PDI, according to GA.

Figure 3. Adverse outcome at two years corrected age



Percentage of children who died (black) or who survived with definitely abnormal outcome (gray), with mildly abnormal outcome (spotted) or with normal outcome (white), according to GA; missings (striped) included.

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 [24], there are very few reports from Europe: only a few from the United Kingdom (12-14), Sweden[11] and Finland.[25] It is difficult to compare survival rates in different studies because of several reasons: some groups present survival rates according toGA, 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^{+0} 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[12, 13, 26], Sweden[11] and Canada.[27,28] Most studies from the United States found higher survival rates: survival at discharge and in the first year 48-62%.[6-8, 24, 26] Survival in the infants born at 25 weeks GA was 64% in our study, comparable to various results from Sweden[11] and Canada[27,28]; somewhat higher than in the United Kingdom[12-14,29] but lower than in the United States.[3,7,8,24,26,30-32] Survival in infants of 26 weeks GA was 83%, rather high compared with literature.[8,13,28,31,32] Jacobs *et al.*[33] 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[34] reported incidences of 25-32% for the combination of serious IVH and PVL; Hack and Fanaroff [24] 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[34] 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%)[7], but Hack and Fanaroff [24] 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.[24]

Outcome at 2 years

Perhaps even more important than survival itself is intact survival. Hack and Fanaroff [24] 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[35] 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[36] 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[29] found in a 10-year cohort of premature infants with a GA <26 weeks 74% free of serious handicaps; Tin[14] 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.[37] 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[8] from the USA suggests an active approach from 24 completed weeks, Kilpatrick[7] 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)[38] and Battin (Canada)[2] 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[36] remarks that in infants born at 24 and 25 weeks the high rate of cognitive problems is concerning. Recently, Wood[39] 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.[40] Recently Lorenz *et al.*[41] 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.

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References

1. Emsley HCA, Wardle SP, Sims DG, Chiswick ML, D'Souza SW. Increased survival and deteriorating developmental outcome in 23 to 25 week old gestation infants, 1990-4 compared with 1984-9. Arch Dis Child Fetal & Neonatal Ed 1998; 78:F99-F104.
2. Battin M, Ling EW, Whitfield MF, Mackinnon M, Effer SB. Has the outcome for extremely low gestational age (ELGA) infants improved following recent advances in neonatal intensive care? Am J Perinatol 1998; 15:469-77.
3. Ferrara TB, Hoekstra RE, Couser RJ, Gaziano EP, Calvin SE, Payne NR *et al.* Survival and follow-up of infants born at 23 to 26 weeks of gestational age: effects of surfactant therapy. J Pediatr 1994; 124:119-24.
4. Hack M, Friedman H, Fanaroff AA. Outcomes of extremely low birth weight infants. Pediatrics 1996; 98:931-7.
5. La Pine TR, Jackson JC, Bennett FC. Outcome of infants weighing less than 800 grams at birth: 15 years' experience. Pediatrics 1995; 96:479-83.
6. Allen MC, Donohue PK, Dusman AE. The limit of viability--neonatal outcome of infants born at 22 to 25 weeks' gestation. N Engl J Med 1993; 329:1597-601.
7. Kilpatrick SJ, Schlueter MA, Piecuch R, Leonard CH, Rogido M, Sola A. Outcome of infants born at 24-26 weeks' gestation: I. Survival and cost. Obstet Gynecol 1997; 90:803-8.
8. Kramer WB, Saade GR, Goodrum L, Montgomery L, Belfort M, Moise KJ, Jr. Neonatal outcome after active perinatal management of the very premature infant between 23 and 27 weeks' gestation. J Perinatol 1997; 17:439-43.
9. McElrath TF, Robinson JN, Ecker JL, Ringer SA, Norwitz ER. Neonatal outcome of infants born at 23 weeks' gestation. Obstet Gynecol 2001; 97:49-52.
10. Oishi M, Nishida H, Sasaki T. Japanese experience with micropremies weighing less than 600 grams born between 1984 to 1993. Pediatrics 1997; 99:E7.
11. Finnstrom O, Olausson PO, Sedin G, Serenius F, Svenningsen N, Thiringer K *et al.* The Swedish national prospective study on extremely low birthweight (ELBW) infants. Incidence, mortality, morbidity and survival in relation to level of care. Acta Paediatr 1997; 86:503-11.
12. Cartlidge PHT, Stewart JH. Survival of very low birthweight and very preterm infants in a geographically defined population. Acta Paediatr 1997; 86:105-10.
13. Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. BMJ 1999; 319:1093-7.
14. Tin W, Wariyar U, Hey E. Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994. BMJ 1997; 314:107-11.
15. Verloove-Vanhorick SP, Verwey RA, Brand R, Bennebroek Gravenhorst J, Keirse MJNC, Ruys JH. Neonatal mortality risk in relation to gestational age and birthweight: Results of a National Survey of Preterm and Very-low-birthweight Infants in the Netherlands. The Lancet 1986; 327:55-7.
16. Hempel MS. The neurological examination technique for toddler-age. 1993. Thesis. University of Groningen.
17. Bayley N. Bayley Scales of Infant Development. New York: Psychological Corporation; 1969.
18. Meulen van der SF, Smrkovsky M. Bayley ontwikkelingsschalen handleiding. Lisse: Swets & Zetlinger BV; 1983.
19. Achenbach TM. Manual for the Child Behavior Checklist/2-3 and 1992 profile. 1992. Burlington, Univerity of Vermont, department of psychiatry.
20. Achenbach TM, Edelbrock C, Howell CT. Empirically based assessment of the behavioral/emotional problems of 2- and 3- year-old children. J Abnorm Child Psychol 1987; 15:629-50.

21. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988; 82:527-32.
22. Giedion A, Haefliger H, Dangel P. Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end-expiratory pressure (PEP). Pediatr Radiol 1973; 1:145-52.
23. An international classification of retinopathy of prematurity. Pediatrics 1984; 74:127-33.
24. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Hum Dev 1999; 53:193-218.
25. Tommiska V, Heinonen K, Ikonen S, Kero P, Pokela ML, Renlund M *et al*. A National Short-Term Follow-Up Study of Extremely Low Birth Weight Infants Born in Finland in 1996-1997. Pediatrics 2001; 107:e2.
26. Philip AG. Neonatal mortality rate: is further improvement possible? J Pediatr 1995; 126:427-33.
27. Lefebvre F, Glorieux J, Laurent-Gagaon T. Neonatal survival and disability rate at age 18 months for infants born between 23 and 28 weeks of gestation. Am J Obstet Gynecol 1996; 174:833-8.
28. Synnes AR, Ling EW, Whitfield MF, Mackinnon M, Lopes L, Wong G *et al*. Perinatal outcomes of a large cohort of extremely low gestational age infants (twenty-three to twenty-eight completed weeks of gestation). J Pediatr 1994; 125:952-60.
29. Cooke RWI. Improved outcome for infants at the limits of viability. European Journal of Pediatrics 1996; 155:665-7.
30. Allen MC. Developmental outcome of neonatal intensive care: what questions are we asking? Curr Opin Pediatr 2000; 12:116-22.
31. Cooper TR, Berseth CL, Adams JM, Weisman LE. Actuarial survival in the premature infant less than 30 weeks' gestation. Pediatrics 1998; 101:975-8.
32. O'Shea TM, Klinepeter KL, Goldstein DJ, Jackson BW, Dillard RG. Survival and developmental disability in infants with birth weights of 501 to 800 grams, born between 1979 and 1994. Pediatrics 1997; 100:982-6.
33. Jacobs SE, O'Brien K, Inwood S, Kelly EN, Whyte HE. Outcome of infants 23-26 weeks' gestation pre and post surfactant. Acta Paediatr 2000; 89:959-65.
34. Gibson AT. The outcome for infants born at extreme prematurity. Current Paediatrics 1998; 8:108-12.
35. Holtrop PC, Ertzbischoff LM, Roberts CL, Batton DG, Lorenz RP. Survival and short-term outcome in newborns of 23 to 25 weeks' gestation. Am J Obstet Gynecol 1994; 170:1266-70.
36. Piecuch RE, Leonard CH, Cooper BA, Kilpatrick SJ, Schlueter MA, Sola A. Outcome of infants born at 24-26 weeks' gestation: II. Neurodevelopmental outcome. Obstet Gynecol 1997; 90:809-14.
37. Johnson A. Follow up studies: a case for a standard minimum data set. Arch Dis Child Fetal Neonatal Ed 1997; 76:F61-F63.
38. Sanders MR, Donohue PK, Oberdorf MA, Rosenkrantz TS, Allen MC. Perceptions of the limit of viability: neonatologists' attitudes toward extremely preterm infants. J Perinatol 1995; 15:494-502.
39. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR, the EPICure Study Group. Neurologic and Developmental Disability after Extremely Preterm Birth. N Engl J Med 2000; 343:378-84.
40. Sulmasy DP, Sugarman J. Are withholding and withdrawing therapy always morally equivalent? J Med Ethics 1994; 20:218-22.
41. Lorenz JM, Paneth N, Jetton JR, Den Ouden L, Tyson JE. Comparison of management strategies for extreme prematurity in New Jersey and the Netherlands: Outcomes and resource expenditure. Pediatrics 2001; 108:1269-74.

CHAPTER 3

Ethics of maintaining extremely preterm infants

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Summary

Advances in pharmacology and technology have pushed back the limits of viability to 23-24 weeks of gestation at the expense of an increasing number of survivors with disabilities. Treatment of these extremely preterm infants should be based on a thorough determination of diagnosis and prognosis, followed by decision-making on the basis of futility of treatment or quality-of-life issues and counseling of parents. This paper reviews survival rates and outcome of infants under 26 weeks of gestation born in Europe and the rest of the world and discusses the role of parents and the influence of condition at birth, gender, and birth weight in ethical decision-making on behalf of these infants. Dutch guidelines on treatment of extremely preterm infants at birth are presented to assist the clinician in facing the challenging ethical, moral, legal, and emotional dilemmas that surround this hot topic in perinatology.

Practice points

- Survival at 22 weeks of gestation has not improved over the past three decades
- Higher survival in pro-active treatment versus a more selective approach
- Surviving infants born at 23-24 weeks of gestation show high rates of disabilities
- Condition at birth is only partially related to survival and later outcome

Introduction

Over the past ten years the ethics of maintaining extremely preterm infants has become a hot topic at medical conferences and is discussed frequently in the medical press. Newer ventilation techniques and medication (antenatal steroids and surfactant) have dramatically improved survival of these tiny infants, but at the expense of worries about their neurodevelopment, growth and later academic achievement. More and more controversy has evolved over whether we are doing the right thing in neonatology.[1] We continue to search for the limits of viability and place it somewhere between 23 and 25 weeks of gestation. Below 23 weeks, it is biologically almost impossible to ventilate a preterm infant because of the immature structure and physiology of the foetal human lung. Inconsistency of pregnancy data or biological variations may account for the occasional survivors who are reported at this gestational age.[2] Since the mid-1980s a gestation of 23 weeks has been an insurmountable biological barrier and neither surfactant, steroids nor new ventilation modalities have been able to change this.[2]

In an ideal world, guidelines about the limits of viability should be readily available. To develop these, one needs recent data about survival and later outcome. Data on survival of infants born at the margins of viability are difficult to compare because survival rates are dependent on the denominator used to calculate them, i.e. on the number of all births (including stillbirths), all live born infants or all infants admitted to the Neonatal Intensive Care Unit (NICU). Survival rates for unborn infants are lower than survival rates reported for infants admitted to the NICU.[3] This should be kept in mind when counselling parents before threatening or imminent preterm delivery. Survival will be higher in a neonatal unit which only admits inborn infants than in a regional referral unit admitting outborn infants. Different attitudes from obstetricians and neonatologists towards resuscitation will also influence survival numbers: a pro-active management results in higher survival rates.[4;5] However, the ultimate goal reaches beyond mere survival and should be to survive without major disabilities. Despite an increase in survival rates of extremely preterm infants during the last decade, this has not been associated with a reduction in disabilities. Most studies report a steady prevalence of disabilities, i.e. an identical increase in the absolute numbers of survivors with and without disabilities, or an increase in the percentage of infants with disabilities.[6]

In this paper we present an overview of survival rates and later outcome of extremely preterm infants born in Europe and the rest of the world and discuss the factors which play an important role in decision-making on behalf of them.

Outcome

Survival

Table 1 shows survival of extremely preterm infants, according to gestational age, in various European countries. The reported percentages are the percentages of live born infants who survived until discharge. Survival is relatively high in Norway, Sweden, Germany and Austria. Markestad *et al.*[7] from Norway contribute their good outcome to a high percentage (95%) of inborn infants, good perinatal care and instillation of surfactant in the delivery room in two-thirds of the infants. Serenius *et al.*[8] report a survival rate similar to their countryman Hakanson[4] in the Northern part of Sweden. The higher survival rate and pro-active attitude is in sharp contrast with the lower survival rate in the Southern part of Sweden, where a more selective approach is used. Herber-Jonat *et al.*[5] state that the relatively high survival in Germany is also the result of pro-active treatment. Weber *et al.* who report the results of 16 NICU's in Austria found their data to be comparable with the rest of Europe, although at the upper range.[9] In Denmark, where continuous positive airway pressure (CPAP) is the ventilatory support of choice, survival data are higher when calculated as a percentage of actively treated infants compared to a percentage of the total number of live born infants.[3]

Table 2 gives some examples of survival of extremely preterm infants born outside Europe, with relatively high survival rates in cases of extremely short gestation (23 weeks).

Neurodevelopmental and cognitive outcome

The problem of predicting outcome of these very preterm infants is perfectly described by Jobe in an editorial in which he asks the ultimate question "Is any very preterm infant normal?".[10] Predictors of early outcome do not predict later outcome very well. Levene, after reviewing the most recent best available data, is uncertain about whether it is right to provide intensive care for all babies referred to their service: only less than 25% of babies born alive ≤ 24 weeks survive with-

Table 1. Survival (until discharge, as % of live born infants) and major complications among extremely preterm infants in Europe.

Country	Year of birth	Survival (% of live born infants)				Major complications (%) at time of hospital discharge, < 26 weeks			Long term outcome in infants <26 weeks
		23 wks	24 wks	25 wks	Remarks	IVH/ PVL	ROP	BPD	
UK[41] (EPICure)	1995	11	26	44		17	14	50	At 6 years: 12% CP; 41 % IQ <82
France[35] (EPIPAGE)	1997	0	31	50		19	17	51	
Belgium[19] (EPIBel)	1999-2000	6	29	56		12/10⋆	20⋆†	45⋆	
Netherlands[42] (LFUPP)	1996-1997	-	40	64		18/9	8	67	At 2 years: 55% abnormal neurological examination or MDI or PDI <-2 SD
Germany[5]	1999-2003		82	NA	22 and 23 wks: 67%	14‡	16‡§	43‡	
Austria[9]	1999-2001	24	57	74		NA	20	35	12% CP at 18 months
Norway[7]	1999-2000	39	60	80	% of infants admitted to NICU	11/6	14†	52	
Sweden[8]	1992-1998	43	63	77		6	15	36	
Finland[18]	1995-1996				22-23 wks: 9% 24-25 wks: 60%	NA	NA	NA	18-24 months:12% CP; 36% ophthalmic abnormalities
Denmark[43]	1998-2001	14	42	75	survival until day 28	NA	NA	NA	1994-1995, 24-25 wks[44]: 12% CP, 30% IQ < 85

Wks = weeks; NA = not available; IVH = intraventricular haemorrhage ≥ grade 3; PVL = cystic periventricular leucomalacia; ROP = retinopathy of prematurity ≥ grade 3; BPD = bronchopulmonary dysplasia = oxygen dependence at 36 weeks postmenstrual age; CP = cerebral palsy; IQ = intellectual quotient; MDI = mental development index; PDI = psychomotor development index. ⋆ = Infants ≤ 26 wks; † = ROP, treated ; ‡ = infants < 25 weeks; § = ROP ≥ grade 2

Table 2. Survival (as % of live born infants) in extremely preterm infants in Canada, USA and Australia.

Country	Year of birth	Survival (% of live born infants)				Major complications (%) at the time of hospital discharge, < 26 weeks			Long term outcome in infants < 26 weeks
		23 wks	24 wks	25 wks	Remarks	IVH/PVL	ROP	BPD	
Canada:									
Effer et al.[32]	1991-1996	NA	56	68	⋆: % of infants	NA	NA	NA	
Chan⋆ et al.[15]	1996-1997	40	57	76	admitted to NICU	19	32	51	
USA:									
El-Metwally et al.[33]	1993-1997	46	59	82		21	22	35	
Lemons[45]	1995-1996	30	50	74		6†	NA	35†	
Australia:									
Doyle et al.[31;46]	1991-1992	10	33	58		8/7	NA	69	11% CP both cohorts;
	1997	41	41	73		NA	NA	NA	18 resp. 24% DQ <-2 SD

NA = not available; IVH = intraventricular haemorrhage ≥ grade 3; PVL = cystic periventricular leucomalacia; ROP = retinopathy of prematurity ≥ grade 3; BPD = bronchopulmonary dysplasia = oxygen dependence at 36 weeks postmenstrual age; CP = cerebral palsy; IQ = intellectual quotient. † = birth weight 500-750 grams (gestational age not available)

out major disability.[11] MacDonald *et al.*[12] describe that 30-50% of the survivors among live born infants <25 weeks have moderate or severe disability. Hintz *et al.*[13] found that in a cohort from the National Institute of Child Health Development [NICHD] Neonatal Research Network, born between 1996-1999 with gestational age <25 weeks and birth weight > 500 grams, 47% had a Mental Developmental Index <70 (-2 SD) and 31% had a Psychomotor Developmental Index <70 at 18-22 months; only 21% was unimpaired. McElrath *et al.* found a 33% survival rate among live born 23-wekers and none were free from substantial morbidity.[14] In a Canadian study of infants admitted to the NICU, only 11% born at 23 weeks of gestation survived without major neonatal morbidity, 21% at 24 weeks and 29% at 25 weeks.[15] Yu found a comparable 33% severe disability rate in survivors born at 23 and 24 weeks.[16]

In many European studies neonatal morbidity (Table 1) is used as a measure for short-term outcome, but, as mentioned before, early outcome does not predict later outcome very well. Hakanson *et al.*[4] from Sweden found that 43% of infants born at or below 25 weeks who were actively treated, survived without bronchopulmonary dysplasia (BPD), severe retinopathy (ROP) or severe intraventricular haemorrhage (IVH), compared to 28% of the infants who were more selectively treated. Another Swedish study with an active treatment approach reported that 81% of the survivors went home without severe ROP/IVH or periventricular leucomalacia and 36% with BPD.[17] Markestad *et al.* from Norway described that 44%, 49% and 67% of infants born at respectively 23, 24 and 25 weeks survived "without severe illness".[7] In a Finnish study 100% of the infants born at 22-23 weeks and 62% of the infants born at 24-25 weeks had at least one morbidity, defined as severe ROP/BPD/abnormal neurological examination at 36 weeks.[18] In the EPIBel-study (gestational age <26 weeks) the chance to survive free from serious neonatal morbidity was less than 15%.[19] In the EPICure-study 49% of survivors were disabled at 30 months (23% were severe disabled).[20] At 6 years of age cognitive impairment (<-2 SD) was present in 21%, but this value rose to 41% when the results were compared with those for their classmates.[21] These high rates of disabilities remain a major challenge.

Decision-making

Role of the parents

Codes of medical ethics require doctors to give absolute priority to their patient's welfare and have advocated that a physician has no duty to treat, especially when the treatment is futile (no chance, no purpose, unbearable) and that in this event the physician, and not the parents, has the authority to decide.[22] Involvement of the parents in the decision-making process implies that they have a correct insight as to whether care is ethically justified, optional or still the subject of investigations.[22]

In 2000 the results of a large European study were published in which a hypothetical case of extreme prematurity was presented to physicians and nurses (EURONIC group).[23] In Great Britain and the Netherlands, parental wishes appeared to exert influence on the treatment decision. In many countries resuscitation guidelines mention an individual approach at a gestational age less than 24 weeks, with the goal of a parental consult. Recently Peerzada *et al.* published a survey in which they reported that 93% of the neonatologists in Sweden would resuscitate a very preterm infant if they considered treatment clearly beneficial, despite parental requests to withhold treatment. When the respondents considered treatment to be of uncertain benefit, only 25% would honour parental requests to withhold treatment. Thus in general the respondents envisioned a very limited parental role in delivery room decision-making for extremely preterm infants.[24] This same survey was done earlier in the USA, also by Peerzada, and here 76% of the respondents would honour parental requests to withhold treatment when it was considered to be of uncertain benefit.[25] Fear of litigation however, especially in the USA, might increase resuscitation of infants born near the limits of viability: Ballard *et al.* showed that there was a strong disposition among neonatologists towards respecting parental wishes in a hypothetical case of a 23-weker and that this disposition was stronger when neonatologists were given additional reasons to be concerned about litigation.[26]

Influence of condition at birth

There is much controversy about whether cardiopulmonary resuscitation in the delivery room always indicates a uniformly bad prognosis. However, the characteristics of the resuscitation may predict outcome. The question is if there is any ethically relevant information that can be obtained by examining an infant

of 23 or 24 weeks' gestation immediately after birth and whether this information is critical in making a decision to resuscitate or not. Nevertheless, 75% of the Swedish physicians in the earlier mentioned study of Peerzada[24] found the condition of the infants at delivery to be (very) important in delivery room decision-making. Shankaran studied 1,016 infants born with a gestational age ≤24 weeks, birth weight ≤750 grams and a 1-minute Apgar score ≤3. She found 60% to have a severe neurological impairment at 18-22 months.[27] Janvier and Barrington suggest that extensive resuscitation can be followed by intact survival if the resuscitation required is brief. After 3 minutes of active resuscitation and a continuous heart rate <100 beats/minute, short-term outcome is very poor.[28] Often the decision to continue intensive care is based on the efficacy of positive pressure ventilation in the delivery room, but this is not really evidence-based as nearly all publications on the efficacy of neonatal resuscitation define "resuscitation" as external cardiac massage, epinephrine administration or both.[29]

Influence of gender and birth weight

Males tend to be at a disadvantage: most studies show significant better survival in preterm infants of female gender[8;30-35] and a greater risk for impaired outcome in males.[13;20] Morse[36] described the best survival in black females and the worst survival in white males. Because of this male disadvantage, some authors advise to start active treatment in males one gestational age-week later than in females.[37]

The question remains whether survival without severe disabilities is possible when birth weight is below 500 grams. Lucey *et al.*[38] described an overall survival rate of 17% in a large cohort of infants who weighed 401-500 grams at birth. The survivors experienced a high rate of serious morbidities in the neonatal period. Because there is very little information about long-term outcomes of these foetal infants, Professor Jerold Lucey concluded we are all engaged in a large uncontrolled experiment.[38]

Conclusion

There is widespread agreement that the aim of neonatal resuscitation should be a qualitatively acceptable survival of the child. In the USA guidelines state that it is inappropriate to resuscitate infants <400 grams or <23 weeks.[12] Most

European and Canadian guidelines propose an active approach at 25 and 26 weeks, and a flexible approach at 23 and 24 weeks, depending on the opinion of the parents and the condition of the infant at birth. Nevertheless, more and more infants born at 23 and 24 weeks are resuscitated, especially in Sweden, Norway and Germany. In future studies the qualities of life of these infants, their neuro-developmental outcome and later academic achievements have to be shown.

In the Netherlands, extremely preterm infants are not routinely resuscitated and intensive care will be withdrawn if treatment is clearly futile. This policy is based on reports from the Dutch Medical Association and the Dutch Paediatric Association, which argue that withholding or withdrawing life-sustaining treatment in newborn infants with extremely poor prognoses is justifiable medical practice and that decisions should be taken by the medical and nursing team, together with well-informed parents.[39] In Table 3 the Dutch guidelines are illustrated.

Table 3. Consensus on treatment of extremely premature infants at birth in the Netherlands (Dutch Paediatric Association, November 2005).

Gestational age in weeks & days	**Intrauterine referral to level 3 perinatal center**	**Antenatal steroids**	**Caesarean section**	**Neonatal treatment in the delivery room**
$<24^{+0}$	No	No	Only on maternal indication	Family-centred comfort care
$24^{+0} - 24^{+6}$	Indicated	Can be considered	Only on maternal indication	Family-centred comfort care, unless an active approach seems justified
$25^{+0} - 25^{+6}$	Indicated	Yes	Rarely on foetal indication	Active approach, unless comfort care seems more justified
$\geq 26^{+0}$	Indicated	Yes	Yes, unless an active approach does not seem justified	Active approach, unless comfort care seems more justified

If a child weighs less than 500 grams at birth, neonatal treatment will be withheld, except for family-centred comfort care.

Lorentz reminds us how difficult it is to decide before delivery, so an option could be to start intensive care to extremely preterm infants, then reconsider and eventually withdraw treatment. There are little data to support the predictive value of the condition at birth for survival.[29] Levene warns us to keep in mind that treatment of extremely preterm infants (23 and 24 weeks of gestation) should be viewed as an experimental therapy with properly informed consent rather than the automatic process that it often becomes.[11] Because of the often poor long-term neurological and mental outcome of these very immature infants, decisions about justified care should include the alternative of no life-supporting treatment.[40]

References

1. Singh J, Lantos J, Meadow W. End-of-life after birth: death and dying in a neonatal intensive care unit. Pediatrics 2004;114:1620-6.
2. Hussain N, Rosenkrantz TS. Ethical Considerations in the Management of Infants Born at Extremely Low Gestational Age. Semin.Perinatol. 2003;27:458-70.
3. Molholm HB, Greisen G. Preterm delivery and calculation of survival rate below 28 weeks of gestation. Acta Paediatr. 2003;92:1335-8.
4. Hakansson S, Farooqi A, Holmgren PA, Serenius F, Hogberg U. Proactive Management Promotes Outcome in Extremely Preterm Infants: A Population-Based Comparison of Two Perinatal Management Strategies. Pediatrics 2004;114:58-64.
5. Herber-Jonat S, Schulze A, Kribs A, Roth B, Lindner W, Pohlandt F. Survival and major neonatal complications in infants born between 22 0/7 and 24 6/7 weeks of gestation (1999-2003). Am J Obstet Gynecol 2006;195:16-22.
6. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved Survival Rates With Increased Neurodevelopmental Disability for Extremely Low Birth Weight Infants in the 1990s. Pediatrics 2005;115:997-1003.
7. Markestad T, Kaaresen PI, Ronnestad A, Reigstad H, Lossius K, Medbo S *et al*. Early Death, Morbidity, and Need of Treatment Among Extremely Premature Infants. Pediatrics 2005;115:1289-98.
8. Serenius F, Ewald U, Farooqi A, Holmgren PA, Hakansson S, Sedin G. Short-term outcome after active perinatal management at 23-25 weeks of gestation. A study from two Swedish tertiary care centres. Part 2: infant survival. Acta Paediatr. 2004;93:1081-9.
9. Weber C, Weninger M, Klebermass Kea. Mortality and morbidity in extremely preterm infants (22 to 26 weeks of gestation): Austria 1999-2001. Wien Klin Wochenschr 2005;117/21-22:740-6.
10. Jobe AH. Predictors of outcomes in preterm infants: Which ones and when? J Pediatr. 2001;138:153-6.
11. Levene M. Is intensive care for very immature babies justified? Acta Paediatr 2004;93:149-52.
12. MacDonald H. Perinatal care at the threshold of viability. Pediatrics 2002;110:1024-7.

13. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD, for the National Institute of Child Health and Human Development Neonatal Research Network. Changes in Neurodevelopmental Outcomes at 18 to 22 Months' Corrected Age Among Infants of Less Than 25 Weeks' Gestational Age Born in 1993-1999. Pediatrics 2005;115:1645-51.
14. McElrath TF, Robinson JN, Ecker JL, Ringer SA, Norwitz ER. Neonatal outcome of infants born at 23 weeks' gestation. Obstet Gynecol 2001;97:49-52.
15. Chan K, Ohlsson A, Synnes A, Lee DS, Chien LY, Lee SK. Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. Am.J Obstet.Gynecol. 2001;185:220-6.
16. Yu VY,.Doyle LW. Regionalized long-term follow-up. Semin Perinatol 2004;9:135-44.
17. Serenius F, Ewald U, Farooqi A, Holmgren PA, Hakansson S, Sedin G. Short-term outcome after active perinatal management at 23-25 weeks of gestation. A study from two Swedish perinatal centres. Part 3: neonatal morbidity. Acta Paediatr. 2004;93:1090-7.
18. Tommiska V, Heinonen K, Ikonen S, Kero P, Pokela ML, Renlund M *et al.* A National Short-Term Follow-Up Study of Extremely Low Birth Weight Infants Born in Finland in 1996-1997. Pediatrics 2001;107:e2.
19. Vanhaesebrouck P, Allegaert K, Bottu J, Debauche C, Devlieger H, Docx M *et al.* The EPIBEL Study: Outcomes to Discharge From Hospital for Extremely Preterm Infants in Belgium. Pediatrics 2004;114:663-75.
20. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR *et al.* The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Arch.Dis.Child.Fetal Neonatal Ed. 2005;90:F134-F140.
21. Marlow N, Wolke D, Bracewell MA, Samara M, the EPICure Study Group. Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth. N Engl J Med 2005;352:9-19.
22. Van Reempts PJ,.Van Acker KJ. Ethical aspects of cardiopulmonary resuscitation in premature neonates: where do we stand? Resuscitation 2001;51:225-32.
23. De Leeuw R, Cuttini M, Nadai M, Berbik I, Hansen G, Kucinskas A *et al.* Treatment choices for extremely preterm infants: an international perspective. J Pediatr. 2000;137:608-16.
24. Peerzada JM, Schollin J, Hakansson S. Delivery Room Decision-Making for Extremely Preterm Infants in Sweden. Pediatrics 2006;117:1988-95.
25. Peerzada JM, Richardson DK, Burns JP. Delivery room decision-making at the threshold of viability. J Pediatr. 2004;145:492-8.
26. Ballard DW, Li Y, Evans J, Ballard RA, Ubel PA. Fear of litigation may increase resuscitation of infants born near the limits of viability. J Pediatr. 2002;140:713-8.
27. Shankaran S, Johnson Y, Langer JC, Vohr BR, Fanaroff AA, Wright LL *et al.* Outcome of extremely-low-birth-weight infants at highest risk: Gestational age [less-than or equal to]24 weeks, birth weight [less-than or equal to]750 g, and 1-minute Apgar [less-than or equal to]3. Am.J.Obstet. Gynecol. 2004;191:1084-91.
28. Janvier A,.Barrington KJ. The Ethics of Neonatal Resuscitation at the Margins of Viability: Informed Consent and Outcomes. J Pediatr. 2005;147:579-85.
29. Lorenz JM. Prenatal counseling and resuscitation decisions at extremely premature gestation. J Pediatr. 2005;147:567-8.
30. Bacak SJ, Baptiste-Roberts K, Amon E, Ireland B, Leet T. Risk factors for neonatal mortality among extremely-low-birth-weight infants. Am.J Obstet.Gynecol. 2005;192:862-7.
31. Doyle LW,.for the Victorian Infant Collaborative Study Group. Outcome at 5 Years of Age of Children 23 to 27 Weeks' Gestation: Refining the Prognosis. Pediatrics 2001;108:134-41.
32. Effer SB, Moutquin JM, Farine D, Saigal S, Nimrod C, Kelly E *et al.* Neonatal survival rates in

860 singleton live births at 24 and 25 weeks gestational age. A Canadian multicentre study. BJOG. 2002;109:740-5.
33. El Metwally D, Vohr B, Tucker R. Survival and neonatal morbidity at the limits of viability in the mid 1990s: 22 to 25 weeks. J Pediatr. 2000;137:616-22.
34. Fanaroff AA, Wright LL, Stevenson DK, Shankaran S, Donovan EF, Ehrenkranz RA *et al*. Very-low-birth-weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, May 1991 through December 1992. Am.J Obstet.Gynecol. 1995;173:1423-31.
35. Larroque B, Breart G, Kaminski M, Dehan M, Andre M, Burguet A *et al*. Survival of very preterm infants: Epipage, a population based cohort study. Arch.Dis.Child.Fetal Neonatal Ed. 2004;89: F139-F144.
36. Morse SB, Wu SS, Ma C, Ariet M, Resnick M, Roth J. Racial and Gender Differences in the Viability of Extremely Low Birth Weight Infants: A Population-Based Study. Pediatrics 2006;117: e106-e112.
37. Roze JC, Breart G. Care of very premature infants: looking to the future. European Journal of Obstetrics & Gynecology and Reproductive Biology 2004;117:S29-S32.
38. Lucey JF, Rowan CA, Shiono P, Wilkinson AR, Kilpatrick S, Payne NR *et al*. Fetal infants: The fate of 4172 infants with birth weights of 401 to 500 grams - The Vermont Oxford Network experience (1996-2000). Pediatrics 2004;113:1559-66.
39. Walther FJ. Withholding treatment, withdrawing treatment, and palliative care in the neonatal intensive care unit. Early Hum.Dev. 2005;81:965-72.
40. Zetterstrom R. Decisions on therapeutic intervention in neonatal intensive care. Acta Paediatr. 2004;93:148.
41. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR, for the EPICure Study Group. The EPICure Study: Outcomes to Discharge From Hospital for Infants Born at the Threshold of Viability. Pediatrics 2000;106:659-71.
42. Rijken M, Stoelhorst GMSJ, Martens SE, van Zwieten PHT, Brand R, Maarten Wit J *et al*. 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. Pediatrics 2003;112:351-8.
43. Greisen G. Managing births at the limit of viability: the Danish experience. Semin. Fetal Neonatal Med. 2004;9:453-7.
44. Hansen BM, Hoff B, Greisen G, Mortensen EL. Early nasal continuous positive airway pressure in a cohort of the smallest infants in Denmark: neurodevelopmental outcome at five years of age. Acta Paediatr. 2004;93:190-5.
45. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ *et al*. Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 Through December 1996. Pediatrics 2001;107:e1.
46. Doyle LW. Neonatal intensive care at borderline viability--is it worth it? Early Hum Dev. 2004;80:103-13.

CHAPTER 4

The effect of perinatal risk factors on growth in very preterm infants at 2 years of age: the Leiden Follow-up Project on Prematurity

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Abstract

Objective: To describe growth in infants < 32 weeks GA. To assess the relationship between growth and perinatal factors (like intrauterine growth retardation and the postnatal use of dexamethasone) and neurodevelopmental outcome.
Design: Regional, prospective study in two health regions in the Netherlands. Part of the Leiden Follow-Up Project on Prematurity (LFUPP).
Patients: 196 live born infants with GA < 32 weeks.
Methods: At two years corrected age length, weight and head circumference of 160 of 196 surviving infants (82%) were evaluated. Standard Deviation Scores were calculated and means were compared to Dutch growth references. Mean SDS for length was corrected for the mean SDS for target-height. Birth weight (BW)-SDS for gestational age (GA) was calculated according to Swedish references.
Results: Length, weight and weight-for-length were equally impaired in both sexes at two years in premature infants compared to Dutch growth charts. Catch-up in length and weight occurred mostly in the first year of life. Intrauterine growth retardation was associated with impairment of all growth parameters. The use of postnatal dexamethasone was associated with shorter length, lower weight, lower weight for length and smaller head circumference; this effect remained after correction for GA, BW and BW-SDS. Growth retardation (length and weight) was associated with an abnormal neurologic examination; smaller head circumference also with mental and psychomotor delay.
Conclusion: Growth at two years corrected age in children born < 32 weeks is impaired. Postnatal dexamethasone is associated with impairment of all growth parameters including head circumference, which may be a significant contributing factor for abnormal neurodevelopmental outcome.

Introduction

In the last decades an increase in survival of very premature infants is described, but concern remains about their neurodevelopmental outcome and catch-up growth. Most studies describe growth (length and weight) to lag behind in very low birth weight infants, although different percentages of catch-up growth are reported.[1-5] Authors usually agree that most catch-up growth occurs in the first year of life and that later catch-up is disappointing. Because postnatal growth seems to be related to neurodevelopmental outcome[5;6], paediatricians usually aim for rapid catch-up growth in the first years in these preterm infants.

Different causes for poor growth are reported, like intrauterine growth retardation[4;7] and the presence of risk factors like chronic lung disease.[8;9] Data about the use of postnatal dexamethasone and growth are conflicting. Romagnoli reported no differences at the corrected age of 3 years in premature infants with or without dexamethasone[10;11];Yeh *et al.*[12] found impaired growth (length and head circumference) at two and eight years of age after the use of dexamethasone.
The purpose of this prospective study was to describe length, weight, weight-for-length and head circumference of premature infants at the corrected age of two years, compared to the Dutch growth references.[13] Furthermore we assessed the relationship between growth and perinatal parameters like body size at birth, bronchopulmonary dysplasia and use of postnatal dexamethasone. The possible relationship between growth and the neurologic examination and the mental and psychomotor development at two years was also analysed.

Patients and methods

The data of all live born infants with a gestational age of < 32 weeks, born in 1996/1997, in the regions The Hague and Leiden were studied. At the corrected age of two years, 196 of the 225 infants (87%) were alive. Data were taken from the The Leiden Follow-Up Project on Prematurity, a Dutch regional prospective study, which included live born infants of < 32 weeks of gestation, born in 1996/1997 in the health regions The Hague, Leiden and Delft (n=266).[14] The infants from the health region of Delft were excluded because of the high percentage of missing growth data (59%).

Antenatal and perinatal data were collected including health status and diseases of the mother, socio-economic status, diseases and medication during pregnancy, gestational age, birth weight and data about perinatal morbidity and medication. Twenty-three infants were considered small for gestational age (SGA) with birth weight < P_{10} (-1.3 standard deviation (SD) according to the charts of Niklasson[15]); for infants born between 24 – 28.5 weeks the reference-data were extrapolated.

Twenty-nine infants received dexamethasone. In 1996/1997 dexamethasone was given in an initial dose of 0.5 mg/kg, tapered over 42 days to 0.1 mg/kg. It was started at a mean postnatal age of 17.5 days (range 5 – 42 days) and given for an average of 38 days (range 5 – 60 days with one infant receiving dexamethasone for 143 days). The cumulative dose ranged between 2.0 and 14.3 mg/kg. It was not possible to distinguish the influence of prenatal or postnatal steroids: 25 of the 115 infants who received antenatal steroids were also treated with dexamethasone postnatally; only 4 infants received dexamethasone without antenatal steroids.

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

Follow-up

At term age and at the corrected age of one and two years a neonatologist experienced in developmental examination assessed the infants. A complete physical examination was performed and data about length, weight and head circumference were collected. Length was measured in supine position with straight back and knee on a standardized infantometer. Infants were weighed undressed on a calibrated infant balance scale. Head circumference was measured with a standard measuring tape taking the largest measurement across the occipito-frontal line. Length (L), Weight (W) and head circumference (HC) were expressed as standard deviation scores (SDS) according to the Dutch growth charts[13] at the ages of one and two years. To correct for genetic growth potential, at the age of two years another outcome measure for length was used: SDS_{Lcorr}. In SDS_{Lcorr}, length is corrected for the target height (TH). The formula used was TH boys = (height father + height mother + 13)/2 + 4.5 cm.; TH girls = (height father + height mother – 13)/2 + 4.5 cm. Parental heights were obtained by self-report. SDS for the TH were calculated: based on the mean ± SD adult height for males (184 ± 7.1 cm) and females (170.6 ± 6.5 cm). Infants born from non-Caucasian

parents were also plotted on the Dutch growth charts because at the age of two years the influence of ethnic origin is negligible.[16;17]

At term age special growth curves were developed because the growth charts according to Niklasson[15] can be used until the postmenstrual age of 40 weeks and the growth charts according to Fredriks[13] from 42 weeks onwards. So for the children examined between 40 – 42 weeks postmenstrual age the two reference-curves were interpolated.

None of the included infants had a post-hemorrhagic hydrocephalus for which a ventriculoperitoneal shunt was needed. In 3 patients a single lumbar puncture was performed with good result; the head circumference of all these infants were within the normal range at two years.

At the corrected age of two years infants were neurologically examined according to Hempel[18] 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 mild deviations in muscle tone regulation, reflexes, fine or gross motor performance were present, or normal (N).

Mental and psychomotor development was assessed by a developmental psychologist using the Dutch version of the Bayley-Scales of Infant Development I (BSID I).[19;20] During the study period the BSID II were not validated yet 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) ≥ 84 (≥ -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).

Statistical analyses

SPSS 11 for Windows was used for statistical analyses. Fischer's Exact test and X^2–test were used to evaluate associations in a 2x2 table. The two-sample *t* test was used for comparison of continuous variables. The one-sample *t* test was used to compare means with Dutch growth charts. Correction for possible confounding variables was done with linear regression with GA, BW and SDS_{BW} as confounders. Differences were considered significant when $p < 0.05$.

Results

At two years the length and weight of 160 children were obtained (82% of 196), 66 females and 94 males. Data of 36 children remained unknown, mainly because of departure to other countries (5 children) or to untraceable places. There were no differences between the lost-to-follow-up group and the study group in perinatal parameters, but the parents of the lost-to-follow-up group had lower socio-economic status (SES) and were more often non-Caucasian (Table 1). Head circumference at two years was measured in 142 children (72%), 59 girls and 83 boys.

Twenty-three (14 %) infants (12 females, 11 males) were born small for gestational age (SGA, < P_{10}). Three infants had birth weights > 2 SDS.

Table 1. Characteristics of the infants from the health regions Leiden/The Hague

	Growth known: number of infants (%) (total n = 160)	**Growth unknown: number of infants (%) (total n = 36)**
Male gender	94 (59)	21 (58)
Multiple birth	49 (31)	12 (33)
Non-Caucasian ⋆	37 (23)	14 (47)
SES⋆ low (< 2)	56 (36)	15 (53)
high (2 – 3)	100 (64)	13 (47)
Antenatal steroids	115 (74)	22 (76)
Postnatal steroids	29 (18)	5 (14)
RDS none	72 (45)	14 (44)
grade 1-2	40 (25)	6 (19)
grade 3-4	47 (30)	12 (37)
O_2 – 28 days	46 (29)	9 (27)
BPD – 36 wks	35 (22)	7 (20)
PDA	35 (22)	9 (26)
NEC	14 (9)	4 (12)
Cystic PVL	7 (4)	0 (0)
IVH none	125 (78)	29 (81)
grade 1-2	27 (17)	4 (11)
grade 3-4	7 (5)	3 (8)
Gestational age (mean, range)	29.5 wks (23.7 – 31.9)	29.0 wks (25.6 – 31.9)
Infants with GA < 28 wks	39 (24)	10 (28)
Birth weight (mean, range)	1292 grams (530 – 2382)	1208 grams (830 – 1800)
Infants with BW < 1000 grams	39 (24)	9 (25)

SES = socioeconomic status; RDS = respiratory distress syndrome; BPD = bronchopulmonary disease; PDA = patent ductus arteriosus; NEC = necrotising enterocolitis; PVL = periventricular leucomalacia; IVH = intraventricular haemorrhage.
⋆ significant difference between the two groups

Length

Mean SDS for length (SDS_L) at two years was lower in the preterm group (-0.25) compared with the reference group ($p = 0.008$). When length was corrected for target height, it was even more abnormal in preterm infants (-0.46; $p < 0.001$) (Table 2).

Mean SDS_{Lcorr} at two years in relation to gender, perinatal factors (like SGA, BPD, cystic PVL and the postnatal use of dexamethasone) and the neurological and developmental examination at two years, are shown in Table 3. The mean SDS_{Lcorr} was significantly lower compared to the Dutch reference group, in all subgroups.

In Table 4 the regression coefficients of the linear regressions are given. SDS_L at two years was positively associated with GA, BW and SDS_{BW}. The mean SDS_L in infants with BPD was 1.00 SD lower compared to infants without BPD; in infants who received dexamethasone postnatally, the mean SDS_L was also 1.00 SD lower compared to infants without dexamethasone. After correction for GA, BW and SDS_{BW}, this difference still was 0.77 SD. For length corrected for target height numbers are about the same (data not shown).

Table 2. Mean SDS for length, weight, weight for length, BMI and head circumference at term, 1 and 2 years of age in infants born < 32 weeks compared to the reference group

	term age		1 year		2 years	
	Mean-SDS (95% CI)	**% < -2 SD**	**Mean-SDS (95% CI)**	**% < -2 SD**	**Mean-SDS (95% CI)**	**% < -2 SD**
Length	-1.30 (-1.55 ; -1.05)★	31.2	-0.26 (-0.44 ; -0.08)★	5.8	-0.25 (-0.42 ; -0.07)★	5.0
Lcorr					-0.46 (-0.67 ; -0.26)★	12.2
Weight	-0.99 (-1.21 ; -0.78)★	21.8	-0.52 (-0.71 ; -0.34)★	12.2	-0.58 (-0.78 ; -0.38)★	11.9
W/L			-0.39 (-0.58 ; -0.19)★	11.0	-0.62 (-0.82 ; -0.42)★	12.5
BMI			-0.43 (-0.63 ; -0.23)★	11.0	-0.57 (-0.77 ; -0.38)★	10.6
HC	0.29 (0.10 ; 0.47)★	2.7	0.58 (-0.08 ; 1.25)	3.2	0.10 (-0.09 ; 0.27)	4.2

Lcorr = length corrected for target height, W/L = weight for length, BMI = body mass index, HC = head circumference; SDS = standard deviation score

★significantly different compared to the reference group (Dutch growth charts)

Table 3. Growth parameters (mean-SDS and 95% CI) at 2 years in infants born < 32 weeks

		N	Lcorr	Weight	Weight-for-length	Head circumference
Female		66	-0.46 (-0.78;-0.15)★	-0.57 (-0.87;-0.26)★	-0.63 (-0.94;-0.31)★	-0.13 (-0.37;0.11)
Male		94	-0.46 (-0.74;-0.19)★	-0.59 (-0.85;0.32)★	-0.61 (-0.88;-0.35)★	0.25 (-0.01;0.51)
SGA	–	137	-0.37 (-0.60;-0.15)★	-0.43 (-0.63;-0.22)★	-0.48 (-0.70;-0.27)★	0.17 (-0.02;0.36)
	+	23	-1.03 (-1.59;-0.47)★	-1.50 (-2.00;-1.01)★	-1.51 (-1.95;-1.06)★	-0.40 (-0.95;0.14)
BPD	–	123	-0.27 (-0.51;-0.03)★	-0.34 (-0.55;-0.12)★	-0.46 (-0.70;-0.23)★	0.15 (-0.04;0.35)
	+	35	-1.15 (-1.49;-0.82)★	-1.38 (-1.75;-1.0)★	-1.16 (-1.54;-0.79)★	-0.11(-0.55;0.32)
PVL	–	152	-0.43 (-0.64;-0.22)★	-0.51 (-0.70;-0.32)★	-0.56 (-0.75;-0.36)★	0.13 (-0.04;0.31)
	+	7	-1.27 (-3.01;0.46)	-2.33 (-3.81;-0.85)★	-2.23 (-3.71;-0.76)★	-1.01 (-2.71;0.69)
Dexa	–	131	-0.30 (-0.52;-0.08)★	-0.36 (-0.56;-0.16)★	-0.45 (-0.67;-0.23)★	0.25 (0.06;0.44)★
	+	28	-1.27 (-1.76;-0.78)★	-1.56 (-2.01;-1.11)★	-1.37 (-1.77;-.98)★	-0.62 (-1.08;-0.15)★
Neur.	N	111	-0.34 (-0.58;-0.11)★	-0.30 (-0.52;-0.09)★	-0.34 (-0.57;-0.11)★	0.18 (0.01;0.36)★
	MA	33	-0.66 (-1.16;-0.15)★	-1.12 (-1.59;-0.64)★	-1.09 (-1.51;-0.66)★	0.30 (-0.21;0.81)
	DA	16	-0.89 (-1.72;-0.06)★	-1.37 (-2.09;-0.64)★	-1.58 (-2.25;-0.92)★	-0.85 (-1.47;-0.24)★
MDI	N	92	-0.53 (-0.80;-0.28)★	-0.43 (-0.68;-0.18)★	-0.52 (-0.75;-0.29)★	0.33 (0.11;0.55)★
	MD	17	-0.71 (-1.28;-0.13)★	-0.81 (-1.44;-0.19)★	-0.81 (-1.51;-0.11)★	0.11 (-0.43;0.65)
	SD	20	-0.39 (-1.15;0.37)	-0.97 (-1.64;-0.29)★	-0.98 (-1.67;-0.29)★	-0.62 (-1.17;-0.06)★
PDI	N	86	-0.48 (-0.71;-0.24)★	-0.50 (-0.77;-0.23)★	-0.61 (-0.87;-0.36)★	0.15 (-0.07;0.36)
	MD	27	-0.73 (-1.34;-0.11)★	-0.32 (-0.79;0.15)	-0.32 (-0.81;0.17)	0.49 (0.01;0.98)★
	SD	13	-0.96 (-1.74;-0.18)★	-1.49 (-2.08;-0.90)★	-1.38 (-2.05;-0.71)★	-0.82 (-1.57;-0.06)★

SGA = small for gestational age; BPD = bronchopulmonary dysplasia; PVL = cystic periventricular leucomalacia; dexa = postnatal dexamethasone; Neur. = neurologic examination according to Hempel; N = normal; MA = mildly abnormal; DA = definitely abnormal; MDI = mental developmental index; MD = mild delay; SD = severe delay; PDI =psychomotor developmental index; Lcorr = length corrected for target height; SDS = standard deviation score.
★ significant difference compared to the reference group (Dutch growth charts)

Weight

Mean SDS for weight (SDS_W) at two years was lower in the preterm born children (-0.58) compared to the reference group ($p < 0.001$; Table 2). For all factors listed in Table 3 weight was smaller at two years in the preterm born children compared to the Dutch reference group. SDS_W was positively associated with GA, BW and SDS_{BW} (Table 5). SDS_W of infants with BPD was1.04 SD lower compared to infants without BPD; the difference was 1.82 SD for infants with or without cystic PVL and 1.20 SD for infants who received dexamethasone compared to infants who did not. After correction for confounders

(GA, BW and SDS_{BW}) these differences remained highly significant (resp. 0.60, 1.47 and 0.89 SD for BPD, PVL and use of dexamethasone). The mean SDS_W of infants having a mildly abnormal neurologic examination was 0.81 SD lower than in neurologically normal infants; SDS_W was 1.06 SD lower in definitely abnormal infants.

Weight-for-length

Mean SDS for weight-for-length ($SDS_{W/L}$) at two years was lower (-0.62) in the preterm group compared with normal Dutch children ($p < 0.001$; Table 2). The results for $SDS_{W/L}$ were comparable with SDS_L and SDS_W: a smaller weight-for-length in the premature infants compared to the reference group for all perinatal and postnatal factors listed in Table 3.

$SDS_{W/L}$ was associated with GA, BW and SDS_{BW}, but also with BPD, cystic PVL, the postnatal use of dexamethasone and the neurologic examination and the PDI (Table 5). After correction for confounding factors like GA, BW and SDS_{BW}, all parameters except BPD and PDI were still associated with weight-for-length. The use of postnatal dexamethasone for example remained associated with lower weight-for-length (difference 0.58 SD, $p = 0.040$), also after correction for BPD (difference 0.65 SD, $p = 0.042$).

Head circumference

Head circumference (HC) was not different at two years in the premature born infants compared to the Dutch references, although the head circumference of the premature males tended to be bigger than in the reference group (Table 3). Perinatal factors like SGA and BPD did not result in smaller HC, but use of postnatal dexamethasone, an abnormal neurological examination or a severe delay in MDI or PDI were associated with smaller HC compared to the reference group (Table 3).

Table 4 shows the positive association of GA, BW and SDS_{BW} and head circumference. Infants with cystic PVL had a lower mean SDS_{HC} (difference 1.15 SD, after correction for confounders 0.97 SD). The SDS_{HC} of infants who received dexamethasone was 0.87 SD lower (after correction for confounders still 0.78 SD lower) compared to the infants who did not receive dexamethasone. There was also a relationship between smaller HC and an abnormal neurologic examination according to Hempel (difference 1.04 SD for definitely abnormal vs. normal infants) and between smaller HC and abnormal mental and psychomotor devel-

Tabel 4. Relationship between perinatal factors and SDS_L and SDS_{HC} at 2 years in infants born < 32 weeks

		SDS_L at 2 years		SDS_{HC} at 2 years	
Perinatal factor:		**regression-coefficient (95% CI)**	**regression-coefficient (95% CI), corr.†**	**regression-coefficient (95% CI)**	**regression-coefficient (95% CI), corr.†**
GA (wks)		0.13 (0.04;2.11)★		0.10 (0.01;0.19)★	
BW (kg)		1.07 (0.65;1.49)★		0.84 (0.39;1.28)★	
SDS_{BW}		0.26 (0.10;0.43)★		0.24 (0.06;0.42)★	
BPD (+ vs. -)		-1.00 (-1.38;-0.61)★	-0.80 (-1.25;-0.36)★	-0.27 (-0.70;0.16)	0.09 (-0.40;0.58)
PVL (+ vs. -)		-1.22 (-2.05;-0.38)★	-0.97 (-1.76;-0.17)★	-1.15 (-1.95;-0.34)★	-0.97 (-1.77;-0.16)★
Dexa (+ vs. -)		-1.00 (-1.43;-0.58)★	-0.77 (-1.25;-0.28)★	-0.87 (-1.31;-0.42)★	-0.78 (-1.30;-0.26)★
Neur.	MA vs N	-0.51 (-0.94;-0.08)★	-0.47 (-0.90;-0.05)★	0.11 (-0.31;0.54)	0.19 (-0.25;0.63)
	DA vs N	-0.38 (-0.96;0.20)	-0.10 (-0.70;0.50)	-1.04 (-1.59;-0.48)★	-0.84 (-1.44;-0.24)★
MDI	MD vs N	-0.33 (-0.92;0.26)	-0.02 (-0.61;0.56)	-0.22 (-0.76;0.32)	-0.01 (-0.57;0.55)
	SD vs N	-0.41 (-0.97;0.14)	-0.24 (-0.77;0.29)	-0.95 (-1.46;-0.44)★	-0.82 (-1.33;-0.31)★
PDI	MD vs N	-0.05 (-0.54;0.44)	0.08 (-0.39;0.54)	0.35 (-0.12;0.81)	0.41 (-0.05;0.86)
	SD vs N	-0.88 (-1.54;-0.22)★	-0.75 (-1.36;-0.14)★	-0.97 (-1.57;-0.36)★	-0.87 (-1.45;-0.28)★

GA = gestational age; BW = birth weight; BPD = bronchopulmonary dysplasia; PVL = cystic periventricular leucomalacia; dexa = postnatal dexamethasone; Neur. = neurologic examination according to Hempel; N = normal; MA = mildly abnormal; DA = definitely abnormal; MDI = mental developmental index; MD = mild delay; SD = severe delay; PDI = psychomotor develomental index; HC = head circumference; SDS = standard deviation score.; ★ = significant; † = corrected for GA and BW-SDS.

opmental index (resp. 0.95 and 0.97 SD smaller head circumference for severe delayed infants compared to normal infants). After correction for confounders these associations remained significant.

No significant association between growth and other perinatal factors like for example intraventricular haemorrhage, patent ductus arteriosus, necrotising enterocolitis or rethinopathy of prematurity was found.

Although there was a negative influence of the postnatal use of dexamethasone on all growth parameters, no association was found between the cumulative dose of dexamethasone and growth, nor between the duration of the dexamethasone-course or the date of starting dexamethasone.

Not all infants who received dexamethasone developed BPD (defined as need of oxygen at the postmenstrual age of 36 weeks); likewise not all infants who

Tabel 5. Relationship between perinatal factors and SDS_W and $SDS_{W/L}$ at 2 years in infants born < 32 weeks

	SDS_W at 2 years		$SDS_{W/L}$ at 2 years	
Perinatal factor:	**regression-coefficient (95% CI)**	**regression-coefficient (95% CI), corr.†**	**regression-coefficient (95% CI)**	**regression-coefficient (95% CI), corr.†**
GA (wks)	0.16 (0.06;0.26)★		0.13 (0.03;0.23)★	
BW (kg)	1.53 (1.07;1.98)★		1.34 (0.87;1.81)★	
SDS_{BW}	0.45 (0.26;0.64)★		0.43 (0.24;0.62)★	
BPD (+ vs.-)	-1.04 (-1.49;-0.59)★	-0.60 (-1.09;-0.11)★	-0.70 (-1.17;-0.22)★	-0.21 (-0.73;0.31)
PVL (+ vs.-)	-1.82 (-2.75;-0.90)★	-1.47 (-2.31;-0.63)★	-1.68 (-2.61;-0.74)★	-1.37 (-2.24;-0.50)★
Dexa (+ vs.-)	-1.20 (-1.68;-0.72)★	-0.89 (-1.42;-0.38)★	-0.92 (-1.42;-0.42)★	-0.58 (-1.10;-0.26)★
Neur. MA vs N	-0.81 (-1.28;-0.34)★	-0.75 (-1.19;-0.30)★	-0.74 (-1.22;-0.27)★	-0.68 (-1.15;-0.22)★
DA vs N	-1.06 (-1.70;-0.43)★	-0.70 (-1.33;-0.08)★	-1.24 (-1.88;-0.61)★	-0.95 (-1.60;-0.30)★
MDI MD vs N	-0.38 (-1.03;0.26)	0.05 (-0.56;0.66)	0.29 (-0.93;0.34)	0.08 (-0.53;0.69)
SD vs N	-0.54 (-1.14;0.07)	-0.26 (-0.82;0.29)	-0.46 (-1.05;0.13)	-0.21 (-0.77;0.35)
PDI MD vs N	0.18 (-0.35;0.72)	0.31 (-0.17;0.79)	0.29 (-0.23;0.82)	0.38 (-0.11;0.87)
SD vs N	-1.00 (-1.72;-0.28)★	-0.80 (-1.44;-0.16)★	-0.76 (-1.47;-0.05)★	-0.58 (-1.23;0.07)

GA = gestational age; BW = birth weight; BPD = bronchopulmonary dysplasia; PVL = cystic periventricular leucomalacia; dexa = postnatal dexamethasone; Neur. = neurologic examination according to Hempel; N = normal; MA = mildly abnormal; DA = definitely abnormal; MDI = mental developmental index; MD = mild delay; SD = severe delay; PDI = psychomotor developmental index; SDS = standard deviation score;
★ = significant; † = corrected for GA, BW and BW-SDS

Table 6. Mean SDS for growth at 2 years in infants with Bronchopulmonary Dysplasia and/or Dexamethasone

	BPD + /Dex + (n = 21) mean SDS (95% CI)	**BPD + /Dex – (n = 14) mean SDS (95% CI)**	**BPD – /Dex + (n=7) mean SDS (95% CI)**
Length-corr	-1.29 (-1.76;-0.82)	-0.97 (-1.48;-0.45)	-1.22 (-2.89;0.45)
Length	-1.21 (-1.66;-0.75)	-0.69 (-1.11;-0.26)	-0.44 (-1.87;0.99)
Weight	-1.69 (-2.14;-1.24)	-0.90 (-1.54;-0.26)★	-1.15 (-2.79;0.48)
Weight-for-length	-1.44 (-1.85;-1.03)	-0.75 (-1.46;-0.03)	-1.30 (-2.66;0.05)
Head circumference	-0.59 (-1.09;-0.08)	0.61 (-0.06;1.28)★	-0.72 (-2.21;0.77)

BPD = bronchopulmonary dysplasia; Dex = dexamethasone;★ significant difference to BPD +/Dex +

developed BPD received dexamethasone, so the numbers of infants with BPD and dexamethasone are not the same. Table 6 shows that from all infants with BPD, the ones who received dexamethasone have lower weight ($p = 0.035$) and smaller head circumference ($p = 0.004$) compared with the infants with BPD who did not receive dexamethasone. In this table is also illustrated that among all infants who received dexamethasone, there is no difference in growth between the infants with or without BPD.

Catch-up growth

In 40% of the infants at term age SDS_W was below –1.3 and in 50% SDS_L below –1.3, while in only 11% the SDS_{HC} was below –1.3. Percentages of children with SDS_L, SDS_{Lcorr}, SDS_W, $SDS_{W/L}$ and SDS_{HC} below -2 SDS at different times (term age, the corrected age of one and two years) are listed in Table 2. Between term age and the age of 1 year the percentage of children with very low length or weight decreased fast, but between the ages of one and two years the numbers remained about the same, suggesting that catch-up growth occurred mostly in the first year of life. In this cohort there were a limited number of infants with very small head circumference and this number remained equal over time.

Catch-up growth was worse in the SGA-infants (n = 23): at two years 17 % had L and Lcorr < -2 SDS, 26 % had W and W/L < -2 SDS and 14 % HC < -2 SDS.

Discussion

Comparison to Dutch growth charts

We found shorter length, lower weight and lower weight-for-length at two years in very preterm infants compared with the Dutch growth charts. Smaller length and weight at this age were also described by Ford *et al.*[3] when they compared very low-birth-weight children (< 1500 grams) with normal birth weight children (> 2500 g). As shown in Table 2 a number of children at two years had growth parameters < –2 SDS. Hack[4] found 15.5% subnormal length (< P_3) at 20 months corrected age in a cohort of infants born < 1500 g compared to 5% in our cohort with L-SDS < -2 SD (= P_2); when we use length corrected for target height we found about the same percentage as in the American study (12%).

Head circumference at two years was comparable with the Dutch growth

charts, in contrast with Daily *et al.*[2] who showed that 45% of infants born < 800 g at 3 years still had a head circumference < P_5. Maybe this percentage is so much higher because of the extremely low birth weight of the infants included in their study: in our study only 15 infants (9%) had a birth weight < 800 grams. Casey *et al.*[1] divided a large cohort of preterm infants in three birth weight groups (≤ 1250 grams, 1250 – 2000 grams and 2000 – 2500 grams), in which they found significant differences between the 3 subgroups in length, weight and head circumference at two years.

SDS_L, SDS_W and $SDS_{W/L}$ at two years were remarkably similar for males and females. In literature the influence of gender on growth is often not analysed and if so, results are not correspondent. Casey *et al.*[1] also found almost similar growth patterns for both sexes (and larger head circumference in the heaviest preterm group compared to their reference group). Others, however, have reported better growth in males.[9;21]

Small for gestational age

We found significant differences in weight (0.76 SD) and weight-for-length (0.82 SD) at two years in infants born SGA compared to infants born non-SGA, but unlike others[4;5;7;22] we only found small differences in length and head circumference in these infants. However, when we used SDS_{BW} as a continuous variable, we found significantly lower length, smaller weight and weight-for-length and smaller head circumference at two years in infants with lower SDS_{BW}.

In the literature different definitions have been used for SGA. We plotted the LFUPP-infants in the reference curves according to Niklasson[15], Marsal[23] and Usher & McLean[24]: mean SDS_{BW} was -0.16, -1.24 and 0.13 respectively and the number of infants with SDS_{BW} < P10 (-1.3 SD) was 14, 45 and 22% respectively. We concluded that our infants resembled most the group of infants described by Niklasson *et al.* and decided to use their reference curves.

Influence of postnatal dexamethasone

In this study a negative influence of the postnatal use of dexamethasone on length, weight, weight-for-length and head circumference was found, which remained after correction for confounders. There was no association between the cumulative dose of dexamethasone and growth parameters. An explanation for the absence of this association could be that the cumulative dose was high in all children (2 – 14.3 mg/kg), in comparison with the cumulative dosage in

presently used short courses (2.3 mg/kg dexamethasone), and that above a certain threshold of dexamethasone the dose-response relationship becomes less prominent. An additional explanation may be that the study group receiving dexamethasone was too small to detect subtle dose-effect relationships.

Many studies have concentrated on short-term influences of dexamethasone and data about later catch-up growth show conflicting results. The group of O'Shea[25] found in 2 cohorts with or without dexamethasone, similar proportions of infants with head circumference, length or weight below the 10th percentile at 1 year of age. Yeh *et al.*[12] studied infants who received an early course of dexamethasone to prevent chronic lung disease compared with a control group; they found a shorter height and smaller head circumference at school age in the infants who received dexamethasone.

Murphy *et al.*[26] showed on MRI at term age 35% reduction of cortical grey matter in infants who received dexamethasone compared to infants who did not. This is consistent with the increase of abnormal neurologic findings in newborns that received postnatal dexamethasone in recent literature. We also found an association between smaller head circumference and abnormal neurologic examination and also between smaller head circumference and severe delay in psychomotor and mental developmental index. Infants who received dexamethasone more often had smaller head circumference and more developmental delay. It is difficult to distinguish if this delay and abnormal neurologic findings are a consequence of the use of dexamethasone or of the smaller head circumference.

In general, head circumference is known to be related to mental and motor development.[5;27-30] Forslund *et al.*[31] found a neurologic optimality score to be related to head circumference but not to length or weight. In this study we found a relationship also between lower weight and weight-for-length at two years and abnormal neurologic development. There are not many studies concentrating on the association of later growth with neurodevelopmental outcome, but recently Latal-Hajnal *et al.*[6] reported that impaired postnatal growth (weight for length < P_{10} at two years) rather than being SGA was associated with abnormal neurodevelopmental outcome at that age.

Other perinatal factors

BPD was related to smaller length, weight and weight-for-length, which could be explained by the higher energy expenditure in the infants with chronic lung disease. Daily *et al.*[2] found no relation between BPD and growth at 3 years of age

in a cohort of infants < 800 grams; Dusick *et al.*[5] found BPD not to be related to poor growth at two years. Other studies[8;9;32] however do report impaired growth in infants with higher medical risk like BPD, severe IVH or PVL. In our study cystic PVL was also associated with all growth parameters except weight-for-length.

Our study was not designed as a randomized controlled trial to assess the effect of postnatal dexamethasone on growth and the number of infants who received dexamethasone might be too small. Still, the differences in mean growth parameters including head circumference at two years in infants who did or did not receive dexamethasone, are significant in this prospective regional study. The differences in weight and head circumference at two years in infants who received dexamethasone within the group infants with BPD, illustrate the additional negative effect of dexamethasone on top of the BPD. We realize that in the years 1996/1997 we gave higher doses and longer courses of dexamethasone than is recommended today, however, the question remains if one should give dexamethasone at all or prefer other glucocorticosteroids. Shinwell *et al.*[33] described a decline in the use of dexamethasone by neonatologists in Israel (22% in the years 1993/1994 down to 6% in 2001). Jobe reported figures of 23% (Vermont Oxford Network) and 19% (Neonatal Research Network) of infants with birth weight of 501 – 1000 g still receiving postnatal corticosteroids.[34]

In this study not only length and weight but also weight-for-length ratio is analysed, which is necessary to get an impression of the body composition. Because of the influence of the parental height at two years, it is also important to relate the length of the children to target height, which was done in this study. In addition, the reference for SDS_{BW} (as a measure of being small for gestational age)[15] was carefully chosen after a study of mostly used definitions for SGA.

In conclusion, we found significantly shorter length, smaller weight and smaller weight-for-length at two years corrected age in these preterm born children compared to the Dutch growth charts. Head circumference was comparable with the reference group. The number of children with length, weight and weight-for-length < –2 SD at two years was about 12%; 4% had a head circumference < -2 SD. Infants with BPD and cystic PVL showed reduced growth. Postnatal use of dexamethasone was negatively associated with all growth parameters, especially head circumference. SDS_{BW} was also associated with impaired growth. Part of the growth retardation may be explained as a result of intrauterine growth retarda-

tion, but also by the use of postnatal dexamethasone in case of BPD. Catch-up growth in weight and length occurred mostly in the first year of life. Children with impaired growth (length, weight, weight-for-length and head circumference) had an abnormal neurologic examination and in case of smaller head circumference also more psychomotor and mental delay.

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References

1. Casey PH, Kraemer HC, Bernbaum J, Yogman MW, Sells JC. Growth status and growth rates of a varied sample of low birth weight, preterm infants: a longitudinal cohort from birth to three years of age. J Pediatr. 1991;119:599-605.
2. Daily DK, Kilbride HW, Wheeler R, Hassanein R. Growth patterns for infants weighing less than 801 grams at birth to 3 years of age. J Perinatol. 1994;14:454-60.
3. Ford GW, Doyle LW, Davis NM, Callanan C. Very low birth weight and growth into adolescence. Arch Pediatr Adolesc Med. 2000;154:778-84.
4. Hack M, Weissman B, Borawski-Clark E. Catch-up growth during childhood among very low-birth-weight children. Arch Pediatr Adolesc Med. 1996;150:1122-9.
5. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? Semin Perinatol 2003;27:302-10.
6. Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr. 2003;143:163-70.
7. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch.Dis.Child Fetal Neonatal Ed 2000;82:F208-F214.

8. Huijsman WA, de Ridder M, de bruin NC, van Helmond G, Terpstra N, van Goudoever JB *et al*. Growth and body composition in preterm infants with bronchopulmonary dysplasia. Arch.Dis. Child Fetal Neonatal Ed 2003;88:F46-F51.
9. Morris BH, Smith KE, Swank PR, Denson SE, Landry SH. Patterns of physical and neurologic development in preterm children. J Perinatol. 2002;22:31-6.
10. Romagnoli C, Zecca E, Luciano R, Torrioli G, Tortorolo G. A three year follow up of preterm infants after moderately early treatment with dexamethasone. Arch Dis Child Fetal Neonatal Ed 2002;87:F55-F58.
11. Romagnoli C, Zecca E, Luciano R, Torrioli G, Tortorolo G. Controlled trial of early dexamethasone treatment for the prevention of chronic lung disease in preterm infants: a 3-year follow-up. Pediatrics 2002;109:e85.
12. Yeh TF, Lin YJ, Lin HC, Huang CC, Hsieh WS, Lin CH *et al*. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Engl J Med. 2004;350:1304-13.
13. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E *et al*. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res. 2000;47:316-23.
14. Stoelhorst GMSJ, Rijken M, Martens SE, Brand R, den Ouden AL, Wit JM *et al*. Changes in Neonatology: Comparison of Two Cohorts of Very Preterm Infants (Gestational Age <32 Weeks): The Project on Preterm and Small for Gestational Age Infants 1983 and The Leiden Follow-Up Project on Prematurity 1996-1997. Pediatrics 2005;115:396-405.
15. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand. 1991;80:756-62.
16. Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM. Height, weight, body mass index and pubertal development reference values for children of Turkish origin in the Netherlands. Eur J Pediatr. 2003;162:788-93.
17. Fredriks AM, van Buuren S, Jeurissen SE, Dekker FW, Verloove-Vanhorick SP, Wit JM. Height, weight, body mass index and pubertal development references for children of Moroccan origin in The Netherlands. Acta Paediatr. 2004;93:817-24.
18. Hempel MS. The neurological examination technique for toddler-age. Thesis. University of Groningen. 1993.
19. Bayley N. Bayley Scales of Infant Development. New York: Psychological Corporation, 1969.
20. Meulen van der SF, Smrkovsky M. Bayley ontwikkelingsschalen handleiding. Lisse: Swets & Zetlinger BV, 1983.
21. Guo SS, Roche AF, Chumlea WC, Casey PH, Moore WM. Growth in weight, recumbent length, and head circumference for preterm low-birthweight infants during the first three years of life using gestation-adjusted ages. Early Hum Dev 1997;47:305-25.
22. Gortner L, van Husen M, Thyen U, Gembruch U, Friedrich HJ, Landmann E. Outcome in preterm small for gestational age infants compared to appropriate for gestational age preterms at the age of 2 years: a prospective study. Eur J Obstet Gynecol Reprod Biol. 2003;110 Suppl 1: S93-S97.
23. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85:843-8.
24. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr. 1969;74:901-10.
25. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG. Randomized

Placebo-controlled Trial of a 42-Day Tapering Course of Dexamethasone to Reduce the Duration of Ventilator Dependency in Very Low Birth Weight Infants: Outcome of Study Participants at 1-Year Adjusted Age. Pediatrics 1999;104:15-21.
26. Murphy BP, Inder TE, Huppi PS, Warfield S, Zientara GP, Kikinis R *et al*. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. Pediatrics 2001;107:217-21.
27. Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. J Pediatr. 2003;142:463-8.
28. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med. 1991;325:231-7.
29. Kitchen WH, Doyle LW, Ford GW, Callanan C, Rickards AL, Kelly E. Very low birth weight and growth to age 8 years. II: Head dimensions and intelligence. Am J Dis Child 1992;146:46-50.
30. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. Arch.Dis. Child Fetal Neonatal Ed 2003;88:F492-F500.
31. Forslund M, Bjerre I. Follow-up of preterm children: II. Growth and development at four years of age. Early Hum.Dev. 1990;24:107-18.
32. DeWitt SJ, Sparks JW, Swank PB, Smith K, Denson SE, Landry SH. Physical growth of low birthweight infants in the first year of life: impact of maternal behaviors. Early Hum Dev. 1997;47:19-34.
33. Shinwell ES, Karplus M, Bader D, Dollberg S, Gur I, Weintraub Z *et al*. Neonatologists are using much less dexamethasone. Arch Dis Child Fetal Neonatal Ed. 2003;88:F432-F433.
34. Jobe AH. Postnatal corticosteroids for preterm infants - do what we say, not what we do. N Engl J Med. 2004;350:1349-51.

CHAPTER 5

Similar growth in preterm infants with intra- or extrauterine growth restriction

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Submitted

Abstract

Objective: To analyse the influence of preterm growth restraint (PGR) in preterm infants born appropriate-for-gestational-age (AGA) on growth achievement at 2 years of age and to compare their growth with preterm small-for-gestational-age (SGA) infants.

Design: Regional, prospective study of infants born < 32 weeks gestational age (GA). Length, weight and head circumference were measured at term, 1 and 2 years of age and expressed as Standard Deviation Scores (SDS). PGR was defined as length and/or weight at term age < -1.3 SD.

Results: Of the 158 infants, 23 (14%) infants were SGA, 61 (39%) were AGA-PGR and 74 (47%) AGA-nonPGR. At all ages the SGA-infants had the lowest length, weight and head size. At 2 years of age AGA-PGR-infants had a similar mean length as SGA-infants (-0.68 vs. -0.80 SDS), a lightly bigger head circumference (-0.09 vs. -0.40 SDS) and a higher weight (-0.93 vs. -1.50 SDS) and weight-for-length (-0.79 vs. -1.51 SDS). The AGA-nonPGR-infants displayed growth parameters comparable to the Dutch reference group, except for a relatively large head circumference (0.38 SDS). After correction for confounders PGR remained the most important predictor for sub-optimal growth at 2 years in the AGA-infants.

Conclusion: Preterm infants, who experience preterm growth restraint, are at increased risk for sub-optimal growth at the corrected age of 2 years. Their growth is similar to that of SGA-infants concerning length and head circumference.

Introduction

Advances in neonatal care have resulted in an improvement of survival of premature infants, but survivors have remained at an increased risk of neurological sequelae and sub-optimal growth. Sub-optimal growth may be the result of a complex interaction of perinatal factors including inadequate nutrition and is common in extremely preterm children, particularly when the infants are born small-for-gestational-age (SGA)[1], when they have bronchopulmonary disease (BPD)[2] or when prolonged courses of systemic steroids have been given for BPD.[3-5] Most clinicians strive at a normal growth pattern of preterm infants, as a sign of sufficient nutrient intake, which is believed to be crucial for early brain development.[6]

We have recently postulated that the extra-uterine growth restriction of AGA born preterm infants who suffer from medical complications in the neonatal period may have a similar effect on later growth as intrauterine growth restriction leading to SGA at term. Thus, "preterm growth restraint" (PGR) may be the relevant issue, more than the environment where it is experienced (in utero or ex utero).[7] Indeed, in a nationwide cohort of very preterm infants born in the nineteen-eighties, infants who experienced PGR displayed a growth pattern similar to that of preterm SGA-infants.[8] An association between the incidence of in-hospital growth failure in extremely low birth weight infants and growth failure at 2 years of age was described earlier by Dusick *et al.*[9]

In a previous study in a regional cohort of very preterm infants from the nineteen-nineties, we found impaired growth at 2 years of age and postnatal dexamethasone to be related to sub-optimal growth.[10] In the present study we compared various growth parameters until the corrected age of 2 years of three subgroups (SGA, AGA-PGR and AGA-nonPGR) in the same cohort.

Methods

Data were taken from the Leiden Follow-Up Project on Prematurity (LFUPP), a Dutch regional prospective study, which included live born infants < 32 weeks of gestation, born in 1996/1997 in the health regions The Hague, Leiden and Delft (n=266).[11] The infants from the health region Delft were excluded because of a high percentage of missing growth data (59%). At the corrected age of 2 years,

196 of the 225 infants (87%) born in the regions The Hague and Leiden were alive. From 160 survivors (82% of 196) length and weight were measured at the corrected age of 2 years. From 36 children no data could be obtained. No differences were observed between the lost-to-follow-up group and the study group in perinatal parameters, but the parents of the lost-to-follow-up group had lower socio-economic status and were more often non-Caucasian. Head circumference at 2 years was measured in 142 children (72%).

For this analysis small-for-gestational-age was defined as birth weight <-1.3 SD (P_{10}) according to Niklasson.[12] All other infants were considered appropriate-for-gestational-age (AGA), including three infants with birth weights >2 SD. In the AGA-infants preterm growth restraint (PGR) was defined as length and/or weight at term age less than -1.3 SD. When the postmenstrual age (PMA) was <40 weeks (29 infants, 18%) growth parameters were compared to Niklasson[12]; when PMA was >42 weeks (45 infants, 29%) the Dutch nation-wide growth reference was used[13]; and for the children examined between 40 – 42 weeks PMA (84 infants, 53%) the two reference-curves were interpolated. In 2 infants data concerning length and weight at term age were missing, so the final cohort consisted of 158 infants. Seven infants were examined not precisely at term age (resp. at 46, 48, 49, 51 and 58 weeks PMA); when we excluded these infants and analysed the data, results remained the same (data not shown).

Antenatal and perinatal data were collected including health status and diseases of the mother, socio-economic status, diseases and medication during pregnancy, gestational age, birth weight and data about perinatal morbidity and medication. In 28 cases dexamethasone was administered. In 1996/1997 dexamethasone was given in an initial dose of 0.5 mg/kg/day, tapered over 42 days to 0.1 mg/kg/day.

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

Follow-up

At term age and at the corrected age of 1 and 2 years four neonatologists experienced in developmental examination assessed the infants. A complete physical examination was performed and data about length, weight and head circumference were collected. Length was measured in supine position with straight back and knee on a standardised infantometer. Infants were weighed undressed on a calibrated infant balance scale. Head circumference was measured with a standard

measuring tape taking the largest measurement across the occipito-frontal line. Length (L), weight (W) and head circumference (HC) were expressed as standard deviation scores (SDS) according to the Dutch growth charts at the ages of 1 and 2 years.[13] Because of differences in length due to differences in genetic growth potential, at the age of 2 years another outcome measure for length was added: Lcorr-SDS. In Lcorr-SDS, length was corrected for target height (TH). Target height was calculated as [mean parental height + or – 13 cm]/2 + 4.5 cm, in which 4.5 cm represents the secular trend per generation of 30 years.[13] Height of both parents was obtained in 93% of the infants. At 2 years of age a mental developmental index (MDI) and a psychomotor developmental index (PDI) were assessed by a developmental psychologist using the Dutch version of the Bayley-Scales of Infant Development I (BSID I). During the study period the BSID II were not validated yet for the Dutch population. The BSID I have a mean value of 100 and a standard deviation of 16.

Statistical analyses

SPSS 11 for Windows was used for statistical analyses. Fischer's Exact test and X^2–test were used to evaluate associations in a 2x2 table. The two-sample *t* test was used for comparison of continuous variables. The one-sample *t* test was used to compare means with Dutch growth charts. A multiple regression analyses was conducted with growth parameters at 2 years as dependent variables and GA, BW-SDS, PVL, BPD, dexamethasone and PGR as independent variables. Differences were considered significant when $p < 0.05$.

Results

Twenty-three (14.6%) of the 158 children analysed at 2 years could be classified as SGA, 61 (38.6%) as AGA-PGR and 74 (46.8%) as AGA-nonPGR. Characteristics of the 3 groups including mean gestational age (GA) and mean birth weight (BW) are listed in Table 1. Mean BW, multiple birth, patent ductus arteriosus (PDA), use of surfactant, need of oxygen at 28 days, bronchopulmonary dysplasia (BPD), use of postnatal dexamethasone, still being admitted at term and the MDI and PDI were significantly different in the 3 groups. Among the AGA-infants GA, BW, female gender, respiratory distress syndrome (RDS), use

Table 1. Characteristics of SGA-, AGA-PGR- and AGA-nonPGR-infants

	SGA n (%)	AGA-PGR n (%)	AGA-nonPGR n (%)
Total infants	(n = 23)	(n = 61)	(n = 74)
GA (wks, mean+range)	30.4 (26.1-31.9)	28.4 (23.7-31.9)	30.1 (25.9-31.9)
BW (grams, mean+range)*	943 (530-1210)	1118 (550-1928)	1540 (900-2382)
Male gender	11 (48)	31 (51)	50 (68)
Multiple birth*	2 (9)	20 (33)	27 (37)
PDA*	4 (17)	21 (34)	9 (12)
surfactant*	5 (22)	37 (61)	24 (32)
O2-28 days*	6 (26)	34 (56)	5 (7)
BPD 36 wks*	5 (22)	27 (44)	3 (4)
NEC	3 (13)	7 (12)	3 (4)
Cystic PVL	2 (9)	2 (3)	3 (4)
IVH grade 3/4	-	4 (6)	3 (4)
Dexamethasone*	4 (17)	23 (38)	1 (1)
Still admitted at term*	8 (35)	22 (37)	8 (11)
Normal neurol. exam. at term	6 (26)	31 (51)	41 (55)
Normal neurol. exam. at 2 yrs	15 (65)	36 (59)	59 (80)
BSID MDI – mean (SD)*	96 (30)	91 (25)	104 (23)
PDI – mean (SD)*	92 (20)	92 (20)	102 (20)

GA = gestational age; BW = birth weight; PDA = patent ductus arteriosus; BPD = bronchopulmonary dysplasia; NEC = necrotising enterocolitis: PVL = periventricular leucomalacia; IVH = intraventricular haemorrhage; MDI = mental developmental index; PDI = psychomotor developmental index; SGA = small-for-gestational age; AGA = appropriate-for-gestational age; PGR = preterm growth restraint. *Significant difference between the 3 groups.

of surfactant, patent ductus arteriosus (PDA), need of oxygen at 28 days, BPD, postnatal dexamethasone, abnormal neurological examination at 2 years and both lower PDI and MDI were associated with PGR. Multiple birth, race, necrotising enterocolitis, periventricular leucomalacia (PVL) and intraventricular haemorrhage were not associated with PGR. For all growth parameters, PGR was an important predictor for sub-optimal growth at 2 years in the AGA-infants. Mean differences were 0.97 SD for length, 0.60 SD for length corrected for target height, 0.93 SD for weight, 0.57 SD for weight-for-length and 0.47 SD for head circumference. For length, PGR remained a significant predictor after correction for confounding factors like GA, BW-SDS, PVL, BPD and use of dexamethasone (mean SDS was 0.88 lower in AGA-PGR-infants compared to AGA-nonPGR-infants).

Growth parameters for the 3 groups (SGA, AGA-PGR and AGA-nonPGR) at term age and at 1 and 2 years corrected age are shown in Table 2. Compared to Dutch nation-wide reference diagrams, mean SDS for L, Lcorr, W and W/L were significantly lower in the SGA- and AGA-PGR-infants at all ages. Head circumference was only smaller in the SGA-infants at term age and at 1 year of age; at 2 years of age HC was similar to the reference group. Growth of the infants in the AGA-nonPGR-group was similar to the reference group, except for mean L-SDS at 1 and 2 years of age and the mean HC-SDS at all ages, which were larger than in the reference group. After correction for the target height, length at 2 years was close to the mean of the reference group.

Growth was significantly different in the 3 groups: $p < 0.001$ for L and W, $p = 0.002$ for Lcorr, $p = 0.003$ for W/L and 0.005 for HC. In the AGA-group the infants with PGR grew significantly worse than the infants without PGR. The SGA-infants had the lowest mean SDS for length, weight and head circumfer-

Table 2. Comparison of mean growth-SDS at different ages in SGA-, AGA-PGR- and AGA-nonPGR-infants

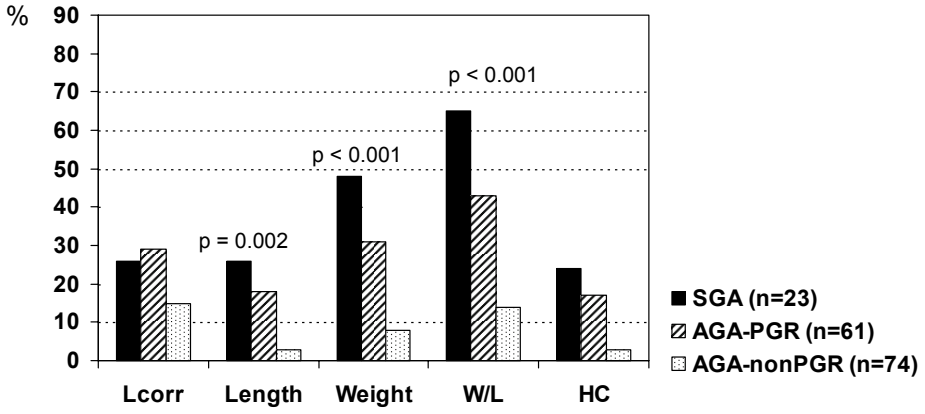
	Age (yr)	SGA (n = 23) Mean-SDS (95% CI)	AGA-PGR (n = 61) Mean-SDS (95% CI)	AGA-nonPGR (n = 74) Mean-SDS (95% CI)
Length	term	-3.38 (-3.93;-2.82)★	-2.00 (-2.22;-1.78)★	-0.04 (-0.22;0.14)
	1	-1.13 (-1.65;-0.60)★	-0.70 (-0.94;-0.46)★	0.37 (0.16;0.59)†
	2	-0.80 (-1.35;-0.25)★	-0.68 (-0.91;-0.44)★	0.29 (0.07;0.51)†
Length-corr	2	-1.03 (-1.59;-0.47)★	-0.70 (-1.08;-0.33)★	-0.11 (-0.36;0.15)
Weight	birth	-1.85 (-2.04;-1.67)★	-0.14 (-0.33;0.05)	0.34 (0.18;0.50)†
	term	-2.76 (-3.15;-2.36)★	-1.69 (-1.89;-1.48)★	0.02 (-0.15;0.19)
	1	-1.72 (-2.22;-1.23)★	-0.82 (-1.10;-0.54)★	0.06 (-0.16;0.27)
	2	-1.50 (-2.00;-1.01)★	-0.93 (-1.25;-0.62)★	-0.01 (-0.25;0.23)
Weight-for-length	1	-1.36 (-1.84;-0.87)★	-0.44 (-0.76;-0.13)★	-0.07 (-0.34;0.19)
	2	-1.51 (-1.95;-1.06)★	-0.79 (-1.13;-0.46)★	-0.22 (-0.50;0.05)
Head circumference	birth	-1.22 (-1.72;-0.72)★	1.46 (-0.36;3.28)	0.28 (0.05;0.51)†
	term	-0.85 (-1.29;-0.42)★	-0.19 (-0.41;0.03)	1.03 (0.82;1.24)†
	1	-0.61 (-1.14;-0.09)★	-0.08 (-0.36;0.19)	0.50 (0.25;0.75)†
	2	-0.40 (-0.95;0.14)	-0.09 (-0.37;0.19)	0.38 (0.13;0.64)†

★ significantly smaller than the reference group; † significantly larger than the reference group
SGA = small-for-gestational-age; AGA = appropriate-for-gestational-age; PGR = preterm growth restraint

ence at all ages. At 2 years the mean SDS for length (L), length corrected for target height (Lcorr) and head circumference (HC) were similar in SGA- and AGA-PGR-infants; W-SDS and W/L-SDS were significantly lower in the SGA-infants compared to the AGA PGR-infants, 0.57 and 0.72 SD respectively.

Figure 1 shows the percentages of the 2 year old children in the three groups, who had a growth parameter of less than -1.3 SD. Significant differences were observed for length, weight and weight-for-length.

Figure 1. Comparison of percentage of infants with growth-SDS < -1.3 (P_{10}) at the corrected age of 2 years, between SGA-infants, AGA-PGR-infants and AGA-nonPGR-infants



Lcorr = length corrected for target height; W/L = weight-for-length; HC = head circumference; SGA = small-for-gestational age; AGA = appropriate-for-gestational age; PGR = preterm growth restraint.

Discussion

In this prospective regional study of very preterm infants, 45% of the infants born AGA experienced extra-uterine growth restriction (preterm growth restraint). After 2 years, their mean length was similar to SGA born children, and significantly lower than AGA-nonPGR children and population references. Weight for age and for length of AGA-PGR children were also significantly lower than population references, but higher than of SGA born children. Head circumference was within the normal range for each group at 2 years. Growth in AGA-nonPGR children was normal for the population and for target height.

These findings support our hypothesis that preterm growth is an important predictor for growth later in childhood, and are in agreement with the similar growth patterns over a period of 19 years of preterm born children either born SGA or AGA with PGR. In that cohort a more strict definition was used of SGA and PGR (-2 SDS instead of –1.3 SDS).[8] We chose -1.3 SD because if we had used -2 SDS in our study only 5 infants (0.6%) would have been classified as SGA; 35 infants (26% of the non-SGA-infants) had a weight or length < -2 SD at term age. Our results are also compatible with those of Jordan *et al.*[2], who described significant catch-up between birth and 36 months which was greater for SGA- than for AGA-infants; in their group AGA-infants with serious neonatal pathology had lower length at term age compared to AGA-infants without serious pathology, but weight and head circumference did not differ. Recently Casey *et al.*[14] published a study in which very-low-birth-weight infants who developed postnatal growth problems demonstrated lower physical size at 8 years of age compared to infants with adequate postnatal growth.

Suboptimal growth of preterm babies is observed in multiple studies. Clark *et al.* described the incidence of extra-uterine growth retardation (defined as growth < P10 at the moment of discharge from the hospital) in a large cohort infants born between 23 and 34 weeks' gestation to be 28%, 34% and 16% for weight, length and head circumference, respectively.[15] In our study these numbers were 23%, 12% and 10% for the whole group but 31%, 18% and 17% for the AGA-PGR-group. Recently the National Institute of Child and Human Development (NICHD) Neonatal Research Network reported that 97% of infants with a birth weight < 1500 grams at 36 weeks post conceptional age had weights less than the 10th percentile and they conclude that optimising nutritional support of these very preterm infants remains a challenge.[16] Clark *et al.* found male

gender, need for respiratory support and exposure to steroids to be associated with extra-uterine growth retardation.[15] We also found RDS and use of postnatal dexamethasone to be associated with PGR, but in our study female gender was associated with PGR.

The decrease in L-SDS, W-SDS and HC-SDS between birth and term age in the AGA-PGR-infants is probably mainly due to significant morbidity in the neonatal period. Indeed, RDS, PDA and BPD occurred more often in the AGA-PGR-group; furthermore these infants received more often postnatal dexamethasone which is also described to have a negative influence on growth.[17] Nowadays however this drug is used much less in neonates.[18] Ehrenkranz *et al*.[19] also reported that preterm infants who survived without developing BPD, severe intraventricular haemorrhage or necrotising enterocolitis, gained weight faster than comparable infants with those morbidities. In our study, it is not clear whether the differences in neurological performance, MDI and PDI at 2 years between the AGA-PGR- and AGA-nonPGR-children, are the result of more significant neonatal morbidities or poorer catch-up growth in the AGA-PGR-children.

In this study data on growth were missing from 36 infants (18%). However, the study group and the lost-to-follow-up group did only differ in socio-economic status and race, and because we found no association between growth and these two parameters, it is not likely that including these infants would have made the results different.

We have now shown evidence, that a proper early postnatal growth is also a good predictor of normal growth in early childhood. However, it was recently suggested that rapid catch-up growth of preterm infants may also have long-term effects that may be harmful, such as the development of insulin resistance[20], particularly if body mass index SDS increases during childhood and adolescence. However, the respective roles of environmental and genetic factors in the development of insulin resistance is still unknown.[21;22]

In conclusion, preterm infants born AGA who grow poorly up to term age, show sub-optimal growth at 2 years of age, similarly to preterm infants born SGA. After correction for confounders the effect of sub-optimal early growth remains. Weight of AGA-PGR infants at 2 years is also low, but not as low as of SGA-infants.

"What is already known on this topic"

- Growth in preterm infants is usually impaired
- Several risk factors can be pointed out for this impaired growth, like bronchopulmonary dysplasia and use of postnatal corticosteroids

"What this study adds"

- Preterm infants who suffer from preterm growth restraint (extra-uterine growth retardation), display similar growth as preterm infants who experience intra-uterine growth retardation
- Preterm growth restraint is an important predictor for sub-optimal growth at 2 years of age

References

1. Gortner L, van Husen M, Thyen U, Gembruch U, Friedrich HJ, Landmann E. Outcome in preterm small for gestational age infants compared to appropriate for gestational age preterms at the age of 2 years: a prospective study. Eur J Obstet Gynecol Reprod Biol 2003;110 Suppl 1: S93-S97.
2. Jordan IM, Robert A, Francart J, Sann L, Putet G. Growth in extremely low birth weight infants up to three years. Biol Neonate 2005;88:57-65.
3. Morris BH, Smith KE, Swank PR, Denson SE, Landry SH. Patterns of physical and neurologic development in preterm children. J Perinatol 2002;22:31-6.
4. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. Arch.Dis. Child Fetal Neonatal Ed 2003;88:F492-F500.
5. Wang D, Vandermeulen J, Atkinson SA. Early life factors predict abnormal growth and bone accretion at prepuberty in former premature infants with/without neonatal dexamethasone exposure. Pediatr Res 2007;61:111-6.
6. van Wassenaer A. Neurodevelopmental consequences of being born SGA. Pediatr Endocrinol Rev 2005;2:372-7.
7. Wit JM, Finken MJJ, Rijken M, de Zegher F. Preterm Growth Restraint: A Paradigm That Unifies Intrauterine Growth Retardation and Preterm Extrauterine Growth Retardation and Has Implications for the Small-for-Gestational-Age Indication in Growth Hormone Therapy. Pediatrics 2006;117:e793-e795.
8. Finken MJJ, Dekker FW, de Zegher F, Wit JM, for the Dutch Project on Preterm and Small-for-Gestational-Age-. Long-term Height Gain of Prematurely Born Children With Neonatal Growth Restraint: Parallellism With the Growth Pattern of Short Children Born Small for Gestational Age. Pediatrics 2006;118:640-3.
9. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? Semin Perinatol 2003;27:302-10.

10. Rijken M, Wit JM, Le Cessie S, Veen S. The effect of perinatal risk factors on growth in very preterm infants at 2 years of age: The Leiden Follow-Up Project on Prematurity. Early Hum Dev. 2007; 83:527-34.
11. Stoelhorst GMSJ, Rijken M, Martens SE, Brand R, den Ouden AL, Wit JM *et al*. Changes in Neonatology: Comparison of Two Cohorts of Very Preterm Infants (Gestational Age <32 Weeks): The Project on Preterm and Small for Gestational Age Infants 1983 and The Leiden Follow-Up Project on Prematurity 1996-1997. Pediatrics 2005;115:396-405.
12. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand 1991;80:756-62.
13. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E *et al*. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res 2000;47: 316-23.
14. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics 2006;118:1078-86.
15. Clark RH, Thomas P, Peabody J. Extrauterine Growth Restriction Remains a Serious Problem in Prematurely Born Neonates. Pediatrics 2003;111:986-90.
16. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ *et al*. Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 Through December 1996. Pediatrics 2001;107:e1.
17. Weiler HA, Paes B, Shah JK, Atkinson SA. Longitudinal assessment of growth and bone mineral accretion in prematurely born infants treated for chronic lung disease with dexamethasone. Early Hum Dev 1997;47:271-86.
18. Shinwell ES, Karplus M, Bader D, Dollberg S, Gur I, Weintraub Z *et al*. Neonatologists are using much less dexamethasone. Arch Dis Child Fetal Neonatal Ed 2003;88:F432-F433.
19. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL *et al*. Longitudinal Growth of Hospitalized Very Low Birth Weight Infants Pediatrics 1999;104:280-9.
20. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089-97.
21. Finken MJ, Keijzer-Veen MG, Dekker FW, Frolich M, Hille ET, Romijn JA *et al*. Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life Insulin resistance 19 years after preterm birth. Diabetologia 2006;49:478-85.
22. Ingelfinger JR. Prematurity and the legacy of intrauterine stress. N Engl J Med 2007;356:2093-5.

CHAPTER 6

Is hypotension a major risk factor for neurological morbidity at term age in very preterm infants?

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Early Human Development 2003; 75: 79-89

Abstract

Objective: To investigate the influence of perinatal risk factors, especially hypotension, on neuromotor status at term in surviving preterm infants born before 32 weeks of gestation.

Methods: This study is part of the Leiden Follow-Up Project on Prematurity: a prospective, regional study of 266 live born infants with a gestational age < 32 weeks born in 1996 – 1997. Twenty-eight infants died before term age. Two hundred and eleven infants were examined neurologically at term according to Prechtl. The findings were classified as normal (N), mildly abnormal (MA) or definitely abnormal (DA). Hypotension was defined as a mean arterial blood pressure < 30 mmHg on at least two occasions.

Results: One hundred and six (50%) infants were classified as neurologically N, 92 (44%) infants were classified as MA and 13 (6%) infants as DA. Hypotension, bronchopulmonary dysplasia, flaring and cystic periventricular leucomalacia were risk factors for neurological morbidity. Of the 68 infants with hypotension 33 (49%) were classified as MA and 7 (10%) as DA. Of the 141 infants without hypotension 58 (41%) were MA, and 5 (4%) were DA. The odds ratio of hypotension for neurological morbidity was 1.9 (95% CI 1.06 - 3.40), adjusted for gestational age, birth weight, small for gestational age and gender it was 1.96 (95% CI 1.02 - 3.77). The adjusted odds ratio of PVL was 18.6 (4.4 - 78.5), of flaring was 2.37 (1.18 - 4.74) and of BPD was 2.44 (1.08 - 5.5).

Conclusions: Apart from gestational age, periventricular leucomalacia, and bronchopulmonary dysplasia, hypotension in preterm infants is a major risk factor for neurological morbidity at term.

Introduction

Preterm birth is associated with an increased risk of neurological disorders[1;2], including cerebral palsy[3] and mental retardation[4;5], learning difficulties[6-8] and behavioural problems.[9] Due to major recent advances in neonatal intensive care, approximately 85% of preterm infants < 31 weeks gestational age (GA) now survives.[10] The purpose of the present study is to investigate the influence of perinatal risk factors on neurological condition at term.

Hypoxic-ischemic brain events and intracranial haemorrhages in the perinatal period are common complications associated with the development of cerebral palsy in preterm infants.[11] Disturbances of blood pressure play an important role in the pathogenesis of these intracranial lesions.[12-14] Previous studies in preterm infants < 31 weeks have shown a significant association between a mean arterial blood pressure (MABP) < 30 mmHg and severe cerebral haemorrhage or ischemia or death within 48 hours.[15;16]

This study addressed the question if hypotension, defined as a MABP < 30 mmHg irrespective of GA, affects neurological morbidity at term age in very preterm infants. Neurological morbidity at term was chosen as an outcome parameter because (a) it evaluates the functional status of the nervous system, (b) it is known to be a significant predictor of major and minor neurological dysfunction at school-age[17], and (c) in contrast to functional evaluations at older age, it has the advantage of the absence of interference with environmental factors and later occurring illnesses. Additional questions were: (a) does hypotension have a greater impact on immature infants (GA < 27 wks) than on more mature (GA ≥ 27 wks) ones, because of the higher vulnerability to cerebral haemorrhage and ischemia of more immature infants and (b) can other adverse neonatal events, possibly leading to hypotension, predict adverse neurological outcome equally well as hypotension, or is hypotension by itself the better predictor of the neurological condition.[18-20]

Patients and methods

Patients

The present study is part of the Leiden Follow-Up Project on Prematurity (LFUPP), which is a geographically defined collaborative follow-up study of preterm infants in the Dutch health regions The Hague, Leiden and Delft. Two hundred and sixty-six live born infants born between January 1996 and January 1998 with a GA < 32 weeks were included. The mean age at birth was 29.2 weeks (range of 23.4 – 31.6 wks), the mean BW was 1250 gram (SD 383 g). One hundred and sixty-three (61%) infants were born in a university centre and immediately admitted to a neonatal intensive care unit (NICU), 103 (39%) infants were delivered in centres without a NICU. These neonates were either transported to a NICU or stayed in a regional hospital, depending on whether or not they needed intensive care. The in-hospital mortality rate was 11% (29 of the 266 children died; 28 before term age, one after term age). From the remaining 237 children 211 were included in this analysis. These infants all had a detailed and age-specific neurological examination according to Prechtl.[21] Twenty-six infants were not examined according to Prechtl. They were excluded from the present analysis because we were of the opinion that a standard clinical neurological examination would overlook mild neurological findings. These 26 infants as a group did not differ in mean GA, mean BW, gender, PVL, BPD and SGA from the 211 infants included into the analysis. There was, however a significant difference in the percentage who suffered from hypotension; 33 % in the study group versus 12 % in the group of the 26 excluded infants (Chi-Square Test, $p < 0.035$). A detailed dataset of antenatal and perinatal factors was collected including mother's health, socio-economic status, pregnancy induction, disease and medication during pregnancy, reliability of GA, birth weight (BW), Apgar scores, cardiovascular and respiratory complications, neurological abnormalities and cerebral ultrasound findings.

Definitions

Cerebral ultrasound scans were performed as part of the clinical work-up. For study purposes an ultrasound scan was made in all infants at term. The ultrasound scans were performed through the anterior fontanel using an Ultramark 4-sector scanner with multifrequency head (5 or 7.5 MHz). Haemorrhages were graded according to Papile *et al.*[22] Flaring was defined as areas of increased echogenicity

in the periventricular region distinct from the ventricles. Periventricular leucomalacia (PVL) was defined as parenchymal lesions of increased echogenicity in the periventricular region distinct from the ventricles, which were replaced by cystic areas. Hypotension: MABP < 30 mmHg on at least two occasions, measured intra-arterially (umbilical) in 43% of the infants and/or with the oscillometric technique (Dinamap monitor, Critikon, Inc., Tampa, Fla.). Small for gestational age (SGA): birth weight < P10.[23] Patent ductus arteriosus: a clinical diagnosis confirmed by cardiac ultrasonography. Bronchopulmonary dysplasia (BPD): oxygen need at 36 weeks postconceptional age.[24] Sepsis: a clinical diagnosis confirmed by positive blood cultures.

Neurological examination

The remaining 211 infants were examined according to Prechtl by specially trained paediatricians. These infants were the subjects of the present paper. The neurological findings were classified as normal (N), mildly abnormal (MA), or definitely abnormal (DA). Definitely abnormal means the presence of a full-blown neonatal neurological syndrome, such as apathy or hyperexcitability, hypotonia or hypertonia, hypokinesia or hyperkinesia, or a hemi syndrome. Mildly abnormal denotes the presence of only part of such a syndrome. Examples of minor neurological signs are an abnormal posture, abnormal head control, frequently occurring tremors or startles and absent or abnormal responses or reflexes.[25]

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center. Parental informed consent was obtained.

Statistical analysis

The X^2 – test and the Student's *t* - test were used for univariate analyses, Fisher's exact test was used where appropriate. Correction for confounding variables was done with ordinal logistic regression analysis contrasting normal with mildly and definitely abnormal infants, using GA, BW, gender, SGA, BPD and PVL as confounders. P-values < 0.05 were considered significant.

Results

At term 106 (50%) of the 211 infants were classified as neurologically N, 92 (44%) infants as MA and 13 (6%) as DA. The risk factors for neurological morbidity at term age are summarised in Table 1. Infants born before 27 weeks of gestation showed more a DA outcome than infants born after 27 weeks of gestation (15% versus 5%) although the difference did not reach statistical significance ($p = 0.133$). Infants below 1250 grams at birth were more often categorised as neurologically MA and DA infants ($p = 0.02$). Also infants born SGA ($n = 28$) had a higher risk for neurological morbidity than the 182 AGA infants. Additional factors associated with neonatal neurological morbidity were flaring, PVL, BPD, diuretics, dexamethasone postnatal given and hypotension in the neonatal period. For example, of the 68 infants with hypotension 33 (49%) were classified as MA and 7 (10%) as DA, whereas in the group of 141 infants without hypotension 58 (41%) were MA and 5 (4%) were DA (Table 1, Fig. 1). Of two children the blood pressure variables were not available.

Gender, prolonged rupture of membranes, sepsis, meningitis, respiratory distress syndrome (RDS), pneumothorax, pneumonia, prolonged mechanical venti-

Figure 1. Distribution of neurological morbidity at term in infants with and without hypotension

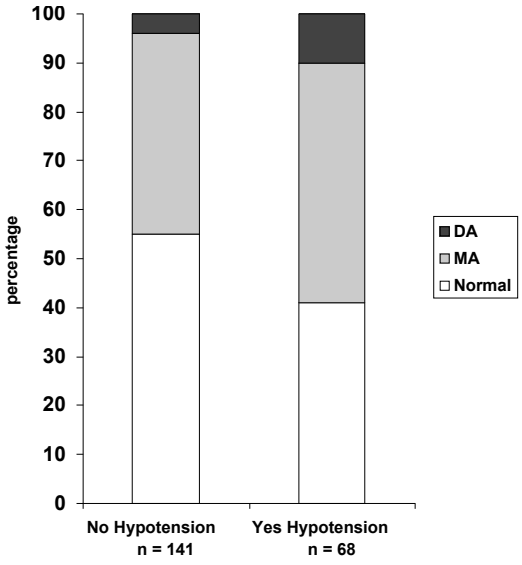

Table 1. Risk factors for neurological morbidity at term

	Neurological classification			
	Normal (n=106)	**Mildly Abnormal (n=92)**	**Definitely Abnormal (n=13)**	**P⋆**
GA, mean in wks (sd)	29.5 (1.9)	29.6 (1.9)	28.4 (2.1)	0.103
< 27 weeks n (%)	12 (44)	11 (41)	4 (15)	0.133
≥ 27 weeks n (%)	94 (51)	81 (44)	9 (5)	
Gender				
Female n (%)	50 (55)	36 (40)	5 (5)	0.49
Male n (%)	56 (47)	56 (46)	8 (7)	
BW, mean in gr (sd)	1332 (362)	1255 (364)	1101 (417)	0.062
< 1250 gr n (%)	43 (42)	50 (48)	10 (10)	0.020
≥ 1250 gr n (%)	62 (58)	42 (39)	3 (3)	
SGA n (%)	7 (25)	17 (61)	4 (14)	0.008
AGA n (%)	98 (54)	75 (41)	9 (5)	
Hypotension				
Yes n (%)	28 (41)	33 (49)	7 (10)	0.049
No n (%)	78 (55)	58 (41)	5 (4)	
IVH				
Grade 3 or 4 n (%)	5 (42)	5 (42)	2 (16)	0.305
Grade 1 or 2 n (%)	18 (50)	14 (39)	4 (11)	
No n (%)	80 (50)	72 (45)	7 (4)	
Flaring:Yes n (%)	16 (37)	21 (49)	6 (14)	0.025
No n (%)	89 (54)	70 (42)	7 (4)	
PVL				
Yes n (%)		3 (43)	4 (57)	< 0.001
No n (%)	105 (52)	87 (43)	9 (5)	
O_2 at 28 days				
Yes n (%)	23 (42)	26 (47)	6 (11)	0.145
No n (%)	81 (53)	64 (42)	7 (5)	
BPD				
Yes n (%)	14 (33)	24 (56)	5 (12)	0.005
No n (%)	91 (55)	66 (40)	8 (5)	
Diuretics**				
Yes n (%)	17 (37)	23 (50)	6 (13)	0.028
No n (%)	89 (54)	69 (42)	7 (4)	
Dexamethasone**				
Yes n (%)	12 (35)	17 (50)	5 (15)	0.030
No n (%)	94 (53)	74 (42)	8 (5)	
Bilirubin, mean in mmol/l(sd)	193 (41)	195 (39)	199 (45)	0.9

GA = gestational age; BW = birth weight; SGA = small for gestational age; IVH = intraventricular haemorrhage; PVL = cystic periventricular leucomalacia; BPD = bronchopulmonary dysplasia;
**Diuretics, Dexamethasone were given postnatal.
⋆ P-value of one-way ANOVA, or Fisher's exact test, where appropriate.

lation, surfactant therapy, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage (IVH) and post haemorrhagic ventricular dilatation were not related to the neurological condition at term.

Table 2 summarises the raw odd ratios of the risk factors mentioned above and the odd ratio's adjusted for GA, BW, SGA and gender. After correction for the latter confounders, hypotension, PVL, flaring and BPD remained associated with neurological dysfunction at term. PVL was the most important factor. Adjusted for PVL, the odds ratio of hypotension was slightly smaller (OR = 1.87, 95% CI 0.94 -3.71, p = 0.07).

To increase our understanding of the role of hypotension, the characteristics of infants (and their mothers) with or without hypotension were compared (Table 3). This table presents available data of all the surviving infants. There were no significant differences between the two groups with respect to mater-

Table 2. Raw and adjusted Odds ratio's of risk factors for neurological morbidity at term age

		Adjusted for GA, BW, Gender, SGA
	Raw OR (95% CI)	**OR (95% CI)**
Gestational Age (wks) <27 wks	0.96 (0.83-1.10) 1.56 (0.70-3.48)	- -
Male gender	1.38 (0.80-2.37)	-
Birth weight (gr.) < 1250 gr	0.99 (0.99-1.00) 2.05 (1.19-3.53)	
SGA	3.41 (1.50-7.74)	
O_2 need at 28 days	1.70 (0.92-3.15)	1.49 (0.67-3.33)
BPD	2.60 (1.30-5.03)	2.44 (1.08-5.51)
IVH grade 3 and 4	13.87 (4.15-46.43)	1.53 (0.44-5.28)
PVL	20.1 (5.03-80.24)	18.60 (4.40-78.50)
Flaring	2.20 (1.13-4.32)	2.37 (1.18-4.74)
Hypotension	1.90 (1.06-3.40)	1.96 (1.02-3.77)
Diuretics	2.20 (1.10-4.20)	2.00 (0.93-4.31)
Dexamethasone*	2.37 (1.13-4.96)	2.36 (0.98-5.67)
Bilirubine	1.00 (0.99-1.00)	1.00 (0.99-1.01)

OR = odds ratio; GA = gestational age; SGA = small for gestational age; BPD = bronchopulmonary dysplasia; IVH = intra ventricular haemorrhage; PVL = cystic periventricular leucomalacia,
*Dexamethasone postnatal given.

nal and obstetrical complications like pre-eclampsia and intra-uterine growth retardation. Moreover, the use of anti-hypertensive medication in the mother was not associated with hypotension in the newborn. Substantial differences in neonatal morbidity were found. Infants with hypotension were of lower GA and BW than those without hypotension. In addition, the presence of hypotension was associated with RDS, oxygen need at 28 days, BPD, PVL, PDA, diuretics and postnatal treatment with dexamethasone and lower Apgar scores at both 5 and 10 minutes. Infants with hypotension did not have more IVH ($p = 0.13$). Infants with hypotension were more often of a multiple pregnancy, they were less often transported postnatal, they were less often born by caesarean section and the mothers of hypotensive infants were more often treated with Indomethacine medication before delivery. Except for postnatal transport, which is known to have a negative influence on outcome[26], none of these factors was significantly related to neurological morbidity at term.

Finally, we saw no difference in neurological outcome at term between the infants born with a GA < 27 weeks (MA + DA = 14 (61%)) having hypotension and the infants with hypotension and born with a GA ≥ 27 wks (MA + DA = 26 (58%)). This suggests that the more immature infants were not more susceptible to the adverse effect of hypotension.

Table 3. Characteristics of infants with and without hypotension

	HYPOTENSION		P*
	No N=163 (%)	Yes N=70 (%)	
INFANT			
Gestational Age <27 weeks	8 (5)	22 (31)	<0.001
Male Gender	96 (59)	37 (53)	0.47
Birth weight <1250 gr	66 (41)	47 (67)	<0.001
SGA	22 (14)	9 (13)	0.99
Apgar-score: 5 min.	8.0 (1.5)	7.5 (1.9)	0.02
10 min.	9.1 (1.1)	8.7 (1.5)	0.03
IVH	4 (3)	5 (8)	0.13
PVL	1 (1)	6 (9)	0.004
Flaring	31 (19)	21 (30)	0.09
RDS	79 (50)	52 (74)	<0.001
O_2 need at 28 days	27 (17)	37 (54)	<0.001
BPD	21 (13)	26 (38)	<0.001
Diuretics	21 (13)	25 (36)	<0.001
Postnatal Dexamethasone	13 (8)	22 (31)	<0.001
Patent ductus arteriosus	31 (19)	27 (39)	0.002
Meningitis	4 (3)	2 (3)	0.99
NEC	13 (8)	7 (10)	0.80
Sepsis (clin symptoms or positive blood culture)	131 (78)	54 (89)	0.06
Inotropics	3 (2)	49 (70)	<0.001
MOTHER:			
Pre-eclampsia	19 (12)	3 (4)	0.07
Indocid treatment	16 (10)	23 (33)	<0.001
Anti-hypertensive treatment	32 (21)	8 (12)	0.7
Antenatal Glucocorticosteroids	114 (74)	52 (80)	0.4
PROM	48 (30)	17 (25)	0.52
Caesarean Section	75 (46)	21 (30)	0.03
Multiple birth	46 (28)	29 (41)	0.07
Transport	64 (40)	13 (9)	0.002
SES	3.6 (1.3)	4.4 (1.3)	<0.001
Age	30.3 (4.7)	31.1 (4.6)	0.22
Smoking during pregnancy	18 (13)	12 (18)	0.41

* P-value of Student's t-test, or Fisher's exact test, where appropriate.
SGA = small for gestational age; IVH = intraventricular haemorrhage; PVL = cystic periventricular leucomalacia; BPD = bronchopulmonary dysplasia; RDS = respiratory distress syndrome; NEC = necrotising enterocolitis; PROM = prolonged rupture of membranes; SES = socio-economic status.

Discussion

Our primary goal was to analyse the influence of perinatal risk factors on neurological morbidity at term. We found that infants who had a mean arterial blood pressure of < 30 mmHg more often showed neurological dysfunction at term than infants without hypotension. After adjustment for gestational age, birth weight, gender and SGA this association remained significant. We chose a MABP of less than 30 mmHg as definition of hypotension in line with other authors who pointed out the relevance of this cut-off point in premature infants < 31 weeks of GA.[15]

Several explanations for the association between hypotension and neurological morbidity can be delineated.

First, fluctuating patterns of cerebral blood flow (CBF) velocity can induce intraventricular haemorrhage.[14;27;28] In addition, sustained hypotension plays an important role in the pathogenesis of intracranial lesions.[15] In our study group, hypotension was clearly related to neurological morbidity at term. This neurological morbidity could not be attributed to IVH caused by hypotension, since IVH was not related to hypotension (Table 3). The relation between hypotension and PVL could explain only part of neonatal neurological morbidity. This implies that another part of neurological morbidity related to hypotension escapes the ultrasonic eye.[29]

Second, increased neurological morbidity in the hypotensive infants might have been due to disorders causing the hypotension. No association was found between hypotension and sepsis or prolonged rupture of membranes. However, the infants with hypotension had a lower GA and birth weight and more respiratory problems. Theoretically, changes in intrathoracic pressure associated with removal of spontaneous breathing effort may decrease venous return and cardiac output; these in turn may lead to hypotension if ventilator settings are not appropriately adjusted, particularly in the presence of hypovolemia.[30] These findings reinforce the concept that the overall condition of the infant and particularly RDS is an important determinant of cerebral pathology.[16] Furthermore, infants who developed hypotension had lower Apgar scores than those without hypotension. This illustrates the entanglement of risk factors, and reminds us of the danger of pinpointing only one factor as the major risk factor.

Third, the association between hypotension and neonatal neurological morbidity may have been induced by the treatment of the hypotension. The majority of

infants were treated with dopamine, some were treated with volume expansion only. Various studies have suggested that dopamine treatment may put preterm infants at risk for IVH and/or PVL, since they may have an increased responsiveness to the hemodynamic actions of dopamine and an inadequate auto regulation of CBF.[31-33]

This study showed no difference in neurological outcome at term comparing the more immature infants (GA < 27 wks) with the more mature ones. Especially, the younger infants were not more often categorised as MA than the older ones. Nevertheless they were somewhat more often classified as DA (15% versus 5%). Summarising, we found that hypotension in very preterm infants is associated with an increased neurological morbidity at term. At this point of time it is not clear whether this association persists with advancing age. We do know however, that neurological morbidity at term is a substantial risk factor for neurological dysfunction, behavioural and learning problems at school age.[17;34] Long-term follow-up is planned to study this correlation at school age.

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References

1. Finnstrom O, Olausson PO, Sedin G, Serenius F, Svenningsen N, Thiringer K *et al*. Neurosensory outcome and growth at three years in extremely low birthweight infants: Follow-up results from the Swedish national prospective study. Acta Paediatr 1998;87:1055-60.
2. Volpe JJ. Neurologic outcome of prematurity. Arch Neurol 1998;55:297-300.
3. Cooke RWI. Trends in incidence of cranial ultrasound lesions and cerebral palsy in very low birthweight infants 1982-93. Arch Dis Child Fetal Neonatal Ed 1999;80:F115-F117.
4. McCarton CM, Wallace IF, Divon M, Vaughan HG, Jr. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. Pediatrics 1996;98:1167-78.
5. Saigal S, Szatmari P, Rosenbaum P, Campbell D, King S. Intellectual and functional status at school entry of children who weighed 1000 grams or less at birth: a regional perspective of births in the 1980s. J Pediatr 1990;116:409-16.

6. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Hum Dev 1999;53:193-218.
7. Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. Br J Obstet Gynaecol 1998;105:162-8.
8. Saigal S, Szatmari P, Rosenbaum P, Campbell D, King S. Cognitive abilities and school performance of extremely low birth weight children and matched term control children at age 8 years: a regional study. J Pediatr 1991;118:751-60.
9. Stevenson CJ, Blackburn P, Pharoah PO. Longitudinal study of behaviour disorders in low birthweight infants. Arch.Dis.Child Fetal Neonatal Ed 1999;81:F5-F9.
10. Gross SJ, Slagle TA, D'Eugenio DB, Mettelman BB. Impact of a matched term control group on interpretation of developmental performance in preterm infants. Pediatrics 1992;90:681-7.
11. Volpe JJ. Brain injury in the premature infant. Neuropathology, clinical aspects, pathogenesis, and prevention. Clin Perinatol 1997;24:567-87.
12. Calvert SA, Hoskins EM, Fong KW, Forsyth SC. Periventricular leukomalacia: ultrasonic diagnosis and neurological outcome. Acta Paediatr Scand. 1986;75:489-96.
13. Calvert SA, Ohlsson A, Hosking MC, Erskine L, Fong K, Shennan AT. Serial measurements of cerebral blood flow velocity in preterm infants during the first 72 hours of life. Acta Paediatr Scand 1988;77:625-31.
14. van Bel F, Van de Bor M, Stijnen T, Baan J, Ruys JH. Aetiological role of cerebral blood-flow alterations in development and extension of peri-intraventricular haemorrhage. Dev Med Child Neurol 1987;29:601-14.
15. Miall-Allen VM, de Vries LS, Whitelaw AG. Mean arterial blood pressure and neonatal cerebral lesions. Arch Dis Child 1987;62:1068-9.
16. Miall-Allen VM, de Vries LS, Dubowitz LM, Whitelaw AG. Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks' gestation. Pediatrics 1989;83:657-61.
17. Hadders-Algra M, Huisjes HJ, Touwen BC. Perinatal correlates of major and minor neurological dysfunction at school age: a multivariate analysis. Dev Med Child Neurol. 1988;30:472-81.
18. Pharoah PO, Cooke T, Cooke RW, Rosenbloom L. Birthweight specific trends in cerebral palsy. Arch Dis Child 1990;65:602-6.
19. Sinha SK, D'Souza SW, Rivlin E, Chiswick ML. Ischaemic brain lesions diagnosed at birth in preterm infants: clinical events and developmental outcome. Arch Dis Child 1990;65:1017-20.
20. Watkins AM, West CR, Cooke RW. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. Early Hum.Dev. 1989;19:103-10.
21. Prechtl HF. The neurological examination of the fullterm newborn infant. Clin Dev Med 63. London, Heinemann.1977.
22. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
23. Kloosterman GJ. On uterine growth. The significance of prenatal care. Int J Gynecol Obstet 1970;8:895-912.
24. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
25. Jurgens-van der Zee AD, Bierman-van Eendenburg ME, Fidler VJ, Olinga AA, Visch JH, Touwen BC *et al*. Preterm birth, growth retardation and acidemia in relation to neurological abnormality of the newborn. Early Hum Dev 1979;3:141-54.

26. Verloove-Vanhorick SP,Verwey RA, Ebeling MC, Brand R, Ruys JH. Mortality in very preterm and very low birth weight infants according to place of birth and level of care: results of a national collaborative survey of preterm and very low birth weight infants in The Netherlands. Pediatrics 1988;81:404-11.
27. Perlman JM, McMenamin JB,Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage. N Engl J Med 1983;309:204-9.
28. Perlman JM, Goodman S, Kreusser KL,Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. N Engl J Med 1985;312:1353-7.
29. Mallard JR. A brief personal account of the Aberdeen story--with particular reference to SPECT and MRI. J Med Eng Technol 1993;17:176-9.
30. Miall-Allen VM,. Whitelaw AG. Effect of pancuronium and pethidine on heart rate and blood pressure in ventilated infants. Arch Dis Child 1987;62:1179-80.
31. Jorch G, Jorch N. Failure of autoregulation of cerebral blood flow in neonates studied by pulsed Doppler ultrasound of the internal carotid artery. Eur J Pediatr 1987;146:468-72.
32. Seri I, Rudas G, Bors Z, Kanyicska B, Tulassay T. Effects of low-dose dopamine infusion on cardiovascular and renal functions, cerebral blood flow, and plasma catecholamine levels in sick preterm neonates. Pediatr Res 1993;34:742-9.
33. Van de Bor M,Walther FJ. Cerebral blood flow velocity regulation in preterm infants. BiolNeonate 1991;59:329-35.
34. Hadders-Algra M, Huisjes HJ, Touwen BC. Perinatal risk factors and minor neurological dysfunction: significance for behaviour and school achievement at nine years. Dev Med Child Neurol. 1988;30:482-91.

CHAPTER 7

Respiratory and neurodevelopmental outcome at 2 years of age in very preterm infants with bronchopulmonary dysplasia: the Leiden Follow-Up Project on Prematurity

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Submitted

Abstract

The objective of this study was to describe the incidence of bronchopulmonary dysplasia (BPD) in a regional, prospective study of live born infants < 32 weeks gestational age (GA), born in 1996/1997 in the Netherlands. Furthermore we wanted to analyse associations between BPD and respiratory but also neurodevelopmental outcome at 2 years of age. BPD was defined as supplemental oxygen at 36 weeks postmenstrual age (PMA). At 2 years of age, a neurodevelopmental examination and a psychological examination (Bayley Scales of Infant Development) was performed. At 36 weeks PMA, 49 infants (21% of the survivors at that time, 18.5% of all live born infants) had BPD. Respiratory problems were the cause of death in 50%. Infants with BPD had lower GA and birth weight compared to infants without BPD (27.5 vs. 30 weeks, 948 vs. 1378 grams). At 2 years of age BPD-children had more respiratory problems and used more lung medication than children without BPD. The mean MDI and PDI were lower in BPD-children compared to children without BPD (88 and 87 compared to 101 and 99). Eighty percent of the children without BPD had a normal neurological examination compared to 38% of the children with BPD. Results remained the same when infants with severe cerebral problems were excluded.

Conclusion: About 20% of very preterm infants < 32 weeks suffered from BPD**.** Preterm infants with BPD had more pulmonary problems and showed more abnormal neurodevelopmental outcome at 2 years of age compared to preterm infants without BPD.

Introduction

Bronchopulmonary dysplasia (BPD) was originally described by Northway[1] in 1967 and was defined in preterm infants as chronic respiratory failure in combination with characteristic pulmonary radiographic changes after prolonged mechanical ventilation. In 1979 Bancalari defined BPD as a continued oxygen dependency during the first 28 days plus compatible clinical and radiographic changes.[2] In 1988 it has been proposed to use the need for supplemental oxygen at 36 weeks postmenstrual age (PMA) as a better criterion for BPD.[3] The latest definition dates from 2000, when the National Institute of Health in the USA organised a workshop to come up with a definition of BPD based on severity.[4;5] These changes in definitions originate from a transforming pattern (clinically as well as radiologically) of presentation of BPD. In the past, severe BPD ("classic BPD") was seen in premature infants who received aggressive ventilation and had a prolonged exposure to high inspired oxygen concentrations. Atelectasis and fibrosis were seen as a result from mechanical injury. The "new" BPD is thought to be a result of an arrest in lung development for which various factors might be responsible: exposure of the immature lung to gas breathing, volutrauma, oxygen toxicity, inflammatory processes due to ante- or postnatal infections, exposure of immature pulmonary vasculature to increased flow through a persistent ductus arteriosus (PDA) and other hormonal and nutritional factors.[2]

Another reason for refining the definition of BPD was to be able to improve the prediction for long-term outcome in premature infants. Although analyses of associations between outcome and BPD is complicated by coexisting morbidities, most authors find more developmental problems at later ages in infants with BPD compared to infants without BPD.[6;7] Ehrenkranz *et al*. found an increase in adverse neurodevelopmental outcome as the severity of BPD, identified by the latest NIH consensus, worsened.[8] More hospitalisation and more pulmonary problems at later ages are also described.[5;9]

The purpose of the present prospective regional study was to analyse associations between BPD and perinatal risk factors like respiratory distress syndrome (RDS), PDA and duration of mechanical ventilation. At the corrected age of 2 years respiratory problems and neurodevelopmental outcome were analysed and related to BPD.

Patients and methods

The Leiden Follow-Up Project on Prematurity, 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). Details about the LFUPP-cohort are described previously.[10]

Data collection

Antenatal and perinatal data were collected including diseases of the mother, socio-economic status (SES), diseases and medication like antenatal steroids during pregnancy, gestational age, birth weight, Apgar score and data about perinatal morbidity and medication. Severity of respiratory distress syndrome (RDS), incidence of patent ductus arteriosus (PDA) and use of surfactant were registrated. Bronchopulmonary dysplasia (BPD) was defined as need of oxygen at 36 weeks postmenstrual age (PMA), but need of oxygen at 28 days was also noted. Dexamethasone was given in 1996/1997 in an initial dose of 0.5 mg/kg/day, tapered over 42 days to 0.1 mg/kg/day. 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 considered to be normal when there was no neurological 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 Medical Ethics Committee of the LUMC approved the study and informed consent of the parents was obtained.

Follow-up

Children were assessed at two years of age (corrected for prematurity) by 4 neonatologists experienced in developmental assessment. The examination included a general examination and a neurological examination according to Hempel, focused on major as well as minor neurological dysfunctions.[11] The children were considered definitely abnormal (DA) in case of definite neurological dysfunction, mildly abnormal (MA) in the presence of mild deviations in muscle tone regulation, reflexes, fine or gross motor performance, or normal (N). Parents were asked if their children suffered from pulmonary problems and if so, if they used inhaled or systemic medication. For this purpose, a recommend selection of questions according to de Boer *et al.* was used, adapted from

two childhood respiratory symptom questionnaires, developed by the American Thoracic Society and the World Health Organisation.[12;13]

Mental and psychomotor development was assessed by a developmental psychologist using the Dutch version of the Bayley-Scales of Infant Development I (BSID I). 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) ≥ 84 (≥ -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).

At two years of age behaviour was assessed using Achenbach's Child Behavior Checklist for 2-3 year old children, completed by the parents. According to this list, behaviour could be assessed by using a total problem score: a score above the 90th centile was defined as clinically abnormal, a score from the 85th through the 90th percentile as borderline clinical; below the 85th percentile as normal.

Statistics

SPSS 11 for Windows was used for statistical analyses. Fischer's Exact test and X^2–test were used to evaluate associations in a 2x2 table. The two-sample *t* test was used for comparison of continuous variables. The independent samples *t* test was used to compare means between the infants with or without BPD. We calculated the correlations between outcome at 2 years and BPD with dexamethasone as a confounder (linear regression). Differences were considered significant when $p < 0.05$.

Results

Neonatal period

At 36 weeks PMA (postmenstrual age), 238 (89.5%) of the 266 live born infants of the LFUPP were still alive. One infant was excluded because of Down's syndrome. In 4 infants it was not known if they had BPD. Forty-nine infants (49/233 = 21% of the survivors, 49/266 = 18.5% of all live born infants) could be classified as having BPD, defined as need of oxygen at 36 weeks PMA. Fourteen (50%) of the 28 infants who did not survive until 36 weeks PMA, died

Table 1. Perinatal factors in survivors at 36 weeks PMA without or with bronchopulmonary dysplasia

	Without BPD N (%)	**With BPD N (%)**
Total number of infants:	184	49
GA (mean + range), weeks	**30.0 (24.7 – 31.9)**	**27.5 (23.7 – 31.7)**
BW (mean + range), grams	**1378 (703 – 2382)**	**948 (530 – 1635)**
Male gender	105/184 (57.1)	28/49 (57.1)
Antenatal steroids (betamethason)		
None	49/175 (28.0)	8/44 (18.2)
Incomplete course (1 gift)	39/175 (22.3)	13/44 (29.5)
Complete course (2 gifts)	87/175 (49.7)	23/44 (52.3)
RDS		
None	**90/181 (49.7)**	**9/49 (18.4)**
Grade 1-2	**53/181 (29.3)**	**14/49 (28.6)**
Grade 3-4	**38/181 (21.0)**	**26/49 (53.1)**
Surfactant	**60/184 (32.6)**	**32/48 (66.7)**
Days on IPPV (mean+range)	**3.7 (0 – 37)**	**17.7 (2 – 44)**
Days on CPAP (mean+range)	**6.6 (0 – 35)**	**20.3 (0 – 63)**
O2-28 days	**18/184 (9.9)**	**46/47 (97.9)**
PDA	**31/184 (16.8)**	**27/49 (55.1)**
IVH		
None	**144/181 (78.3)**	**30/49 (61.2)**
Grade 1 – 2	**26/181 (14.1)**	**17/49 (34.7)**
Grade 3 – 4	**11/181 (6)**	**2/49 (4.1)**
Cystic PVL	**3/180 (1.7)**	**5/49 (10.2)**
ROP		
None	**144/152 (94.7)**	**28/46 (60.9)**
Grade 1 – 2	**7/152 (4.6)**	**18/46 (39.1)**
Grade 3 – 5	**1/152 (0.7)**	**0**
Dexamethasone	**8/183 (4.4)**	**28/48 (58.3)**
Courses of antibiotics		
0 – 1	**123/183 (67.2)**	**9/47 (19.2)**
2 – 3	**56/183 (30.6)**	**31/47 (66.0)**
≥ 4	**4/183 (2.2)**	**7/47 (14.9)**
Still admitted at term	**22/177 (12.4)**	**28/46 (58.3)**
O_2 at home	**0**	**11/49 (22.4)**
Condition normal at discharge	**134/183 (73.2)**	**9/48 (18.8)**

Bold = $p < 0.05$

BPD = bronchopulmonary dysplasia; GA = gestational age; BW = birth weight; RDS = respiratory distress syndrome; IPPV = intermittent positive pressure ventilation; CPAP = continuous positive airway pressure; PDA = patent ductus arteriosus; IVH = intraventricular haemorrhage; PVL = periventricular leucomalacia; ROP = retinopathy of prematurity.

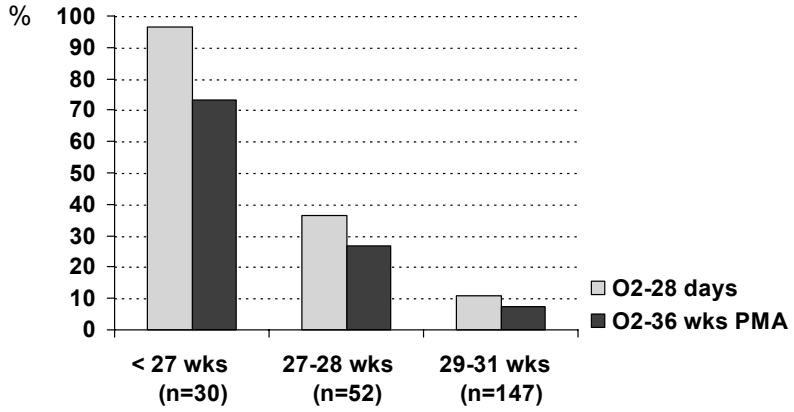
because of pulmonary problems: 9 infants because of solitary pulmonary problems and another 5 infants because of respiratory difficulties combined with other serious neonatal morbidities. Characteristics of the 49 infants with BPD are compared with the 184 infants without BPD (Table 1). Infants with BPD had lower gestational age and lower mean birth weight compared to infants without BPD. There was no difference in gender. Infants with BPD had more severe RDS and were more frequently treated with surfactant. Infants with BPD were significantly longer on the ventilator. Almost all infants with BPD at 36 weeks received supplemental oxygen at 28 days, while only 10% of the infants without BPD received oxygen at that time. Percentages of infants with BPD according to gestational age and birth weight are shown in Figure 1 and 2. Thirty-three percent of the females (32/98) needed supplemental oxygen at 28 days compared to 26% of the males (34/134). If an infant needed oxygen at day 28 (O_2-28), male gender was a risk factor for developing BPD: 28 out of 33 (85%) male infants developed BPD, compared to 19 out of 32 (59%) female infants ($p = 0.02$). Infants with BPD had more often PDA, cystic PVL, severe ROP and they received more courses of antibiotics.

At 2 years of age

From all survivors at 36 weeks PMA, another two infants died during the first year, both of them because of severe BPD. The incidence of pulmonary problems at the corrected age of 2 years in the remaining 231 infants is described in Table 2. Infants with BPD had more periods of coughing, wheezing and shortness of breath and used more pulmonary medication than infants without BPD.

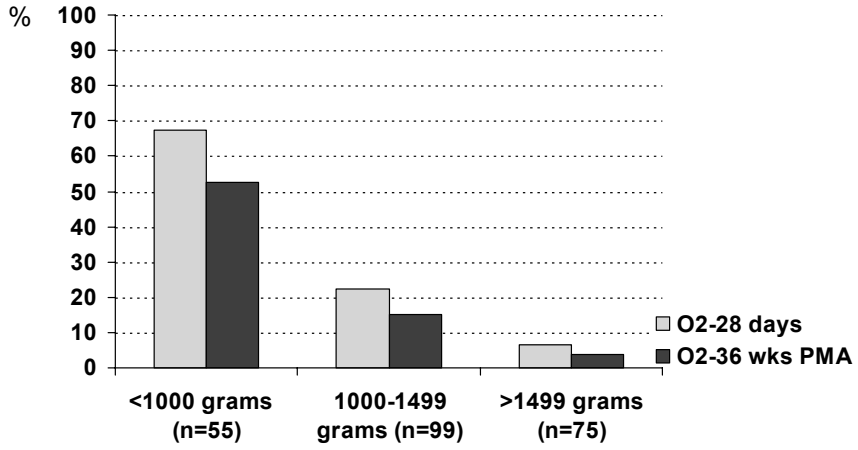
The mental and psychomotor development according to the BSID at the corrected age of 2 years could be assessed in 148 infants (64% of surviving infants with known BPD-status). Parents of the children in the lost to follow-up group were of lower socio-economic status and more frequently of non-Dutch origin. The mean MDI and PDI were significantly lower ($p = 0.006$ resp. 0.003) in infants with BPD compared to infants without BPD (Table 3). When the infants were classified in 3 subgroups (normal, moderate or severe delay), differences between the infants with or without BPD were only significant for the MDI. A neurological examination was performed in 189 infants (81% of the survivors): 80% of the infants without BPD had a normal neurological examination compared to 38% of the infants with BPD (Table 3). Physiotherapy was prescribed in 64% of the infants with BPD compared to only 14% of the infants without

Figure 1. Percentage of infants with BPD according to gestational age



BPD = bronchopulmonary dysplasia; PMA = postmenstrual age; wks = weeks

Figure 2. Percentage of infants with BPD according to birth weight



BPD = bronchopulmonary dysplasia; PMA = postmenstrual age

Table 2. Respiratory problems at 2 years of age in survivors without or with bronchopulmonary dysplasia

	Without BPD N (%)	**With BPD N (%)**
Coughing (irrespective of a common cold) during the last 12 months		
Never	**100/132 (75.8)**	**19/37 (51.4)**
< 1x / month	**24/132 (18.2)**	**7/37 (18.9)**
> 1x / month	**8/132 (6.1)**	**11/37 (29.7)**
Shortness of breath + wheezing during the last 12 months		
never	**108/133 (81.2)**	**19/37 (51.4)**
sometimes	**11/133 (8.3)**	**8/37 (21.4)**
frequently	**14/133 (10.5)**	**10/37 (27.0)**
Parental smoking behaviour	35/131 (26.7)	6/36 (16.7)
Lung medication	**25/133 (18.8)**	**14/37 (37.8)**
Betamimethics (inhaled)	**17/127 (13.4)**	**11/36 (30.6)**
Steroids (inhaled)	14/126 (11.1)	6/36 (16.7)

Bold = $p < 0.05$; BPD = bronchopulmonary dysplasia

Table 3. Mental, psychomotor and neurological outcome at 2 years of age, in infants without or with bronchopulmonary dysplasia

	Without BPD N (%)	**With BPD N (%)**
MDI at 2 years		
Normal	**91/113 (80.5)**	**20/38 (52.6)**
Mild delay	**8/113 (7.1)**	**10/38 (26.3)**
Severe delay	**14/113 (12.4)**	**8/38 (21.1)**
Mean (SD):	**101 (24)**	**88 (25)**
PDI at 2 years		
Normal	78/109 (71.6)	24/39 (61.5)
Mild delay	23/109 (21.1)	7/39 (17.9)
Severe delay	8/109 (7.3)	8/39 (20.5)
Mean (SD):	**99 (21)**	**87 (21)**
Neurological examination		
Normal	**118/147 (80.3)**	**16/42 (38.1)**
Mild abnormal	**18/147 (12.2)**	**17/42 (40.5)**
Definitely abnormal	**11/147 (7.5)**	**9/42 (21.4)**
Physiotherapy	**19/133 (14.3)**	**18/28 (64.3)**

Bold = $p < 0.05$; BPD = bronchopulmonary dysplasia; MDI = mental developmental index; PDI = psychomotor developmental index; SD = standard deviation

BPD ($p < 0.001$). After correction for dexamethasone as the most important confounder, no differences were found in MDI and PDI between the infants with or without BPD. More infants with BPD had an abnormal neurological examination compared to the infants without BPD even after correction for the use of dexamethasone ($p = 0.031$). When infants with a serious IVH (grade 3 or 4) or a cystic PVL were excluded there was still an association between BPD and more delay in MDI and PDI and abnormal neurological examination.

Seven (18%) out of 39 infants with BPD had a clinically abnormal behaviour compared to 9/119 (8%) infants without BPD, which was almost significant ($p = 0.064$). In infants without severe IVH or PVL the numbers were 5/33 (15%) for BPD-children compared to 8/110 (7%) for children without PBD.

Discussion

In this prospective study of very premature infants born in the nineteen-nineties, 21% of the infants alive at 36 weeks PMA, suffered from bronchopulmonary dysplasia, defined as need of supplemental oxygen at 36 weeks. In the infants with birth weight < 1000 grams, 54% (31/57) had BPD, in infants < 1500 grams 29% (46/156). In the non-survivors, pulmonary problems were the cause of death in 50%. Studies in infants born with birth weight < 1000 grams mention 40 – 45% BPD.[7;14] Ehrenkranz *et al.*[8] mention 30% moderate and 16% severe BPD in infants with GA < 32 weeks and birth weight < 1000 grams, alive at 36 weeks PMA. In 3 large neonatal networks (the National Institute of Child Health and Development Neonatal Research Network, the Vermont Oxford Network and the Canadian Neonatal Network) incidences of 27%, 29% and 24% BPD in infants with birth weights between 500 and 1499 grams are recently described.[15] Because of differences in definitions of the cohorts and time periods and differences in clinical definitions of BPD like accepting different oxygen saturations, numbers are difficult to compare. As expected, infants with BPD were of lower gestational age[16] and of lower birth weight. Half of them were born with RDS grade 3 or 4, compared to 21% of the infants without BPD. They received more surfactant and remained longer on the ventilator compared to the infants without BPD (mean 18 versus 4 days). Other possible explanations for the development of BPD like a persistent ductus arteriosus and multiple courses of antibiotics[16]

occurred more frequently in the infants with BPD. Gender was not associated with the incidence of BPD, although more males than females with supplemental oxygen at 28 days developed bronchopulmonary dysplasia at 36 weeks. A complete course of antenatal steroids was given in an equal percentage of the infants with and without BPD.

Infants with BPD are at risk for having pulmonary sequelae and rehospitalisation during childhood.[17] We found significantly more periods of coughing, shortness of breath and wheezing, at the corrected age of 2 years in the infants with BPD compared to the infants without BPD. These children also used more lung medication, especially more betamimethics. Vrijlandt *et al.*[18] found no differences in reported pulmonary problems at the age of 3 – 5 years in premature infants with or without BPD, but a difference in lung function was described. Their definition of BPD however was different than in our study: supplemental oxygen at 28 days combined with radiographic pulmonary manifestations. Ehrenkranz *et al.* observed an increasing incidence of adverse pulmonary outcomes at 18 to 22 months corrected age as the severity of BPD worsened from mild to severe. They also found a substantial rate of adverse pulmonary outcomes in the (preterm) infants without BPD.[8] Many other studies however do not distinguish those children who developed BPD from others who were also premature but did not develop BPD. Furthermore, Greenough[9] reminds us that most studies report the outcome of infants with "classical" BPD and that the long-term outcome of children who have suffered "new" BPD is not known and that these infants require careful follow-up.

In the present study we found an association between BPD and abnormal neurodevelopmental outcome. Comparable results of the BSID at 2 years were found by Singer *et al.*[19]: they describe a mean MDI and PDI of 86 and 84 in preterm infants with BPD compared to a mean MDI and PDI of 99 and 102 in preterm infants without BPD. Although analyses of associations between outcome and BPD are complicated by the existence of coexisting morbidities, we still found an association between BPD and abnormal neurological outcome after correction for the use of dexamethasone. Vohr *et al.*[14] already described BPD as well as the use of postnatal steroids to be a significant risk factor for neurodevelopmental impairment in very preterm survivors at 18 to 22 months. Van Baar *et al.*[20] studied infants < 30 weeks GA at 5.5 years corrected age and they found multiple disabilities to be associated with birth weight and BPD. Moon *et al.*[6] however found only an initial developmental lag in extremely preterm infants with BPD

compared to preterm peers at 1 and 2 years of age; at 4 years corrected age no differences between the groups were evident. Katz-Salamon *et al*. reported that BPD had a deleterious effect on the control of hand and eye coordination and on perception and intelligence, when they compared 43 preterm infants with BPD but without severe IVH or PVL with preterm infants without BPD, IVH and PVL.[21]

The flaws of this study could be that we did not classify BPD according to the latest consensus[4], but this definition was not known yet in the late nineteen-nineties. Furthermore about one third of the children at 2 years could not be assessed according to the BSID. The lost-to-follow-up group had a lower socio-economic status and parents were less often of Caucasian race. However, socio-economic status and race were equally divided in the infants with and without BPD so it is not likely this will influence the outcome. Data about the outcome of very preterm infants with BPD from the Netherlands are scarce. This prospective, regional study of all live born preterm infants in three health regions in the Netherlands finds a comparable incidence of BPD with literature. Respiratory problems at 2 years were analysed according to an international and reproducible questionnaire; the neurological examination was performed in a standardised way.

Despite antenatal steroid use, surfactant replacement therapy, gentle non-invasive ventilation techniques BPD continues to be a major problem[17], especially when people start using less postnatal corticosteroids[22] and therefore follow-up of these infants remains necessary.

References

1. Northway WH, Jr., Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 1967;276:357-68.
2. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. J Pediatr 1979;95:819-23.
3. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
4. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am.J.Respir.Crit Care Med. 2001;163:1723-9.
5. Kinsella JP, Greenough A, Abman SH. Bronchopulmonary dysplasia. The Lancet 2006;367:1421-31.
6. Moon NM, Mohay HA, Gray PH. Developmental patterns from 1 to 4 years of extremely preterm infants who required home oxygen therapy. Early Hum Dev 2007;83:209-16.
7. Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF *et al.* Impact of Bronchopulmonary Dysplasia, Brain Injury, and Severe Retinopathy on the Outcome of Extremely Low-Birth-Weight Infants at 18 Months: Results From the Trial of Indomethacin Prophylaxis in Preterms. JAMA 2003;289:1124-9.
8. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA *et al.* Validation of the National Institutes of Health Consensus Definition of Bronchopulmonary Dysplasia Pediatrics 2005;116:1353-60.
9. Greenough A. Bronchopulmonary dysplasia - Long term follow up. Paediatric Respiratory Reviews 2006;7:S189-S191.
10. Rijken M, Stoelhorst GMSJ, Martens SE, van Zwieten PHT, Brand R, Maarten Wit J *et al.* 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. Pediatrics 2003;112:351-8.
11. Hempel MS. The neurological examination technique for toddler-age. Thesis. University of Groningen. 1993.
12. Brunekreef B, Groot B, Rijcken B, Hoek G, Steenbekkers A, de Boer A. Reproducibility of childhood respiratory symptom questions. Eur Respir J 1992;5:930-5.
13. de Boer A, Steenbekkers A, Brunekreef B, Hoek G, Rijcken B, Groot B. Een vergelijking van twee vragenlijsten naar luchtwegsymptomen bij kinderen. II De samenhang tussen de vragen. T Soc Gezondheidsz 1990;68:483-8.
14. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ *et al.* Neurodevelopmental and Functional Outcomes of Extremely Low Birth Weight Infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics 2000;105:1216-26.
15. Walsh MC, Yao Q, Horbar JD, Carpenter JH, Lee SK, Ohlsson A. Changes in the Use of Postnatal Steroids for Bronchopulmonary Dysplasia in 3 Large Neonatal Networks. Pediatrics 2006;118: e1328-e1335.
16. Chess PR, D'Angio CT, Pryhuber GS, Maniscalco WM. Pathogenesis of bronchopulmonary dysplasia. Semin Perinatol 2006;30:171-8.
17. Bhandari A,. Panitch HB. Pulmonary outcomes in bronchopulmonary dysplasia. Semin Perinatol 2006;30:219-26.
18. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in

prematurely born preschool children with and without bronchopulmonary dysplasia. J Pediatr 2007;150:256-61.
19. Singer L, Yamashita T, Lilien L, Collin M, Baley J. A Longitudinal Study of Developmental Outcome of Infants With Bronchopulmonary Dysplasia and Very Low Birth Weight. Pediatrics 1997;100:987-93.
20. van Baar AL, van Wassenaer AG, Briet JM, Dekker FW, Kok JH. Very Preterm Birth is Associated with Disabilities in Multiple Developmental Domains. J Pediatr Psychol 2005;30:247-55.
21. Katz-Salamon M, Gerner EM, Jonsson B, Lagercrantz H. Early motor and mental development in very preterm infants with chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2000;83: F1-F6.
22. Shinwell ES, Lerner-Geva L, Lusky A, Reichman B, in collaboration with the Israel Neonatal Network. Less postnatal steroids, more bronchopulmonary dysplasia: a population-based study in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2007;92:F30-F33.

CHAPTER 8

Developmental outcome at 18 and 24 months of age in very preterm children: a cohort study from 1996 to 1997

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Abstract

Objective: To determine the effect of prematurity (gestational age (GA) < 32 weeks) on developmental outcome at the corrected age of 18 and 24 months in a regionally defined, prospective cohort study.

Study design: The Leiden Follow-Up Project on Prematurity includes all live-born infants of < 32 wks GA, born in 1996/1997 in 3 Dutch health regions (n=266). Mental and psychomotor developmental indices (MDI, PDI) were determined with the Bayley Scales of Infant Development I: ≥ -1 SDS: normal, -2 to -1 SDS: moderate delay and < -2 SDS: severe delay.

Results: At 18 months 168 (71%) and at 24 months 151 children (64%) of 235 survivors were assessed. Moderate to severely delayed mental and/or psychomotor development occurred in 40% of the children at both ages. Children lost to follow-up were of lower socio-economic status and more frequently of non-Dutch origin. Since non-Dutch origin negatively affected outcome at both test ages, availability of the data of these children would probably have worsened the outcome. Postnatal treatment with dexamethasone was associated with an increased risk of delayed development. Other independent predictors of delayed development were bronchopulmonary dysplasia at 18 months and ethnicity, maternal age at birth, GA, birthweight and gender at 24 months. After adjustment for these other predictors of delayed development, the mean PDI of dexamethasone-treated infants was 16.1 points lower than that of non-treated infants at 18 months (p=0.03) and 12.7 points lower at 24 months (p=0.04).

Conclusions: At 18 and 24 months corrected age, 40 percent of the very prematurely born children had both delayed mental and/or psychomotor development. Treatment with dexamethasone postnatally was a major risk factor for delayed (psychomotor) development.

Introduction

Advances in neonatology have led to an increased survival of very preterm infants.[1] To evaluate the effect of these ongoing changes in neonatal care on morbidity, the neurodevelopmental outcome of these infants is closely monitored.

Previous studies have shown that preterm infants, especially those with chronic lung disease or extensive intraventricular haemorrhage, are at greater risk of developmental disorders.[2-4] Apart from these medical risk factors, social risk factors, such as low socioeconomic status of the parents, may also have negative effects on children's development.[3-5]

In this paper we report on the developmental outcome at 18 and 24 months corrected age of a recent, regional, Dutch cohort of very preterm infants. We will compare the findings to the Dutch reference norms. Furthermore, the influence of both medical and social risk factors on developmental outcome will be examined. In view of recent findings suggesting that postnatal treatment with dexamethasone may have adverse effects on neurodevelopmental outcome[6-8], close attention will be paid to the possible influence of this treatment on developmental outcome.

Development was assessed at both 18 and 24 months to see if a developmental profile could be detected and if so, which medical and/or social factors could explain this difference.

Patients and methods

Patients

The Leiden Follow-Up Project on Prematurity, a regional, prospective study, includes all liveborn infants less than 32 weeks gestational age (GA) from the Dutch health regions Leiden, The Hague and Delft, born in 1996 or 1997 (n=266). All infants $\geq$ 24 weeks GA were actively resuscitated at birth.

The three Dutch health regions used in the study are situated in the Dutch province Zuid-Holland. In the years 1996/1997 this province had 3.34 million inhabitants on a total of 15.53 million people living in the entire Netherlands. With 21% of the total Dutch population living in this province, it is a reasonably

densely populated region. The three studied health regions (The Hague, Delft and Leiden) together had 1.43 million inhabitants at that time, which is 43% of the total inhabitants of the province of Zuid-Holland and 9% of the entire Dutch population. The health region The Hague had the most inhabitants: 49% of the 1.4 million, versus 33% in the health region Leiden and 19% in the health region Delft.

The total number of live births in the Netherlands was 191.000 in the years 1996/1997, 41.250 in the province Zuid-Holland (21% of the total) and 17.450 (9% of total, 43% of live-births in Zuid-Holland) in the three studied health regions. Forty-five percent of the live-births in the studied health regions occurred in the region The Hague, 35% in Leiden and 20% in Delft.

Follow-up of the infants included physical examinations and assessment of neuromotor development by a paediatrician at term and at the corrected ages of 12 and 24 months. Mental and psychomotor development was assessed at 18 and 24 months corrected age by 6 developmental psychologists, who were 'blind' to the child's medical history.

The study was approved by the Ethics Committee of the Leiden University Medical Center. Parental informed consent was obtained.
In this work, all mentioned ages hereafter are corrected for prematurity.

Instruments

Mental and psychomotor development were assessed using the Dutch version of the Bayley Scales of Infant Development I.[9;10] These scales have a population-mean of 100 and a standard deviation of 16. The Mental and Psychomotor Developmental Index (MDI, PDI) range between 51 and 149. If raw test scores were either so low or so high that developmental indices could not be determined, index-scores of 50 and 150, respectively, were given.

An MDI or PDI $\geq$ 84 ($\geq$ -1 SD) was considered normal, an MDI or PDI between 68 and 84 (-2 to -1 SD) was considered as moderate delay and $<$ 68 ($<$ -2 SD) as severe delay.

In accordance with the Bayley manual, a difference of 19 and 15 points at 18 and 24 months respectively between MDI and PDI was considered to be significant ($p < 0.05$). Such a difference was defined as dysharmonic.

For mental development a difference of 14 points between the MDI at 18 and 24 months was considered significant, for psychomotor development a difference of 20 points.

Medical factors

Medical factors were collected on precoded forms. Data collected included: obstetric history, mode of delivery, GA, gender, birthweight, small for GA (birthweight < P10)[11], complications during admission like hypotension (at least twice a mean blood pressure < 30 mmHg, measured oscillometrically [Dynamap] or intra-arterially), bronchopulmonary dysplasia (BPD, supplemental oxygen need at 36 weeks postmenstrual age)[12], intraventricular haemorrhage (IVH)[13], cystic periventricular leucomalacia (PVL)[14] and treatment with dexamethasone in the postnatal period.

Dexamethasone was given with an initial dose of 0.5 mg/kg and tapered over 42 days to 0.1 mg/kg. However, duration of treatment depended on the clinical condition of the child and varied between 5 and 60 days (mean 31 days).

Neurological outcome at term (Prechtl)[15] and at 2 years of age (Hempel)[16] was defined as normal, mildly or definitely abnormal. Definitely abnormal means the presence of a full-blown neurological syndrome like asymmetry, general hyper/hypotonia, hyper/hypokinesia; mildly abnormal the presence of only part of such a syndrome.

Social factors

Socioeconomic status (SES) was determined by the level of education of each parent. A score of 1 was given if the parent's educational level was low (elementary school, lower level secundary or professional education), a score of 2 for an average educational level (medium level secundary or professional education) and a score of 3 for higher levels of education (high level professional education, university).[17]

Ethnicity was defined as Dutch or non-Dutch origin (mostly Turkish, Moroccan or Surinamese origin).

Statistical analysis

The mean MDI and PDI scores of the study population were compared with the reference population using a one sample *t*-test. The observed percentages of children with normal, moderately or severely delayed mental and psychomotor development were compared with the expected values using the chi-square test. ANOVA and bivariate correlation (Pearson/Spearman) were used for univariate analyses.

Multiple linear regression analysis, with the continuous MDI and PDI scores

as dependent variables, was used to estimate the predictive value of medical and social factors on mental and psychomotor outcome. Ethnicity, SES, gender, use of glucocorticosteroids antenatally, maternal age at birth, GA, birthweight (percentile according to GA), extra-uterine transportation, hypotension, IVH, PVL, BPD and treatment with dexamethasone in the postnatal period were the independent predictors. The goodness-of-fit of this model was evaluated by inspection of the histogram of the residuals and scatterplots of the residuals versus covariates.
P-values < 0.05 were considered significant.

Results

The study included 266 children, 92% of eligible infants born in 1996 and 1997 (97% of eligible infants in 1996 and 88% of eligible infants in 1997). Thirty (11%) of the 266 children died, 28 in the neonatal period and 2 more before the age of one year. Treatment was withdrawn in 15 of these infants because it was considered to be medically futile.

In this study, a total of 163 (61%) children were born in hospitals with a neonatal intensive care unit ([NICU], tertiary referral centers), 103 (39%) in hospitals without a NICU. The patient characteristics of the entire cohort are presented in Table 1.

One child was excluded from the analyses because of Down's syndrome. Of the remaining 235 survivors, 168 children (71%) were assessed at 18 months and 151 (64%) at 24 months. Three infants had such severe disabilities that scores of 50 were given for both mental and motor development without actual testing. One child could not be tested due to blindness.
Reasons for the loss-to-follow-up were families moving to other cities or countries and parental refusal to co-operate. Birth characteristics (GA, birthweight, gender) and incidences of respiratory distress syndrome, oxygen dependence at 28 days, BPD, hypotension, IVH, PVL and postnatal treatment with dexamethasone of the lost-to-follow-up-group did not differ from those of the study group. Parents of the children of the lost-to-follow-up-group were of lower SES and were more frequently of non-Dutch origin.

Table 1. Characteristics of the LFUPP-cohort (n=266)

Antenatal steroids, % (n)	75 (182)
Male gender, % (n)	55 (147)
Gestational age:	
weeks, mean (SD)	29.2 (2.1)
24-26 weeks, % (n)	17 (46)
27-28 weeks, % (n)	23 (61)
29-31 weeks, % (n)	60 (159)
Birthweight, mean (SD)	1250 (383)
Small for GA (birthweight <P10), % (n)	13 (33)
Apgar 5 min, mean (SD)	7.7 (1.8)
Extra-uterine transport, % (n)	35 (93)
Hypotension*, % (n)	34 (98)
O2 at 28 days, % (n)	26 (67)
Bronchopulmonary dysplasia**, % (n)	19 (49)
Mechanical ventilation, days, mean (SD)	7.2 (9.3)
Dexamethasone postnatally, % (n)	17 (45)
Intraventricular haemorrhage, % (n)	
none	74 (190)
grade 1-2	18 (48)
grade 3-4	8 (20)
Periventricular leucomalacia (cystic), % (n)	3 (8)
In hospital mortality, % (n)	11 (29)
Dutch origin, % (n)	75 (167)
Level of education mother, % (n)	
high	29 (60)
average	50 (105)
low	21 (44)
Maternal age at birth, yrs, mean (SD)	30.5 (5.6)

LFUPP: Leiden Follow-Up Project on Prematurity; SD: standard deviation
GA: gestational age; * at least twice a mean blood pressure < 30 mmHg;
** O2 at 36 weeks postmenstrual age

Developmental outcome

The results of the assessments at 18 and 24 months of age are presented in Table 2 for MDI and PDI separately.

Mean MDI at 18 and 24 months and PDI at 24 months were significantly lower than 100. At both ages, the percentages of children with normal, moderately delayed and severely delayed development differed ($p<0.001$) from those in the reference population. Delayed development, especially more severely delayed development, occurred more often among the very preterm infants than in the reference population.

At 18 and 24 months of age, both mental and psychomotor development were normal in 60% of the children (98 and 85 children, respectively). Mental and psychomotor development were severely delayed in 11 children (7%) at 18 and 9 children (6%) at 24 months. In the remaining 33-34% of children at least one of the parameters was abnormal.

Table 2. Mental and psychomotor development at 18 and 24 months corrected age

	Mean (SD)	**Range**	**Normal** % (n)	**Moderate delay** % (n)	**Severe delay** % (n)	**Total** n
18 months (mean 18.0, SD 1.3)						
MDI	95.1 (20.7)★	50-142	**73** (121)	**18** (30)	**9** (15)	166★★
PDI	95.7 (25.8)★	50-150	**71** (116)	**11** (18)	**18** (29)	163★★
24 months (mean 24.8, SD 1.6)						
MDI	97.3 (24.8)	50-150	**73** (107)	**12** (18)	**15** (21)	146★★
PDI	95.8 (21.7)★	50-150	**70** (100)	**22** (32)	**8** (12)	144★★
Reference population	100 (16)		**84**	**13.5**	**2.5**	

SD: standard deviation, MDI: mental developmental index, PDI: psychomotor developmental index, Normal: ≥ -1 SD, Moderate delay: -2 to -1 SD, Severe delay: < -2 SD.

★significantly below the test mean of 100, p=0.003 for MDI and p=0.03 for PDI at 18 months, p=0.02 for PDI at 24 months.

★★MDI and PDI could not be determined in respectively 2 and 5 children at 18 months and 5 and 7 children at 24 months.

Intra-individual differences

Significant differences between MDI and PDI at 18 months were found in 59 of 163 children (36%): 31 had better mental development and 28 had better psychomotor development. At 24 months, differences existed in 64 of 142 (45%) children: 33 had better mental development and 31 had better psychomotor development. These intra-individual differences exceeded the expected 5% of children with a dysharmonic profile in the reference population ($p<0.001$).

Changes between the two test ages

Although the mean MDI and PDI at 18 months did not differ from those at 24 months, significant changes between MDI scores at 18 and 24 months were found in 67 of 136 tested infants (49%): 32 infants had a worse mental outcome and 35 children had a better mental outcome at 24 months of age. Changes in PDI scores existed in 45 of 132 tested infants (34%): 23 infants had a worse psychomotor outcome and 22 children had a better psychomotor outcome at 24 months of age. These changes differed ($p<0.001$) from the expected 5% of children with a significant improvement or deterioration in the reference population.

Association between medical factors and developmental outcome

Higher GA was associated with an increase in MDI scores at 18 and 24 months (correlation coefficient $r = 0.29$, $p<0.001$ and $r = 0.19$, $p=0.02$). PDI scores also increased with higher GA at 18 and 24 months ($r = 0.25$, $p=0.001$ and $r = 0.26$, $p=0.001$).

The association of other medical factors with developmental outcome is shown in Table 3 (18 months) and 4 (24 months). Male children had lower MDI scores at both ages and lower PDI scores at 24 months than female children, infants with hypotension in the neonatal period had lower PDI scores at 18 months than those without hypotension. Both MDI and PDI scores were lower at 18 and 24 months in infants with PVL, oxygen dependence at 28 days, BPD, postnatal dexamethasone treatment and neurological abnormalities at term or at 2 years of age.

Better mental than psychomotor development or vice versa at 18 or 24 months of age was not associated with any of the medical factors listed in Tables 3 and 4.

No associations were found between the medical factors and the mental and psychomotor outcome of children whose outcome significantly improved or deteriorated between the age of 18 and 24 months.

Table 3. Mental and psychomotor development at 18 months corrected age in relation to medical factors

	MDI mean; SD (n)			PDI mean; SD (n)*		
Medical factor	**+**	**-**	**p****	**+**	**-**	**p****
antenatal steroids	94; 20 (108)	98; 23 (44)	0.2	95; 24 (107)	98; 28 (43)	0.5
GA < 27 weeks	81; 17 (20)	97; 20 (146)	0.001	82; 27	98; 25 (143)	0.01
birthweight < P10 (SGA)	94; 20 (22)	95; 21 (143)	0.7	99; 19 (21)	95; 27 (141)	0.5
gender: male	91; 21 (93)	100; 19 (73)	0.005	93; 25 (90)	99; 27	0.1
extra-uterine transport	94; 22 (57)	96; 20 (109)	0.5	100; 24 (56)	93; 27 (107)	0.1
hypotension#	92; 20 (56)	97; 21 (108)	0.1	89; 26 (54)	100; 25 (107)	0.01
IVH grade 3-4	95; 25 (11)	95; 20 (151)	0.9	88; 31	97; 25 (148)	0.3
PVL (cystic)	70; 18 (6)	96; 20 (157)	0.002	70; 22	97; 25 (154)	0.01
O2 at 28 days	86; 21 (50)	99; 19 (113)	<0.001	83; 26	102; 23 (110)	<0.001
BPD (O2 at 36 wks)	82; 20 (37)	99;20 (126)	<0.001	81; 27	101; 23 (123)	<0.001
dexamethasone postnatally	81; 17 (27)	98; 20 (138)	<0001	76; 23	99; 25 (135)	<0.001
neurological abnormalities at term	91; 22 (78)	99; 19 (87)	0.02	89; 27 (76)	102; 23 (86)	0.001
neurological abnormalities at 24 months	81; 20 (48)	101; 19 (104)	<0.001	78; 26	103; 22 (102)	<0.001

*numbers are only mentioned again if different from the MDI-number,
** *t*- test, # hypotension: at least twice a mean blood pressure < 30 mmHg,
MDI: mental developmental index; PDI: psychomotor developmental index; SD: standard deviation; GA: gestational age; SGA: small for gestational age; IVH: intraventricular haemorrhage; PVL: periventricular leucomalacia; BPD: bronchopulmonary dysplasia

Table 4. Mental and psychomotor development at 24 months corrected age in relation to medical factors

	MDI mean; SD (n)			PDI mean; SD (n)*		
Medical factor	**+**	**-**	**p****	**+**	**-**	**p****
antenatal steroids	97; 25 (100)	97; 27 (37)	0.9	96; 21 (985)	96; 23	0.9
GA < 27 weeks	91; 24 (21)	98; 25 (125)	0.2	87; 21 (22)	97; 21 (122)	0.03
birthweight < P10 (SGA)	90; 28 (22)	99; 24 (123)	0.1	93; 21	96; 22 (121)	0.4
gender: male	93; 26 (85)	103; 23 (61)	0.02	93; 23 (83)	100; 18	0.04
extra-uterine transport	91; 27 (47)	100; 23 (99)	0.04	96; 24	96; 21 (97)	0.9
hypotension#	95; 24 (50)	99; 25 (95)	0.4	93; 21	98; 22 (93)	0.2
IVH grade 3-4	90; 32 (10)	98; 24 (135)	0.3	83; 26	97; 21 (133)	0.05
PVL (cystic)	69; 21 (5)	98; 25 (140)	0.01	78; 23 (6)	97; 22 (137)	0.04
O2 at 28 days	90; 24 (46)	101; 24 (98)	0.009	86; 20 (47)	101; 21 (95)	<0.001
BPD (O2 at 36 wks)	88; 25 (36)	101; 24 (108)	0.006	87; 21(37)	99; 21 (105)	0.003
dexamethasone postnatally	84; 26 (25)	100; 24 (119)	0.003	82; 21 (26)	99; 21 (116)	<0.001
neurological abnormalities at term	94; 27 (73)	100; 23 (72)	0.2	92; 21 (72)	100; 21 (71)	0.02
neurological abnormalities at 24 months	82; 27 (45)	104; 21 (92)	<0.001	79; 22 (46)	104; 16 (89)	<0.001

*numbers are only mentioned again if different from the MDI-number,

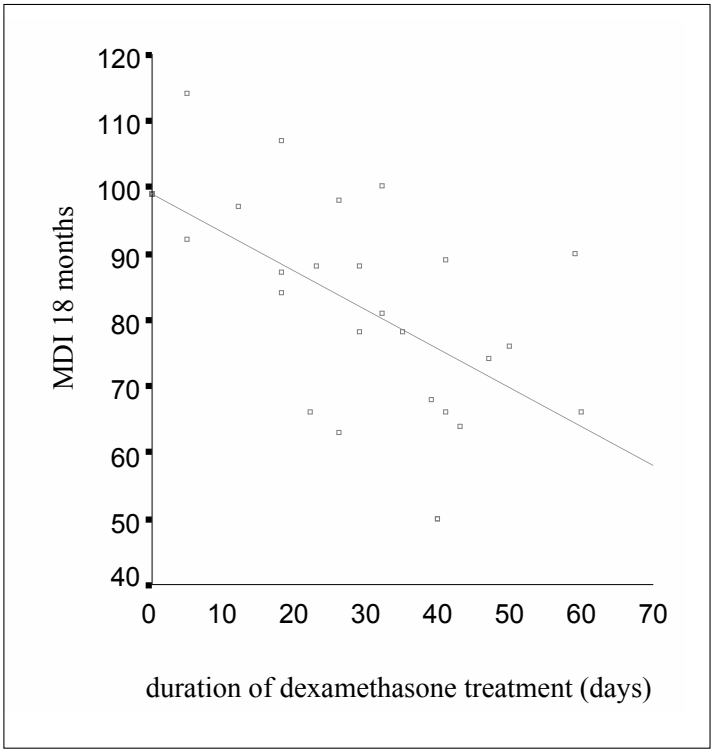
**t- test, # hypotension: at least twice a mean blood pressure < 30 mmHg.

MDI: mental developmental index; PDI: psychomotor developmental index; SD: standard deviation; GA: gestational age; SGA: small for gestational age; IVH: intraventricular haemorrhage; PVL: periventricular leucomalacia; BPD: bronchopulmonary dysplasia

Treatment with dexamethasone in the postnatal period

Twenty-seven infants in the assessed group were treated with dexamethasone postnatally (16%). Treatment was started at a mean age of 19 days (range 5-42), the mean duration of treatment was 31 days (range 5-60). Treatment with dexamethasone was univariately associated with delayed mental and psychomotor development at 18 and at 24 months of age (Tables 3 and 4) and the duration of treatment was associated with delayed mental development at 18 months (r = -0.6, p=0.006; Fig. 1).

Figure 1. MDI-scores at 18 months in relation to duration of dexamethasone treatment postnatally (MDI: Mental Developmental Index)



Association between social factors and developmental outcome

Both ethnicity and SES were divided into three groups. At 18 months of age the percentage of parents of Dutch origin was 80%, while 15% of the parents were of non-Dutch origin and 5% of the children had one parent of Dutch and one of non-Dutch origin.

Twenty-two percent of the mothers and 27% of the fathers had low levels of education, 56% and 39% average levels and 22% and 33% had high levels of education. The percentages found at 24 months were comparable.

Average maternal age at birth was 30.6 years (SD 4.7), which is comparable to the average age at birth of Dutch women of 30.4 years in those years.

Children of Dutch origin had higher MDIs at both 18 and 24 months than children of non-Dutch origin: mean MDI at 18 months was 97 vs. 88 for the non-Dutch children ($p=0.04$), at 24 months the corresponding numbers were 101 and 84 ($p=0.002$).

Higher maternal age at birth was associated with better mental development at 24 months *(*$r = 0.19$, $p=0.03$). Educational level of the parents was not associated with development at 18 or 24 months.

Higher educational levels of the mother and higher maternal age at birth were associated with improvement in mental development between 18 and 24 months ($r = 0.18$, $p=0.004$ and $r = 0.26$, $p=0.003$, respectively).

Multivariate analysis

Univariately, we found that lower maternal age at birth, non-Dutch origin, lower GA, male gender, hypotension, oxygen dependence at 28 days, BPD, postnatal treatment with dexamethasone, PVL and neurological abnormalities at term or 2 years were associated with delayed mental and/or psychomotor development at 18 and/or 24 months. In order to disentangle these univariate effects, a multiple regression analysis with stepwise selection was done. BPD was the only independent predictor for delayed mental development at 18 months. BPD and postnatal treatment with dexamethasone were the independent predictors for delayed psychomotor development at this age. Birthweight and postnatal treatment with dexamethasone were the only independent predictors for delayed psychomotor development at 24 months; ethnicity, maternal age at birth and gender were predictive of delayed mental development as well.

Since postnatal dexamethasone treatment was associated with several of the covariates, we repeated the stepwise analysis without dexamethasone to identify

the confounders of the dexamethasone effect. These confounders were BPD at 18 months and ethnicity, maternal age, birthweight and gender at 24 months for delayed mental development. For delayed psychomotor development these were BPD at 18 months and birthweight at 24 months. The effects of dexamethasone after correction for these significant confounders were a 10.9 (S.E. = 6.3) lower MDI score at 18 and a 9.3 (S.E. = 6.6) lower MDI score at 24 months, and 16.1 (S.E. = 7.3) and 12.7 (S.E. = 6.1) lower PDI scores at 18 and 24 months, respectively (Table 5). When correcting further for all other predictors, the dexamethasone effects were slightly less for mental development but remained approximately the same and significant for psychomotor development (Table 5).

Table 5. Results unstandardized coefficient *(b)* of dexamethasone + S.E. and p-value of multiple linear regression analysis

	Mental Development		**Psychomotor Development**	
	18 months	**24 months**	**18 months**	**24 months**
Confounding				
univariate	-16.9 (S.E. 4.2, p<0.001)	-15.9 (S.E. 5.3, p=0.003)	-23.0 (S.E. 5.2, p<0.001)	-17.2 (S.E. 4.5, p<0.001)
adjusted for significant confounders*	-10.9 (S.E. 6.3, p=0.08)	-9.3 (S.E. 6.6, p=0.16)	-16.1 (S.E. 7.3, p=0.03)	-12.7 (S.E. 6.1, p=0.04)
adjusted for all confounders	-7.3 (S.E. 6.5, p=0.27)	-6.8 (S.E. 7.3, p=0.36)	-15.0 (S.E. 7.9, p=0.06)	-11.0 (S.E. 7.0, p=0.02)

The coefficient (*b*) represents the difference between the mean scores of infants treated and not-treated with dexamethasone postnatally. The minus sign indicates that the mean score of treated infants was lower than that of untreated infants. S.E.: standard error

* Mental development: 18 months: bronchopulmonary dysplasia (*b* =-12.3, p=0.03); 24 months: ethnicity (*b* =-11.4,p<0.001), maternal age (*b* =1.4, p=0.002), birthweight (*b* =0.19, p=0.001), gender (*b* =-10.1, p=0.02). Psychomotor development: 18 months: bronchopulmonary dysplasia (*b* =-14.2, p=0.03); 24 months: birthweight (*b* =0.12, p=0.03)

Discussion

In this study of the developmental outcome at 18 and 24 months corrected age of a cohort of very preterm infants (<32 wks GA) born in 1996/1997, we found that approximately 60% of the children had both normal mental and psychomotor development at both ages. In the remaining 40% of infants, 6-7% had both severe mental and psychomotor delay, while 33-34% had either moderate to severe mental and/or psychomotor delay.

The use of different inclusion criteria makes it difficult to compare these results with previously reported outcome-studies. Most of these studies reported outcome according to birthweight and only included extremely preterm or extremely low birthweight infants. Since the introduction of surfactant, no studies matching our intake criteria were available for comparison. Furthermore, in our study the Bayley Scales of Infant Development I (BSID-1) were used, while most other recent reports on developmental outcome use the second edition of these scales. However, since the BSID-2 was not validated yet for the Dutch population in the study-period, we had to use the first edition. Since the BSID-2 appears to give lower scores than the BSID-1[18], the results probably would have been worse if the BSID-2 could have been used.

The loss-to-follow-up with regard to the Bayley-assessment was considerable in this study. The loss-to-follow-up group differed from the study group in both ethnic origin (more non-Dutch parents in the lost group) and SES (lower educational levels of the parents). Since ethnic origin affected outcome at both test ages, availability of the data of these children would probably have worsened the outcome.

Development was assessed at 18 and 24 months to investigate if a developmental profile could be detected and if so, which medical and/or social factors could explain this difference. Significant differences in mental development between 18 and 24 months existed in 49% of the children. Except higher maternal education and age, which were associated with an improvement in mental outcome, no other social or medical factors were found which could explain this difference.
As reported in previous studies, we also found that medical factors such as lower GA, BPD and neurological abnormalities were univariately associated with delayed mental and/or psychomotor outcome.[2;4] Social factors did not play an important role at 18 months of age, but were associated with poorer outcome at 24 months of age. At this age, delayed mental development occurred more often

in children of young mothers and in children of non-Dutch origin.

The fact that social factors become more important as children grow older has been reported before.[4;19] The association between postnatal dexamethasone treatment and delayed mental and psychomotor outcome however, has been reported only recently. In a double blind randomized controlled trial O' Shea *et al.*[6] found a higher rate of cranial ultrasound abnormalities and cerebral palsy at 12 months corrected age in very low birthweight infants treated with a 42-day course of dexamethasone, but they did not find differences in MDI or PDI scores. Yeh *et al.*[8] reported a higher incidence of neuromotor dysfunction in dexamethasone-treated infants at 24 months corrected age. MDI and PDI scores in the dexamethasone treated infants did not differ from those of the control group. More recently, Shinwell *et al.*[7] reported a higher incidence of cerebral palsy and developmental delay at a mean of 53 months of age in infants treated with dexamethasone before 12 hours of age compared to infants who received placebo. Development was however not assessed with a detailed developmental test and the age at follow-up ranged from 24 to 71 months.

Although our study is not a randomized controlled trial studying the effects of dexamethasone treatment, we did find a strong association between postnatal treatment with dexamethasone and developmental delay. Treatment with dexamethasone was only given to infants with severe respiratory problems to wean them of the ventilator.The poor clinical condition of these infants may have negatively influenced their developmental outcome. Corrected for pulmonary and other perinatal and social risk factors for delayed development however, the association between dexamethasone treatment and delayed psychomotor development remained significant. These findings suggest that dexamethasone should be used with caution.

In conclusion, we found that at 18 and 24 months of age, a considerable percentage (40%) of the very prematurely born children had moderate to severely delayed mental and/or psychomotor development. Early developmental assessment seems therefore useful, since intervention programs like physical and speech therapy can then be started at an early age. In this way the development of some of these children might be improved so that they will be able to follow main stream education later in life.

Postnatal treatment with dexamethasone appeared to be one of the major risk factors for delayed (psychomotor) development.

References

1. Veen S, Ens-Dokkum MH, Schreuder AM, Verloove-Vanhorick SP, Brand R, Ruys JH. Impairments, disabilities, and handicaps of very preterm and very-low-birthweight infants at five years of age. The Collaborative Project on Preterm and Small for Gestational Age Infants (POPS) in The Netherlands. Lancet 1991;338:33-6.
2. Landry SH, Fletcher JM, Denson SE, Chapieski ML. Longitudinal outcome for low birth weight infants: effects of intraventricular hemorrhage and bronchopulmonary dysplasia. J Clin.Exp. Neuropsychol. 1993;15:205-18.
3. Landry SH, Denson SE, Swank PR. Effects of medical risk and socioeconomic status on the rate of change in cognitive and social development for low birth weight children. J Clin.Exp. Neuropsychol. 1997;19:261-74.
4. Weisglas-Kuperus N, Baerts W, Smrkovsky M, Sauer PJ. Effects of biological and social factors on the cognitive development of very low birth weight children. Pediatrics 1993;92:658-65.
5. Bradley RH, Casey PH. Family environment and behavioral development of low-birthweight children. Dev.Med.Child Neurol. 1992;34:822-6.
6. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG. Randomized Placebo-controlled Trial of a 42-Day Tapering Course of Dexamethasone to Reduce the Duration of Ventilator Dependency in Very Low Birth Weight Infants: Outcome of Study Participants at 1-Year Adjusted Age. Pediatrics 1999;104:15-21.
7. Shinwell ES, Karplus M, Reich D, Weintraub Z, Blazer S, Bader D *et al*. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. Arch.Dis.Child Fetal Neonatal Ed 2000;83:F177-F181.
8. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC *et al*. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics 1998;101:E7.
9. Bayley N. Bayley Scales of Infant Development. New York: Psychological Corporation, 1969.
10. Meulen van der SF, Smrkovsky M. Bayley ontwikkelingsschalen handleiding. Lisse: Swets & Zetlinger BV, 1983.
11. Kloosterman GJ. [Intrauterine growth and intrauterine growth curves]. Maandschr. Kindergeneeskd. 1969;37:209-25.
12. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
13. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J.Pediatr. 1978;92:529-34.
14. de Vries L, Dubowitz LM. Hemorrhagic and ischemic lesions of the perinatal brain. Int J Technol. Assess.Health Care 1991;7 Suppl 1:99-105.
15. Prechtl HF. The neurological examination of the fullterm newborn infant. Clin Dev Med 63. London, Heinemann. 1977.
16. Hempel MS. The neurological examination technique for toddler-age. Thesis. University of Groningen. 1993.
17. Westerlaak van JM, Kropman JA, and Collaris JWM Beroepenklapper (Professional Index, Dutch). Nijmegen, Instituut voor Toegepaste Sociologie. 1975.

18. Bayley N. Manual for the Bayley Scales of Infant Development, second edition. San Antonio, TX, The Psychological Corporation. 1993.
19. Resnick MB, Stralka K, Carter RL, Ariet M, Bucciarelli RL, Furlough RR *et al*. Effects of birth weight and sociodemographic variables on mental development of neonatal intensive care unit survivors. Am.J.Obstet.Gynecol. 1990;162:374-8.

CHAPTER 9

Changes in neonatology: Comparison of two cohorts of very preterm infants (GA < 32 wks): The Project On Preterm and Small for gestational age infants 1983 and The Leiden Follow-Up Project on Prematurity 1996-1997

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Abstract

Objective: To determine changes in peri- and neonatal care concerning neonatal mortality and morbidity by comparing two cohorts of very prematurely born infants (gestational age [GA] <32 weeks), one from the 1980s and one from the 1990s.
Methods: The Leiden Follow-Up Project on Prematurity (LFUPP-1996/97), a regional, prospective study includes all infants born alive after a gestational age (GA) <32 weeks in 1996 and 1997 in the Dutch health regions Leiden, The Hague and Delft. The Project On Preterm and Small for gestational age infants (POPS-1983), a national, prospective study from the pre-surfactant era, includes all liveborn infants <32 weeks' GA and/or <1500 g from 1983 (n=1338). For comparison infants from the POPS-1983-cohort with a GA <32 weeks from the same Dutch health regions were selected (n=102).
Results: The absolute number of preterm births in the study-region increased with 30%: 102 in 1983 to on average of 133 in 1996-1997. Centralization of perinatal care improved: the percentage of extra-uterinely transported infants decreased from 61% in 1983 to 35% in 1996-1997. A total of 182 (73%) of the LFUPP-1996/97 infants were treated antenatally with glucocorticosteroids compared with 6 (6%) of the POPS-1983-infants. A total of 112 (42%) of the LFUPP-1996/97-infants received surfactant. In-hospital mortality decreased from 30% in the 1980s to 11% in the 1990s. Mortality of the extremely preterm infants (<27 weeks) decreased from 76% to 33%. The incidence of respiratory distress syndrome remained the same: about 60% in both groups. Mortality from respiratory distress syndrome however decreased from 29% to 8%. The incidence of bronchopulmonary dysplasia increased from 6% to 19%. For the surviving infants, the average length of stay in the hospital and the mean number of NICU-days stayed approximately the same (about 67 days total admission time and 44 NICU days in both groups); including the infants who died, the mean NICU-admission time increased from 27 days in the 1980s to 41 days in the 1990s. Equal percentages of adverse outcome (dead or an abnormal general condition) at the moment of discharge from hospital were found ($\pm$ 40% in both groups).
Conclusions: An increase in the absolute number of very preterm births in this study-region was found, leading to a greater burden on the regional neonatal intensive care units. Improvements in peri- and neonatal care have led to an increased survival of especially extremely preterm infants. However, increased survival has resulted in more morbidity, mainly bronchopulmonary dysplasia, at the moment of discharge from the hospital.

Introduction

Perinatology has changed dramatically over the years. Advances in technology like high frequency oscillation and new ways of treatment like the administration of glucocorticosteroids antenatally and surfactant therapy have resulted in an increasing number of surviving infants. The limit of viability continues to be challenged.

Most studies comparing the outcome of infants born in the pre-surfactant era to that of infants born after the introduction of surfactant are hospital based. These hospitals are most often tertiary care-level centers, which leads to a selection bias as the older or more mature preterm infants who do not need this level of intensive care are not included. In this study we therefore compare a regional based follow-up study: the Leiden Follow-Up Project on Prematurity 1996-1997 (LFUPP-1996/97) to a national follow-up study from the 1980s: the Project On Preterm and Small for gestational age infants 1983 (POPS-1983).[1-3] Changes in neonatal mortality and morbidity are described as well as changes in perinatal and neonatal management.

Patients and Methods

The LFUPP was started in 1996. This regional, prospective study includes all infants born alive after a gestational age (GA) <32 weeks in 1996 and 1997 in the health regions Leiden, The Hague and Delft in the Netherlands.
The three Dutch health regions used in the study are situated in the Dutch province Zuid-Holland. In the years 1996-1997 this province had 3.4 million inhabitants on a total of 15.5 million people living in the entire Netherlands. With 21% of the total Dutch population living in this province, it is a reasonably densely populated region.

Demographic data of the Netherlands and the studied region in 1983 and 1996-1997 as well as socio-economic data are listed in Table 1.

Inclusion was based on postal code; infants whose parents were residing in one of the three health regions but whose child for some reason was born outside the study-region, were included in the study, where as premature infants <32 weeks' GA born in the study region but coming from another geographical area were not.

Table 1. Demographic data of the Netherlands and the study-region in 1983 and 1996-1997

	1983	1996-1997
Number of inhabitants		
The Netherlands	14.339.551	15.493.889
Province Zuid-Holland	3.129.913	3.424.093
Live births		
The Netherlands	170.246	190.982
Study-region	15.605	17.450
Ethnicity		
Nonwhite*	607.216	1.171.113
Personal income, euro/ mo	1469	1656

*mostly Turkish, Moroccan and Surinamese (Creole, Hindu)

The LFUPP-1996/1997 ultimately included 266 infants, constituting 92% of eligible infants born in 1996 and 1997 (97% of eligible infants from 1996 and 88% of eligible infants from 1997). Of these 266 infants, 163 (62%) were born in tertiary-level centers (centers with a NICU), 122 of those (75%) were born in the Leiden University Medical Center. Seventy-one infants (27%) of 266 were born in regional hospitals in The Hague and immediately after birth transported to the NICU of the Juliana Children's hospital in The Hague. This hospital did not have a maternity ward so all children born in The Hague with need for intensive care had to be transported to this hospital.

The Leiden University Medical Center and the Juliana Children's hospital have the same clinical neonatal care, a total of 193 (73%) of the infants were admitted to either one of these hospitals. The other hospitals contributing to this study had the same clinical protocol for resuscitation, with the exception that other NICU-hospitals did not resuscitate infants <25 weeks' GA. In the study-region, full resuscitation in the delivery room was started from a GA of 24^{+0} weeks.

The POPS was started in 1983. This national, prospective study from the pre-surfactant era includes all infants born alive after a GA <32 weeks and/or with a birthweight <1500 g in 1983 in the Netherlands. At that time, no data were routinely available on incidence of preterm or SGA birth and morbidity or mortality by GA or birth weight. Since collecting data on all high-risk newborns

in the Netherlands would have involved 10.000 or more infants per year, we decided to collect data on the smallest and least mature infants with the highest risk of mortality and morbidity.

The POPS-1983 included 1338 infants, constituting 94% of eligible infants born in 1983. A total of 102 of these infants had a GA <32 weeks and were born in the LFUPP-1996/97 health regions. Thirty-three of these infants (32%) were born in centers with a NICU; of those, 24 (73%) were born in the Leiden University Medical Center. Forty-one infants (33%) were born in regional hospitals in The Hague and immediately after birth transported to the NICU of the Juliana Children's hospital in The Hague. As in the 1990s, this hospital did not have a maternity ward. In the 1980s, neonatal care in the LUMC and the Juliana Children's hospital were equal; full resuscitation was also started from a GA of 24^{+0} weeks. GA was generally well known in the Netherlands in the 1980s and certainly in the 1990s, because of good, standardized antenatal care with early (GA 12 weeks) ultrasound assessments.

For comparison of the 2 cohorts, only the infants of the POPS-1983 cohort <32 weeks GA and from the same health regions (selection by postal code) as the infants from the LFUPP cohort were included in the analyses. We choose not to include the SGA-infants >32 weeks GA, these infants are more mature and therefore not comparable to very preterm infants.

In both studies perinatal factors were collected on precoded forms. Data collected included preexisting diseases of the mother, obstetrical history, and neonatal data.

Causes of death were multiple in many infants (eg, both pulmonary and infectious problems). The main cause of death as judged by the pediatrician-neonatologist was used to create Table 2 concerning causes of death.

Not all variables were encoded equally. RDS was divided in grades 1 to 4 in the LFUPP-1996/97. In the POPS-1983, RDS was defined as clinically or roentgenologically present. A dichotomous variable was made for the comparison; both clinically and roentgenologically present RDS was encoded as RDS in the POPS-1983.

Bronchopulmonary dysplasia (BPD) was defined according to Shennan *et al.*[4] in the LFUPP-1996/97 and according to Bancalari *et al.*[5] in the POPS-1983. According to Shennan, an infant suffers from BPD if it is still oxygen dependent at 36 weeks' postmenstrual age. The Bancalari definition includes mechanical ventilation for at least 3 days in the first week after birth, clinical signs of chronic

Table 2. Time and causes of death (in hospital mortality) in 1983 and 1996-1997

	POPS 1983 (n = 31/102)	LFUPP 1996/1997 (n = 29/266)	p*
Day of death, mean (SD)	5.9 (24.2)	12.7 (23.6)	NS
RDS, % (*n*)	52 (16)	45 (13)	NS
Cerebral, % (*n*)	6 (2)	24 (7)	NS
Infectious, % (*n*)	6 (2)	7 (2)	NS
NEC, % (*n*)	3 (1)	10 (3)	NS
Congenital malformation, % (*n*)	10 (3)	7 (2)	NS
Other, % (*n*) †	23 (7)	7 (2)	NS

NS indicates non significant; NEC, necrotizing enterocolitis.
* Student's *t*-test or Chi-square test.
† The 2 infants from the LFUPP group died of multi-organ failure and immaturity; other causes of death were not specified in the POPS.

respiratory disease, oxygen dependency and persistent radiographic changes at 28 days post partum.

The variable 'condition at discharge from hospital' was dichotomous in the LFUPP-1996/97, if any abnormality existed this variable was encoded as abnormal. Abnormalities could include: neurological disorders (on clinical examination), pulmonary problems (BPD), cardiac disorders, feeding problems (eg, tube feeding), visual problems (retinopathy of prematurity) or hearing disorders. In the POPS-1983 this variable could also be encoded dubious; for the comparison dubious cases were considered abnormal.

Both studies were approved by the Ethics Committee of The Leiden University Medical Center. Parental informed consent was obtained.

Statistical analysis

SPSS 10.0 for Windows was used for statistical analyses. The chi-square test was used to compare categorical variables; Fisher's exact test was applied where appropriate. Student's *t* test was used for comparison of continuous variables. The Kaplan-Meier method was used for a survival analysis of the first 28 days post partum. $P < .05$ was considered significant.

Results

In the LFUPP-1996/97 cohort, 266 infants were included over a 2-year period, on average 133 infants per year. In 1983, 102 infants were included. The absolute number of births <32 weeks GA therefore increased by 30%. The number of live births in the Netherlands increased from 170.246 in 1983 to on average 190.982 in 1996-1997. In the study region the number of live births increased from 15.605 in 1983 to 17.450 in 1996-1997 (these numbers were based on the known total number of live births and the number of inhabitants in the study region and the Netherlands). The number of live births in the study region increased over the years, the relative number of preterm births <32 weeks GA in the study region, however, still increased by 0.12% (0.65% of the number of live births in the region in 1983 vs. 0.76% in 1996-1997).

Obstetric history

Socioeconomic status and preexisting diseases of the mother, diseases, intoxications, and medication during pregnancy are shown in Table 3.

Socioeconomic status of the mother (as determined by level of education) was high in 29%, average in 50% and low in 21% of the mothers in the 1990s. The corresponding percentages in the 1980s are 33%, 30% and 37% ($p = .005$). In both groups, however, the number of missings for this variable was considerable: 21% in the LFUPP-1996/97 group and 30% in the POPS-1983 group.

No significant differences or any trends were found between the groups in incidences of diseases before and during pregnancy. The percentage of mothers who smoked during their pregnancy decreased from 24% in the POPS-1983 group to 15% in the LFUPP-1996/97 group ($p = .07$).

Use of antibiotics increased almost 3-fold: 29% of the mothers in the LFUPP-1996/97 group received antibiotics during their pregnancy as opposed to 10% in the POPS-1983 group ($p < .001$), Table 3. The percentage of mothers with prolonged rupture of membranes (PROM) who received antibiotics was higher in the LFUPP-1996/97 group: 48% (45 of 93) versus 9% (4 of 44, $p < .001$). Dividing the PROM in <24 hours and ≥24 hours, the percentage of mothers treated with antibiotics was still significantly higher in the LFUPP-1996/97 cohort in both groups: 33% (6 of 18) versus 4% (1 of 23) when PROM was <24 hours ($p = .01$), and 52% (39 of 75) versus 14% (3 of 21, $p < .001$) when PROM was ≥24 hours. No significant difference was found in frequency of treatment with

Table 3. Comparison of data concerning the obstetric history between 1983 and 1996-1997

	POPS 1983 (n = 102)	LFUPP 1996-1997 (n = 266)	p*
Socioeconomic status, % (*n*)			
High	33 (24/71)	29 (61/210)	.005
Average	30 (21/71)	50 (105/210)	
Low	37 (26/71)	21 (44/210)	
Pre-existing diseases, % (*n*)			
Cardiac disease	2 (2)	2 (4)	NS
Epilepsy	-	0.8 (2)	NS
Diabetes mellitus	1 (1)	2 (5)	NS
Renal disease	2 (2)	2 (4)	NS
Hypertension	4 (4)	3 (7)	NS
Diseases during pregnancy, % (*n*)			
Diabetes gravidarum	5 (5)	2 (6)	NS
Hypertension	10 (10)	9 (23)	NS
Preeclampsia	4 (4)	8 (20)	NS
Eclampsia	1 (1)	2 (4)	NS
Intoxications during pregnancy, % (*n*)			
Smoking	24 (19)	15 (34)	.07
Medication during pregnancy, % (*n*)			
Diuretics	1 (1)	3 (7)	NS
Antihypertensive medication	10 (10)	17 (44)	NS
Tranquilizers	10 (10)	6 (15)	NS
Anti-epileptics	1 (1)	1 (3)	NS
Antibiotics	10 (10)	29 (74)	<.001

NS indicates non significant.
* Chi-square or Student's t-test.

antibiotics in women without PROM: 18% (29 of 165) in the LFUPP-1996/97 group and 10% (6 of 58) in the POPS-1983 group, (p = .2).

For the POPS-1983 group, no data about pregnancy induction (in casu hormone treatment since in vitro fertilization [IVF] was just coming about in the early 1980s) were available. In the LFUPP-1996/97 group, pregnancy was induced in 21 mothers, leading to a total of 36 (14%) of 265 births: hormone treatment in 6 mothers (12 infants [33%]), IVF in 13 (22 infants [61%]) and intracytoplasmatic sperm injection in 2 mothers (2 infants [6%]).

Delivery

Data concerning the delivery are listed in Table 4. Use of tocolytics and antenatal administration of corticosteroids occurred significantly more often in the 1990s cohort. Mean maternal age at birth increased by almost 4 years, from 26.8 in 1983 to 30.5 in 1996-1997.

The percentage of infants delivered vaginally or by caesarean section did not differ between the 2 groups. Although not significant, a greater percentage of 26 and 27 weeks' GA infants were delivered by cesarean section in the 1990s: 19% (4 of 21) in the POPS-1983 and 31% (15 of 49) in the LFUPP-1996/97. In both groups, none of the 24- or 25-week-old infants were delivered by cesarean section.

Table 4. Comparison of data concerning the delivery between 1983 and 1996-1997

	POPS 1983 (n = 102)	**LFUPP 1996-1997 (n = 266)**	**p⋆**
Tocolytics, % (*n*)			
Betamimetics > 24 h	39 (40)	51 (133)	.04
Indocid > 24 h	6 (6)	19 (49)	.002
Antenatal glucocorticoids, % (*n*)	6 (6)	73 (182)	<.001
Maternal age at birth, y, mean (SD)	26.8 (6.7)	30.5 (5.6)	<.001
Mode of delivery, % (*n*)			
Head	46 (47)	46 (123)	NS
Other position	15 (15)	14 (37)	
Caesarean section	39 (40)	40 (106)	NS
Duration of rupture of membranes at delivery, % (*n*)			
No rupture	57 (58)	65 (170)	<.001
< 24 h	22 (23)	7 (19)	
1-7 days	11 (11)	20 (52)	
> 7 days	10 (10)	8 (22)	
Gestational age			
Mean (SD)	29.0 (13.4)	29.2 (14.8)	NS
< 27 weeks, % (*n*)	17 (17)	17 (46)	NS
Certainty of GA, % (*n*)			
Certain	70 (71)	95 (251)	<.001
Dubious	19 (19)	3 (8)	
Uncertain	11 (11)	2 (4)	

NS indicates non significant.
⋆ Chi-square or Student's *t*-test .

The duration of rupture of membranes at delivery differed significantly between the groups. The majority of membrane ruptures was of short duration (<24 hours) in the POPS-1983 group (23 of 44 [52%]) and of longer duration (1-7 days) in the LFUPP-1996/97 group (74 of 93 [80%]).

Mean GA (29 weeks) and the percentage of immature infants (< 27 weeks, 17%) did not differ between the groups (Table 4). GA was certain in 251 (95%) of 263 LFUPP-1996/97 infants, dubious in 8 (3%), and uncertain in 4 (2%). In the POPS-1983 cohort, the corresponding numbers were certain in 71 (70%) of 102, dubious in 19 (19%) and uncertain in 11 (11%, Table 4).

Birth characteristics

A comparison of birth characteristics and neonatal morbidity of the infants from the POPS-1983 and LFUPP-1996/97 is presented in Table 5.

Mean GA; mean birth weight; and percentages of infants who were born SGA (birth weight < 10th percentile)[6], were of male gender, had congenital malformations and were of white race did not differ between the 2 groups.

Although not significant, a 7% increase of infants from multiple births was found. In the LFUPP-1996/97 group, a significant association between multiple

Table 5. Comparison of birth characteristics between 1983 and 1996-1997

Birth characteristic	**POPS 1983 (n = 102)**	**LFUPP 1996-1997 (n = 266)**	**p⋆**
GA, wk, mean	29.0	29.2	NS
Birth weight, g, mean (range)	1234 (540-2580)	1250 (420-2382)	NS
SGA, % (*n*)†	18 (18)	12 (33)	NS
Male gender, % (*n*)	50 (51)	55 (147)	NS
Multiple birth (twin/ triplet), % (*n*)	25 (26)	32 (84)	NS
Congenital malformations, % (*n*)	8 (8)	5 (14)	NS
Inborn (NICU), % (*n*)	32 (33)	62 (163)	<.001
Extrauterine transport, % (*n*)	61 (62)	35 (93)	<.001
White, % (*n*)‡	83 (84/102)	75 (167/209)	NS

NS indicates non significant.
⋆ Student's *t*- or Chi-square test.
† Birth weight <10th percentile.
‡ Nonwhite = mostly Turkish, Moroccan, and Surinamese infants.

birth and assisted reproduction was found: 30 (83%) of 36 infants from multiple births were born after induction of pregnancy versus 55 (17%) of 229 singletons ($p < .001$).

The percentage of infants born in hospitals with a NICU increased from 32% to 62%; the percentage of infants who were transported after birth to centers with a NICU decreased from 61% in the 1980s to 35% in the 1990s ($p < .001$). In both groups, the majority of transported infants were born in the region The Hague; almost all infants in this region had to be transported after birth to the Juliana Children's Hospital. In the POPS-1983 group 41 (66%) of 62 transported infants were transported to this hospital, in the LFUPP-1996/97 group 71 (76%) of 93 transported infants. In the POPS-1983 group 7 (10%) infants of the 69 who were born in a center without a NICU did not have to be transported after birth; the corresponding number in the LFUPP-1996/97 group was 10 (10%) of 103 infants.

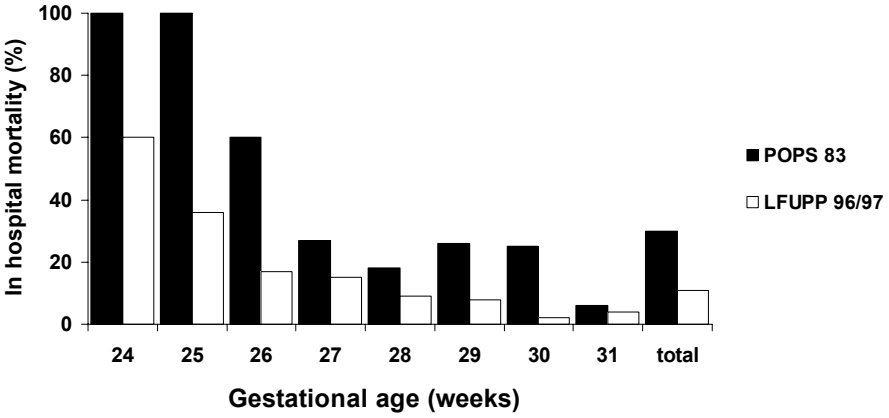
In-hospital mortality

In-hospital mortality was 11% (29 of 266) in the LFUPP-1996/97 and 30% (31 of 102) in the POPS-1983 ($p < .001$). For the immature infants (GA <27 weeks) in-hospital mortality decreased from 76% (13 of 17) to 33% (15 of 46). In-hospital mortality is shown in Figure 1 according to GA. In the 1990s, mortality was lower in all GA-categories. A survival analysis (Kaplan Meier curve) for the first 28 days is shown in Figure 2 for both the immature and nonimmature infants. In the 1990s, the non-surviving infants died after on average 12.7 days, in the 1980s the corresponding number was 5.9 ($p = .3$, Table 2).

Early neonatal death (within 7 days after birth) was 55% (16 of 29) in the LFUPP-1996/97 group; 34% (10 of 29) died within 24 hours. Twenty nine of the 31 deaths (93%) in the POPS-1983 cohort occurred in the first week after birth, 71% (22 of 31) within 24 hours. Thirty-three percent (5 of 15) of the immature LFUPP-1996/97 infants died within 24 hours compared with 85% (11 of 13) of the immature POPS-1983 infants ($p = .009$). In the older infants (≥27 weeks GA) as well, the percentage of deaths within 24 hours was higher in the POPS-1983 group, although not significant: 61% (11of 18) versus 36% (5 of 14; $p = .2$). Late neonatal death (between 7 and 28 days after birth) was 38% (11 of 29) in the LFUPP-1996/97 group; none of the POPS-1983 infants died in this period. In both groups 2 infants died after 28 days post partum.

Treatment was withdrawn because it was considered to be medically futile in

Figure 1. Mortality according to GA.



52% of the LFUPP-1996/97 deaths and in 45% of the POPS-1983 deaths (p = .6). Withdrawal of treatment occurred in equal percentages in the immature (<27 weeks GA) and more mature infants and in infants who died within or after 24 hours in both groups.

Pulmonary problems seemed to be the most important cause of death, in both groups about 50% of the infants who died in the neonatal period died mainly of RDS (13 of 29 LFUPP-1996/97 group; 16 of 31 POPS-1983 group; Table 2). Mortality from RDS as a function of the number of infants who had RDS, however, decreased significantly: 29% (16 of 55) of the infants with RDS from the POPS-1983 group died from RDS as opposed to 8% (13 of 156) of the infants from the LFUPP-1996/97 (p < .001).

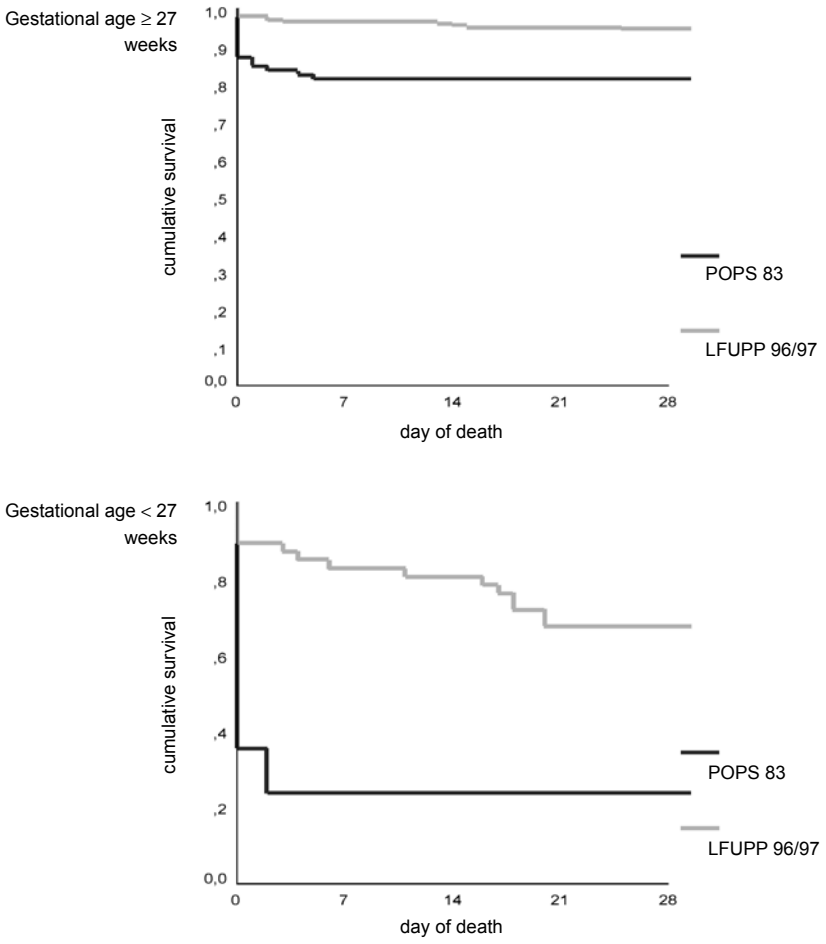
There was a trend towards higher mortality from cerebral causes in the LFUPP-1996/97 cohort: 24% versus 6% in the POPS-1983 cohort. This difference, however, did not reach significance (p = .06).

Neonatal morbidity

A comparison of neonatal morbidity of the infants from the POPS-1983 and LFUPP-1996/97 is presented in Table 6.

The incidence of RDS remained the same, around 60% in both groups. In the LFUPP-1996/97 cohort 24% (29 of 121) of infants whose mothers were treated antenatally with a full course of corticosteroids (2 doses) developed severe RDS (grade 3 to 4) compared with 45 (35%) of 126 in the incompletely or non-

Figure 2. Survival in the first 28 days post partum.



treated infants (p = .04). Of the 6 infants in the POPS-1983 who received corticosteroids antenatally, 2 developed (roentgenologically proven) RDS (33%).

A total of 112 (42%) of the LFUPP-1996/97 cohort were treated with surfactant. Surfactant was given as rescue treatment, not prophylactically at birth. As expected, treatment with surfactant was associated with the severity of the RDS: 95% of infants with RDS grade 3 to 4 received surfactant as opposed to 41% with grade 1 to 2 RDS and 3% of the infants without RDS (p < .001).

Pneumothorax was more frequently found in the POPS-1983 cohort, 15% of the infants had this complication as opposed to 6% in the LFUPP-1996/97

Table 6. Comparison of neonatal morbidity between 1983 and 1996-1997

	POPS 1983 (n = 102)	LFUPP 1996-1997 (n = 266)	p*
Pulmonary problems, % (*n*)			
RDS	57 (55)	60 (156)	NS
Pneumothorax	15 (15)	6 (16)	.01
BPD	6 (6)	19 (49)	<.001
Mechanical ventilation	63 (63)	78 (199)	.004
Days, mean (range)	5.4 (1-39)	9.2 (1-45)	.004
Circulatory disorders, % (*n*)			
PDA	18 (18)	26 (70)	NS
Sepsis (positive bloodculture), % (*n*)	16 (14)	28 (72)	.03
Neurological disorders, % (*n*)			
IVH: none	74 (72)	74 (192)	.02
Grade 1	7 (7)	13 (34)	
Grade 2	14 (14)	5 (12)	
Grade 3	3 (3)	4 (11)	
Grade 4	2 (2)	3 (9)	
Seizures	5 (5)	5 (13)	NS
Hydrocephalus	5 (5)	5 (12)	NS
CNS abnormalities during admission			
Mild	8 (8)	9 (23/261)	NS
Severe	6 (6)	4 (11/261)	NS
NEC, % (*n*)	4 (4)	9 (25/265)	NS
Medication, % (*n*)			
Antibiotics	77 (77)	93 (247)	<.001
Anticonvulsants	22 (22)	19 (51/264)	NS
Diuretics	6 (6)	6 (15/264)	NS
Surfactant	-	42 (112)	<.001
Admission time, d, mean (range)			
NICU			
Survivors	41.2 (8-121)	44.4 (1-215)	.8
All (dead included)	26.7 (0-133)	41.2 (0-215)	.002
Total	66.9 (23-127)	67.2 (13-215)	.9

NS indicates non significant; PDA, patent ductus arteriosus; CNS, central nervous system; NEC, necrotizing enterocolitis.

* Student's *t*- or Chi-square test.

cohort. The percentage of infants mechanically ventilated was significantly higher in the LFUPP-1996/97 cohort: 78% of the infants versus 63% in the POPS-1983 group ($p = .004$). Infants from the LFUPP-1996/97 group were ventilated on average 3.8 days longer than the infants from the POPS-1983 group.

The incidence of BPD increased from 6% in the 1980s to 19% in the 1990s. No differences existed in incidences of patent ductus arteriosus, NEC and neurological disorders like seizures, hydrocephalus, or central nervous system abnormalities during admission.

A trend towards less serious intraventricular hemorrhage (IVH) was found: the percentages of infants with grade 3 or 4 IVH remained about the same, but the percentage with grade 2 IVH decreased from 14% in the 1980s to 5% in the 1990s while the percentage with IVH grade 1 increased from 7 to 13% ($p = .02$). In the LFUPP-1996/97 cohort IVH occurred less frequently in infants whose mothers were treated antenatally with a full course of glucocorticosteroids: 81% (97 of 120) of the fully treated infants did not develop IVH compared with 69% (84 of 122) of the nontreated or incompletely treated infants ($p = .09$).

Sepsis (positive blood culture) occurred more frequently in the 1990s: 28% of the infants from the LFUPP-1996/97 versus 16% in the POPS-1983-cohort ($p = .03$). The percentage of infants who were treated with antibiotics increased from 77% to 93% ($p < .01$).

The average length of stay in the hospital stayed almost the same: 66.9 days (SD: 22.5; range: 23-127) in the 1980s and 67.2 days (SD: 28; range: 13-215) in the 1990s ($p = .9$). The number of NICU-days for survivors was almost equal as well: 41.2 days (SD: 27.3; range: 8-121) in the 1980s and 44.4 days (SD: 33.6; range: 1-215) in the 1990s ($p = .8$). However, including the infants who died, in determining NICU time, this increased from 26.7 days (SD 31.5) in the 1980s to 40.7 days (SD 34) in the 1990s ($p = .002$).

In conclusion, we found no difference in the incidence of RDS and severe IVH; a decrease in the incidence of pneumothorax and an increase in the incidences of BPD and sepsis was found. The deceased infants included, the number of days spent in NICU increased.

Condition at discharge

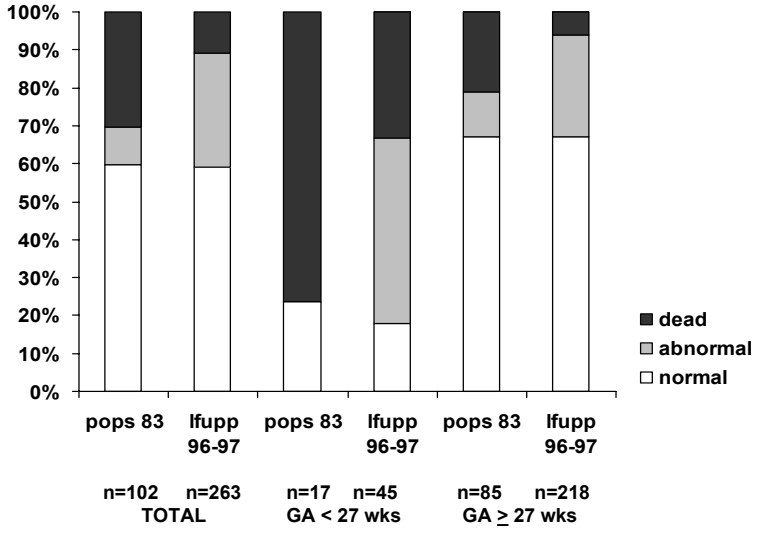
Ten of the 102 patients of the POPS-1983 cohort were considered abnormal at discharge; 8 of these were encoded dubious, and 2 were abnormal. The dubious cases were considered abnormal for the comparison.

In the total group of infants, adverse outcome (dead or abnormal at discharge) was 41% (109 of 263) in the LFUPP-1996/97 group and 40% (41 of 102) in the POPS-1983 group (p = .8, Figure 3).

For the immature infants (GA <27 weeks), adverse outcome was 82% (37 of 45) in the LFUPP-1996/97 group and 77% (13 of 17) in the POPS-1983 group (p = .7). Adverse outcome was found in 33% of the infants of ≥ 27 weeks GA in both groups (Figure 3).

Of the surviving infants, condition at discharge was abnormal in 34% (80 of 234) of the infants in the LFUPP-1996/97 group and in 14% (10 of 71) in the POPS-1983 group (p = .001). None of the 4 surviving immature POPS-1983 infants were found to be abnormal, 73% (22 of 30) of the immature LFUPP-1996/97 infants were (p = .01). Twenty-eight percent (58 of 204) of the surviving LFUPP-1996/97 infants of ≥27 weeks' GA were abnormal, 15% (10 of 67) of the POPS-1983 infants were (p = .03).

Figure 3. Condition at discharge from the hospital



Discussion

In this study, we compared neonatal mortality and morbidity of 2 Dutch cohorts of very preterm infants (GA <32 weeks), one from the 1980s (POPS-1983) and one from the 1990s (LFUPP-1996/97). The number of very preterm births in the studied health regions increased from 102 in 1983 to on average 133 in 1996-1997, an increase in absolute numbers of 30%, which means a greater burden on the regional NICUs.

Obstetrics

Obstetrical management changed in respect to the percentage of mothers treated with corticosteroids antenatally, which increased significantly from 6% in 1983 to 73% in 1996/1997. The 6% in the 1980s cohort may seem somewhat low. This percentage did not appear to be a good reflection of the 17% treated with steroids antenatally in the total POPS-1983-cohort <32 weeks' GA. In 1983, glucocorticoids were not given antenatally in the Leiden University Medical Center. At the time, administration of glucocorticoids antenatally for the acceleration of pulmonary maturation was still a matter of debate in the Netherlands, this therapy was restricted to 41 hospitals.[7] Another possible explanation for the difference could be the percentage of mothers treated with the tocolytic ritodrine. Administration of this ß-agonist is an effective strategy to 'buy time' for the administration of corticosteroids.[8] The percentage of mothers treated with this drug was higher in the total POPS-1983 cohort (52%) compared with the regional cohort (39%). In the total cohort, 30% of the women treated with ß-agonists received corticosteroids as opposed to 4% of the women who were not treated with ß-agonists.

Mothers of the LFUPP-1996/97 cohort were more often treated with antibiotics than those of the POPS-1983 cohort. The percentage of prolonged rupture of membranes did not differ between the two groups; the percentage of mothers with ruptured membranes who received antibiotics however was significantly higher in the LFUPP-1996/97 group. The percentage of membrane ruptures of longer duration (≥24 hours) was indeed higher in the LFUPP-1996/97 group, but treatment with antibiotics occurred more often in the group with ruptures of short duration (<24 hours) as well. Evidence that in women with preterm rupture of membranes, treatment with antibiotics led to a significant prolongation of the pregnancy and a reduction in the incidence of

chorioamnionitis and neonatal infection has probably resulted in an increased percentage of women receiving this treatment.[9]

Fourteen percent of the infants from the LFUPP-1996/97 were born after assisted reproduction, mainly IVF (8%). Since most of these children were part of a twin or triplet, the 7% increase in the percentage of infants from multiple births we found is most likely caused by the increased use of IVF (the first IVF baby in the Netherlands was born in 1983).

Delivery/Birth characteristics

A trend towards a higher percentage of 26- to 27-week-old infants being delivered with a caesarean section was found, which is probably the consequence of the better chance of survival these infants now have, justifying the greater risk the mother is exposed to when undergoing surgery than at natural child birth. GA was certain in 95% in the 1990s and in 70% in the 1980s, the higher certainty-level in the 1990s is very likely due to more early ultrasounds being made nowadays then in the early 1980s. The relatively low certainty-level in the 1980s occurred throughout the GA range of 24 to 32 weeks, therefore probably not resulting in an outcome bias.

Centralization of perinatal care in the study-region has increased: in 1983, 32% of the infants were born in centers with a NICU, in 1996-1997, this number increased to 62%. This increased centralization, not only in our study region but in the entire Netherlands, is mainly attributable to findings of the POPS-1983-study which showed that infants born in NICU's had lower mortality rates than infants transported extrauterinely.[10-13] The still relatively large number of extrauterinely transported infants in the LFUPP-1996/97 group is caused by the fact that all infants treated in the Juliana Children's Hospital in The Hague (27%) were extrauterinely transported to this center because this hospital does not have an obstetric department.

Mortality

As could be expected a significant decrease in overall mortality from 30% in the POPS-1983 group to 11% in the LFUPP-1996/97 group was found. For the extremely preterm infants (GA <27 weeks) mortality decreased from 76% to 33%. In both cohorts the majority of infants died in the first week of life. In the POPS-1983 cohort 71% died within 24 hours, in the LFUPP-1996/97 group 34%. This difference was not caused by a change in attitude towards treatment

withdrawal, since this occurred in 40% of the infants who died within 24 hours in both cohorts. Mortality at later points in time was also found by Meadow *et al.*[14] in their recent study on changes in mortality for extremely low birth-weight infants. Pulmonary problems were the main cause of mortality in both cohorts.

Morbidity

Many studies have shown a decrease in the incidence of RDS in infants whose mothers received antenatal steroids. Crowley[15], in his meta-analysis of randomized trials from 1972-1994, found that antenatal corticosteroid therapy results in an overall reduction of approximately 50% in the odds of contracting neonatal RDS. Regarding these findings and the increased use of antenatal steroids, we expected to find a decrease in the incidence of RDS. The incidence of RDS however, was approximately the same in the 1980s (57%) and 1990s (60%). While the incidence of RDS remained the same, mortality from RDS significantly decreased. This suggests that the severity of RDS is reduced by antenatal treatment with corticosteroids. In the LFUPP-1996/97 cohort, we did indeed find a smaller percentage of infants with severe RDS within the group antenatally treated with a full course of corticosteroids than in the non-treated or incompletely treated infants. Besides this, survival of infants with severe RDS is now better because of treatment with surfactant.

The increased survival of infants with RDS was associated with an increase in the percentage of infants with BPD. BPD was defined according to Shennan in the LFUPP-1996/97 and according to Bancalari in the POPS-1983. The percentage of infants with BPD in the POPS-1983-cohort would probably have been even lower if the Shennan-definition was used since it is not likely that all infants who were oxygen dependent at 28 days post partum would still be at 36 weeks' postmenstrual age. Unfortunately, chart review of POPS-cases to verify this did not yield the necessary data.

A shift towards less serious IVH was found. Although not significant, in the LFUPP-1996/97 cohort, IVH occurred less frequently in infants whose mothers were antenatally treated with a complete course of corticosteroids. A positive influence of antenatal corticosteroids on the incidence of IVH has been found in many studies. The previously mentioned meta-analysis by Crowley[15] showed that corticosteroid therapy reduces the odds of periventricular hemorrhage (odds ratio [OR]: 0.38; 95% confidence interval: 0.23-0.94). Shankaran *et al.*[16] found an odds ratio of 0.39 (95% confidence interval: 0.27-0.57) for the association of a complete course of steroids with grades 3 and 4 IVH.

Sepsis, defined as a positive blood culture, occurred more frequently in the LFUPP-1996/97 group. This could not be explained by a more frequent use of lines, 65 % (163 of 249) of the LFUPP-1996/97 infants had a venous and/or arterial line, and 70% (69 of 99) of the POPS-1983 infants had a venous line. In the LFUPP-1996/97 infants, however, the lines were probably longer in situ because of the increased survival and mortality at later points (Fig 2), which could be an explanation of the increase in the occurrence of sepsis. Unfortunately data about the exact number of days of line-usage are not known in both cohorts, so this is only speculation. Another reason could be that detection techniques are nowadays better than before, leading to a higher number of positive blood cultures. In the Leiden University Medical Center, in the 1980s 'home made' culture bottles were used, where as in the 1990s, these were replaced by industrial culture bottles (BATEC). Furthermore, Beganovic *et al*[17], in their article on the occurrence of sepsis in POPS-1983 infants receiving total parenteral nutrition, described that of the clinically septic infants, only 29% had a positive blood culture.

Time spent in NICU stayed the same for surviving infants. Including the deceased, however, time spent in NICU increased with 14 days, reflecting mortality at later points in time in the 1990s.

The percentage of infants with an adverse outcome (dead or abnormal) at discharge was comparable in both groups. Since mortality decreased considerably, this means that, in this study, increased survival resulted in more morbidity, at this age mainly BPD. The short-term outcome would be even more unfavorable for the LFUPP-1996/97 cohort if the dubious cases in the POPS-1983 cohort would have been considered normal.

We realize that in this comparison of many obstetrical and neonatal data the possibility exists that significant findings are chance findings. However, the significant differences found were mostly highly significant ($p < .001$), and most of them were based on clinical hypotheses, expected and in line with other publications, like for example considerably less mortality and improvement of centralization of perinatal care.

In conclusion, we found in the studied Dutch health regions an increase in the absolute number of very preterm births between 1983 and 1996/1997. Mortality decreased considerably, but the increased number of surviving infants has resulted in more morbidity at the time of discharge from the hospital.

References

1. van Zeben-van der AA T,Verloove-Vanhorick SP, Brand R, Ruys J. Morbidity of Very Low Birthweight Infants at corrected age of two years in a geographically defined population: Report from Project On Preterm and Small for Gestational Age Infants in the Netherlands. The Lancet 1989;333:253-5.
2. Verloove-Vanhorick SP, Verwey RA, Brand R, Bennebroek Gravenhorst J, Keirse MJNC, Ruys JH. Neonatal mortality risk in relation to gestational age and birthweight: Results of a National Survey of Preterm and Very-low-birthweight Infants in the Netherlands. The Lancet 1986;327:55-7.
3. Verloove-Vanhorick SP, Verwey RA, Brand R, Bennebroek GJ, Keirse MJ, Ruys JH. [Neonatal mortality in children born after a very short pregnancy and with a very low birth weight; results of a national study]. Ned.Tijdschr.Geneeskd. 1986;130:1146-9.
4. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
5. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. J.Pediatr. 1979;95:819-23.
6. Kloosterman GJ. [Intrauterine growth and intrauterine growth curves]. Maandschr.Kindergeneeskd. 1969;37:209-25.
7. Verloove-Vanhorick SP and Verwey RA. Project On Preterm and Small for gestational age in the Netherlands. Thesis. Rijksuniversiteit Leiden. 1987.
8. Vause S, Johnston T. Management of preterm labour. Arch.Dis.Child Fetal Neonatal Ed 2000;83: F79-F85.
9. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. Cochrane. Database.Syst.Rev. 2003;CD001058.
10. Kollee LA, Brand R, Schreuder AM, Ens-Dokkum MH, Veen S, Verloove-Vanhorick SP. Five-year outcome of preterm and very low birth weight infants: a comparison between maternal and neonatal transport. Obstet.Gynecol. 1992;80:635-8.
11. Kollee LA, den Ouden AL, Drewes JG, Brouwers HA, Verwey RA, Verloove-Vanhorick SP. [Increase in perinatal referral to regional centers of premature birth in The Netherlands: comparison 1983 and 1993]. Ned.Tijdschr.Geneeskd. 1998;142:131-4.
12. Verloove-Vanhorick SP,Verwey RA, Ebeling MC, Brand R, Ruys JH. Mortality in very preterm and very low birth weight infants according to place of birth and level of care: results of a national collaborative survey of preterm and very low birth weight infants in The Netherlands. Pediatrics 1988;81:404-11.
13. Walther FJ, den Ouden AL,Verloove-Vanhorick SP. Looking back in time: outcome of a national cohort of very preterm infants born in The Netherlands in 1983. Early Human Development 2000;59:175-91.
14. Meadow W, Lee G, Lin K, Lantos J. Changes in Mortality for Extremely Low Birth Weight Infants in the 1990s: Implications for Treatment Decisions and Resource Use. Pediatrics 2004;113:1223-9.
15. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am.J.Obstet.Gynecol. 1995;173:322-35.
16. Shankaran S, Bauer CR, Bain R, Wright LL, Zachary J. Relationship between antenatal steroid administration and grades III and IV intracranial hemorrhage in low birth weight infants. The NICHD Neonatal Research Network. Am.J.Obstet.Gynecol. 1995;173:305-12.
17. Beganovic N, Verloove-Vanhorick SP, Brand R, Ruys JH. Total parenteral nutrition and sepsis. Arch.Dis.Child 1988;63:66-7.

CHAPTER 10

General discussion

The subject of this thesis is follow-up at 2 years of age of extremely preterm (< 27 weeks GA) and very preterm infants (< 32 weeks GA). It is well documented that preterm birth may have adverse effects on a child's development. Given the high risk for residual disability, the monitoring of long term morbidity is a critical function of neonatal care.[1] It is important to register the influence of new techniques in perinatology on the infants born in one's own region or country.

Extremely preterm infants

Based upon the high percentage of adverse outcome at 2 years of age of the infants born at 24 weeks gestational age (chapter 2) and the comparable results of other studies, the decision was made in the Leiden University Medical Center, not to resuscitate infants of a gestational age (GA) below 25 weeks anymore (January 2002). Hereafter, the discussion about the limit of viability originated again in the Netherlands, and the Dutch Paediatric Association developed guidelines about the resuscitation of extremely preterm infants (appendix 1).[2;3] Purpose was that every neonatal centre could get along with these new guidelines. At this moment a complete agreement of the Dutch Association of Obstetrics and Gynaecology with these guidelines is lacking. The only issue no consensus is reached yet, concerns the timing of the precise moment of transfer of the mother in case of imminent preterm birth from 24^{+0} – 24^{+6} weeks gestational age to a level 3 centre. The Dutch Paediatric Association prefers a transfer in this period and the Dutch Association of Obstetrics and Gynaecology proposes to discuss the transfer of the mother in each individual case.[4] So nowadays in the Netherlands, infants born at 24 and 25 weeks are not routinely resuscitated and intensive care will be withdrawn if treatment is clearly futile. If birth weight is less than 500 grams, comfort care is given. This policy is also based on reports from the Dutch Paediatric Association, which argue that withholding or withdrawing life-sustaining treatment in newborn infants with extremely poor prognoses is justifiable medical practice and that decisions should be taken by the medical and nursing team, together with well-informed parents.[5]

The last American Academy of Pediatrics (AAP) statement (2007) about non-initiation or withdrawal of intensive care for high-risk newborns, proposes that these decisions should be based on four key-elements: 1. direct and open communication between health care team and the parents; 2. parents should be active

participants; 3. comfort care should be given in case of non-initiating or withdrawal of intensive care and 4. treatment decisions should be guided primarily by the best interest of the child.[6] Previously (2002) the AAP[7] stated that resuscitation was only inappropriate in infants with a birth weight below 400 grams and/or gestational age below 23 weeks. The last consensus from Australia (2006)[8] defines the "grey zone" between 23 and 25^{+6} weeks GA. It also says: "While there is an increasing obligation to treat with increasing length of gestation, it is acceptable medical practice not to initiate intensive care during this period if parents so wish, after appropriate counselling". In the United Kingdom guidelines advise intensive care in some cases from a GA > 24 weeks, but in any case from 25 weeks GA and upwards.[9]

Previous papers about mortality and outcome of these extremely preterm infants are summarised in chapter 3. It seems that people all over the world are increasingly concerned about the long term outcome of these extremely preterm infants, especially after the publications of the EPICure study group (GA < 26 weeks): at 30 months 49% of the survivors were disabled including 23% of the survivors who were severely disabled.[10;11] At 6 years of age, 78% of the surviving children underwent standardised cognitive and neurological assessments. When the results were compared with their classmates, 41% of the assessed children showed cognitive impairment. Rates of severe, moderate and mild disability were 22%, 24%, and 34% respectively.[12]

Why follow-up at the corrected age of 2 years?

It has been argued that follow-up at 2 years of age is optimal to assess developmental outcome, and although there has been a debate about the use of corrected age in assessing the development of preterm infants, nowadays it is recommended that correction is applied up to at least 2 years of age.[1;13;14] Follow-up at this age provides information at a point where environmental bias (for instance socio-economic status) and loss to follow-up is minimal, but disability and specific serious impairments can be assessed with sufficient reliability.[15] A number of conditions commonly associated with preterm birth are not evident or resolved until approximately 2 years of age (e.g. cerebral palsy, transient dystonia).[1;16] On the other hand Hack *et al.*[17] showed that the Bayley Scales of Infant Development have a poor predictive validity for cognitive function of extremely low birth

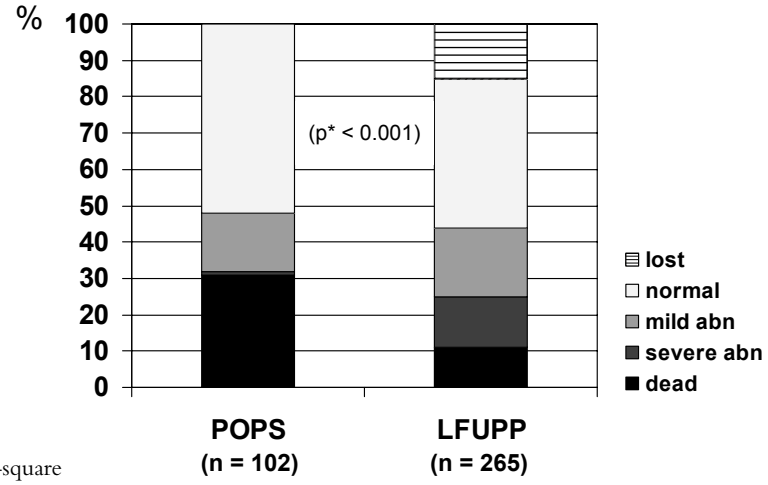
weight children at school age: rates of cognitive impairment < 70 dropped from 39% at 20 months corrected age to 16% at 8 years of age. Prediction was better for ELBW-infants with neurosensory impairments. Marlow *et al.*[12] found the outcome at 30 months of age highly predictable of the outcome at 6 years of age. Doyle *et al.*[18] found the assessment at 2 years of age to be predictive for outcome at later ages (5, 8 and 14 years) too, but mainly in case of severe developmental delay, and the prediction was less accurate for mild or moderate delay.

Of course, later follow-up is also important because preterm born children who appear to be "normal" at 3 years of age are often seen to have problems in motor or visual motor function or deficits at school age.[15] Despite a normal intelligence or being neurologically intact, preterm infants perform less well than their peers on tests of language, visual perceptual organisation and memory.[19;20] O'Brien[21] found in a cohort of preterm infants born < 33 weeks a decrease in Intelligence Quotient from 104 at 8 years to 95 at 15 years. During the same period, the percentage of impairments with disability increased from 11 to 22% and the percentage of impairments without disability from 16 to 26%. It is not clear whether this apparent deterioration in developmental outcome represents genuine deterioration in neurocognitive function or whether this presents the expression of pre-existing cerebral pathology in an increasingly complex environment.[21] In the POPS-cohort, at 9 years of age about one third of the survivors in mainstream education (so they seemed to have a rather normal development at an earlier age) were below the level for their age, compared with 10% of the 9-year-old children in the general population.[22] In contrast, Ment[23] found an improvement in cognitive function (verbal and IQ-scores) over time in VLBW-infants: mean IQ of a cohort infants with birth weight between 600 and 1250 grams, increased from 90 at 36 months corrected age, to 95 at 96 months corrected age. So some studies report an improvement in general development, some a deterioration. However, studies are difficult to compare because of differences in definitions and methods of assessment used in the various follow-up studies.
In conclusion, while follow-up at later ages is also very important and useful, we argue that every very preterm infant should at least be assessed at a follow-up clinic at the corrected age of 2 years.

LFUPP compared to POPS at the corrected age of 2 years

In chapter 9 the LFUPP-cohort is compared to the POPS-cohort but only mortality and neonatal morbidity is described. Because we were also interested in differences in outcome at 2 years of age, we performed some additional analyses. For this purpose only the infants from the POPS-cohort born < 32 weeks and from the same health regions as the LFUPP were included. Seventy (68.6%) of the 102 infants from the POPS-cohort survived until the corrected age of 2 years. Fifty-three children (76%) were classified as having a normal development (developmental quotient > 90 and no motor, visual or hearing disabilities), 16 (23%) had a mild handicap (defined as a DQ between 80 and 90, and/or at least one of the following: a mild neurological disorder such as a slight hemiparesis or quadriparesis, mild visual or hearing defects, or moderate psychosocial problems) and 1 (1%) was severely handicapped (defined as presence of retardation (DQ < 80) and/or at least one of the following: a severe neurological disorder, sever visual or hearing defects or serious psychosocial problems).[24;25] In the LFUPP-cohort, 236 children (89%) survived until the corrected age of 2 years. One infant was excluded because of Down's syndrome. Of the remaining 235 children, 106 children (46%) had a normal outcome (defined as a normal neuro-

Figure 1. Comparison of outcome at 2 years of age in live born infants of the POPS(1983) and LFUPP(1996/1997) cohort

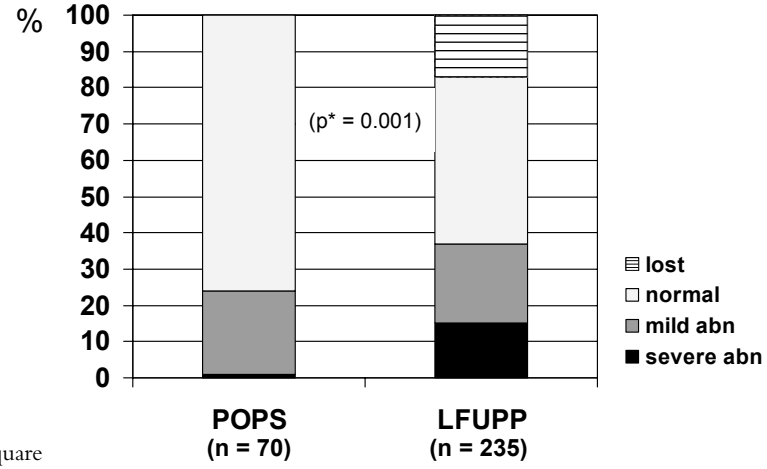


*Chi-square

logical examination according to Hempel[26] and a normal MDI or PDI according to the BSID I), 51 children (22%) a mildly abnormal outcome (mild abnormal neurological examination or moderate delay in MDI or PDI) and 36 children (15%) a definitely abnormal outcome (defined as an definitely abnormal neurological examination or a severe delay in MDI or PDI). Forty infants (17%) were not assessed.

Figure 1 shows the outcome of live born infants of the POPS-cohort and the LFUPP-cohort. Adverse outcome, defined as dead or severely disabled, was 32% (33/102) in the POPS-cohort compared to 29% (66/225) in the LFUPP-cohort. Considering that the outcome in the missing children is perhaps not adverse, the percentage could also be 25% (66/265). In the survivors a normal development was seen in 76% (53/70) in the POPS-cohort compared tot 47% (108/235) in the LFUPP-cohort, the percentage of infants with a severely (or definitely) abnormal outcome increased from 1% (1/70) in the POPS-cohort to 15% (36/235) in the LFUPP-cohort (Fig. 2). After correction for gestational age, differences in outcome remained significant between the two cohorts. So mortality was higher in the nineteen eighties (POPS) compared to the nineteen nineties (LFUPP), but in the survivors more children were severely disabled in the LFUPP compared to the POPS, not only at term age (chapter 9) but also at

Figure 2. Comparison of outcome at 2 years of age in survivors in the POPS(1983) and LFUPP(1996/1997) cohort



*Chi-square

two years of age (Figures 1 and 2). Because the lost-to-follow-up group in the LFUPP had lower socioeconomic status and parents were more often non-Caucasian, the results of the LFUPP are possibly worse, because ethnicity was a risk factor for delayed development (chapter 8) and from literature we know that low socioeconomic status also is associated with abnormal outcome. On the other hand it is difficult to compare the two cohorts in detail because different definitions for outcome were used.

Study design

This study lacks a control group, but this was logistically and financially not possible. The percentage lost-to-follow-up for the neurological and mental or psychomotor developmental assessment was 17% of the survivors. The lost-to-follow-up group differed only in socioeconomic status and ethnicity from the study group. We found a high adverse outcome in the extremely preterm infants, especially in infants born with GA 24 or 25 weeks. Although we realise that the total number of infants with GA < 27 weeks was small, results point into the same direction as found in literature. Furthermore, throughout many chapters in this thesis dexamethasone is associated with abnormal neurodevelopmental outcome or sub-optimal growth.

We realise that the relationships in this descriptive cohort study are not more than associations, and not necessarily causal connections. On the other hand this was a prospective study which included all live born infants from three health regions. Neurological, psychomotor and mental outcome were precisely defined. Furthermore, international data of follow-up studies are important to be aware of, but results of one's own country are also important to know, e.g. for providing quality control for perinatal care in the Netherlands.

The comparison of the LFUPP-cohort with (a part of) the POPS-cohort was in one way accurate because geographically the same infants were included by using postal codes. On the other hand used definitions for the outcome at 2 years of age were not similar. Furthermore many more paediatricians assessed the children at 2 years in the POPS (200 for the whole of the Netherlands) compared to only a few in the LFUPP.

Results of this study in perspective of ongoing changes in perinatology

In this study, several perinatal risk factors like bronchopulmonary dysplasia (chapters 7 and 8), hypotension (chapters 6 and 8), cystic periventricular leucomalacia (chapters 6 and 8) and the postnatal use of dexamethasone (chapters 2, 6 and 8) are associated with adverse neurodevelopmental outcome in very preterm infants. Bronchopulmonary dysplasia, cystic periventricular leucomalacia and the use of dexamethasone were also associated with suboptimal later growth (chapter 4), just like intrauterine growth restriction (resulting in being born small-for-gestational-age) or extra-uterine growth restriction (PGR) in the neonatal period (chapter 5).

The Leiden Follow-Up Project on Prematurity was started more than 10 years ago. The disadvantage of follow-up studies is that during a follow-up period new techniques and interventions have developed, which could have an influence on perinatal care. Nowadays in the 21st century for example we use much lower doses and shorter courses of dexamethasone compared to 1996/1997. Techniques for the cerebral ultrasound scanning have been refined and the use of Magnetic Resonance Imaging (MRI) for detecting cerebral damage has increased. Because of the association of intracerebral abnormalities (especially periventricular leucomalacia) and the use of dexamethasone with abnormal long-term outcome, these risk factors will be discussed in relation to new insights.

Periventricular leucomalacia

Although cystic periventricular leucomalacia (PVL) results in an increased risk of adverse outcome, many of the extremely preterm infants without cystic PVL survive with some degree of disability.[27] Nowadays, not only the cystic PVL but also diffuse PVL is considered the principal form of brain injury, and prognostically important.[19] Already in 1992, de Vries *et al.*[28] described the whole spectrum of leucomalacia using cranial ultrasound. Van Wezel-Meijler *et al.*[29] described in a follow-up study the degree of echogenicity on cranial ultrasound to carry the highest predictive value for abnormal neurodevelopment at 12 months corrected age, compared to duration of flaring on ultrasound and degree of periventricular signal intensity change on magnetic resonance imaging (MRI). Olsen *et al.*[27] found, as expected, significant differences between infants with PVL and normal controls, regarding psychological outcomes. Interestingly, preterm infants with-

out PVL also scored significantly lower than normal controls. So they conclude, like others, that there must be subtle brain changes that cannot be identified by non-functional MRI.

In 1999, Maalouf *et al.*[30] published results of a study in preterm infants with GA < 30 weeks, where they concluded that abnormalities on MRI are commonly seen in the brain of preterm infants in the first 48 hours and that further abnormalities develop between birth and term age. A characteristic appearance on MRI of Diffuse and Excessive High Signal Intensity (DEHSI) in the white matter was associated with the development of cerebral atrophy and might be a sign of white matter disease. The major risk factors for this white matter abnormality are related to perinatal infection and hypotension associated with use of inotropics.[31] Neonatal cranial ultrasound of the very preterm infant demonstrates high reliability in the detection of cystic PVL, but has significant limitations in the detection of the noncystic white matter injury. This restriction of neonatal cranial ultrasound is important, because non-cystic PVL is considerably more common than cystic PVL.[32] For detection of DEHSI (and to help to predict the prognosis), it would be preferable to perform an MRI at term age in preterm infants at risk.

Dexamethasone

After Mammel *et al.*[33] reported in 1983 a significant respiratory benefit from dexamethasone in preterm infants, a widespread use of high doses of dexamethasone for periods as long as 6 weeks or more arose. In the late 1990s, more than 25% of all very low birth weight infants were exposed to postnatal steroid therapy.[34] The first convincing reports of adverse effects of high-dose dexamethasone therapy on subsequent growth and neurodevelopment appeared in 1998/1999.[35;36] This resulted in a decrease in prescription of dexamethasone, demonstrated in a study by Shinwell: use of dexamethasone fell from 22% in 1993/1994 to 6% in 2001, in preterm ventilator-dependent infants.[37] However, in the DART study (Dexamethasone: A Randomized Trial), including infants with GA < 28 weeks or birth weight < 1000 grams, low-dose (0.15 mg/kg/day) dexamethasone treatment after the first week of life, clearly facilitated extubation and shortened the duration of intubation among ventilator-dependent infants, without any obvious short-term complications.[38] Although this trial was stopped because of recruitment difficulties, rates of disabilities or CP at 2 years of age were not substantially different between the groups.[39] Recently another positive

outcome was published by Nixon *et al.*[40] who reported improved respiratory outcome at 8 years of age in preterm born infants treated with dexamethasone, compared to those treated with a placebo, partly as a result from fewer days of mechanical ventilation.

Because dexamethasone facilitates extubation in these infants, the benefits of a brief course of therapy in such infants could outweigh the risks.[41] Grier and Halliday[42] wrote in their guidelines for corticosteroid use in 2005, that there is no role for use of corticosteroids in the first 4 days of life; the use of this drug should be limited to exceptional clinical circumstances, such as ventilator-dependent infants after the second week of life who cannot be weaned from ventilation and whose condition is worsening. If used, corticosteroids should be prescribed at the lowest effective dose for the shortest possible time.

But, dexamethasone is not the only glucocorticosteroid. In 2003 van der Heide-Jalving *et al.*[43] reported fewer short- and long-term adverse effects in infants treated with hydrocortisone compared to dexamethasone in the neonatal period. Recently, Rademaker *et al.*[44] reported MRI-outcomes at school age (7-8 years old) in a large cohort of preterm infants, comparing infants treated with hydrocortisone for BPD with infants who were not treated with postnatal glucocorticosteroids. Infants receiving hydrocortisone had no functional disadvantage or structural impairment with MRI. They also published that cerebral gray matter volume was reduced among preterm children compared with children born at term, but volumes were similar in children treated with hydrocortisone compared to children not treated with hydrocortisone.[45] In another publication of this group, neuromotor development at school age was found to be poorer in preterm infants treated in the neonatal period with dexamethasone for chronic lung disease, compared to infants treated with hydrocortisone or a reference group.[46] These findings are consistent with information from a multicenter randomised trial, in which infants treated with early low-dose hydrocortisone (1 mg/kg/day) showed no evidence of neurodevelopmental compromise at 18 to 22 months corrected age, compared with infants who were treated with a placebo.[47] Kristi Watterberg[41] however remarked that we hopefully have learned from the dexamethasone experience and apply a more scientific approach in case of hydrocortisone. So further randomised trials of low-dose corticosteroids given after the first week of life are warranted and should assess both short- and long-term outcome.[47]

Final conclusion

In the Leiden Follow-Up Project on Prematurity, a prospective regional study of live born infants with gestational age < 32 weeks, mortality was 35% in infants < 27 weeks gestational age (GA) and 6% in infants with GA 27–32 weeks. We found a high adverse outcome in the extremely preterm infants, especially in infants born with GA 24 or 25 weeks. These results are in line with data from international research. Therefore, infants born with a GA of 24 weeks are not actively resuscitated anymore in the Leiden University Medical Center and infants born at 25 weeks GA are resuscitated depending on the opinion of the parents, the viability at birth and the reaction of the infant to stimuli or intubation. Besides these characteristics at birth, we need a reliable parameter that could be obtained by examining an infant of 24 or 25 weeks' gestation, which is critical in making a decision to resuscitate or not. Maybe in these immature infants the well known Apgar Score is a good predictor for outcome. Recently Forsblad *et al.*[48] reported that the Apgar Score predicted short-term outcome in extremely preterm infants at 25 weeks GA, which is in line with an earlier publication of Shankaran *et al.*[49] who found more neurological impairment at 18-22 months in extremely preterm infants with a low Apgar Score.

Next to the high adverse outcome in the extremely preterm infants, we found that 40% of the children with GA < 32 weeks, had moderate or severe delayed mental and/or psychomotor development at 18 and 24 months of age according to the BSID I. Furthermore 20% of the very preterm infants suffered from bronchopulmonary dysplasia (BPD), which was associated with more respiratory problems and abnormal developmental outcome at 2 years of age compared to infants without BPD.

Concerning growth, we found length and weight at 1 and 2 years of age to be lower compared to the Dutch reference group, but head circumference was comparable with the reference group. In addition, we noted that infants who suffered from preterm growth restraint (PGR), displayed similar sub-optimal growth at 2 years of age compared to preterm infants with intra-uterine growth restriction, especially concerning length and head circumference. Reassuringly, preterm infants who did not suffer from PGR, showed growth at 1 and 2 years of age comparable to the Dutch reference group.

Comparison of the results of the 2 cohorts, POPS (1983) and LFUPP (1996/1997) at time of hospital discharge and at 2 years of age, showed that,

unfortunately, despite a decrease in mortality (from 30% to 11%) during the last decade, the number of children with an abnormal outcome has increased. Therefore, future follow-up of the LFUPP-cohort and comparison of these results with the POPS study is recommended.

After being able to increase survival rates of very preterm infants, the most important challenge at present should be, to increase the rate of handicap- or disability-free survival. Further studies are needed to show, if refined ventilation and neuroimaging techniques, and other ways of handling glucocorticosteroids, have already contributed to that end.

References

1. Johnson S, Marlow N. Developmental screen or developmental testing? Early Hum Dev 2006;82:173-83.
2. Nederlands Vereniging voor Kindergeneeskunde. Richtlijn grenzen levensvatbaarheid prematuren (24-26 weken). November 2005. www.pedianet.nl
3. Verloove-Vanhorick SP. Management of the neonate at the limits of viability: the Dutch viewpoint. BJOG: An International Journal of Obstetrics and Gynaecology 2006;113:13-6.
4. Dutch Association of Obstetrics and Gynecology. NVOG-nota: Verwijzing naar een perinatologisch centrum. Mei 2007. www.pedianet.nl
5. Nerderlandse Vereniging voor Kindergeneeskunde. To treat or not to treat? Limits for life-sustaining treatment in neonatology [in Dutch]. 1992. Utrecht, Netherlands, Den Daas.
6. Bell EF. Noninitiation or withdrawal of intensive care for high-risk newborns. Pediatrics 2007;119:401-3.
7. MacDonald H. Perinatal care at the threshold of viability. Pediatrics 2002;110:1024-7.
8. Lui K, Bajuk B, Foster K, Gaston A, Kent A, Sinn J *et al*. Perinatal care at the borderlines of viability: a consensus statement based on a NSW and ACT consensus workshop. Med J Aust 2006;185:495-500.
9. Eaton L. Ethics group rules on treating premature babies. BMJ 2006;333:1033.
10. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR *et al*. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Arch.Dis.Child.Fetal Neonatal Ed. 2005;90:F134-F140.
11. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR, the EPICure Study Group. Neurologic and Developmental Disability after Extremely Preterm Birth. N Engl J Med 2000;343:378-84.
12. Marlow N, Wolke D, Bracewell MA, Samara M, the EPICure Study Group. Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth. N Engl J Med 2005;352:9-19.
13. Marlow N. Neurocognitive outcome after very preterm birth. Arch.Dis Child Fetal Neonatal Ed. 2004;89:F224-F228.
14. Ouden Ld, Rijken M, Brand R, Verloove-Vanhorick SP, Ruys JH. Is it correct to correct? Devel-

opmental milestones in 555 "normal" preterm infants compared with term infants. J Pediatr 1991;118:399-404.
15. Salt A, Redshaw M. Neurodevelopmental follow-up after preterm birth: follow up after two years. Early Hum Dev. 2006;82:185-97.
16. Bracewell M, Marlow N. Patterns of motor disability in very preterm children. Ment Retard Dev Disabil Res Rev 2002;8:241-8.
17. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D *et al*. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:333-41.
18. Doyle LW, Casalaz D. Outcome at 14 years of extremely low birthweight infants: a regional study. Arch.Dis.Child.Fetal Neonatal Ed. 2001;85:F159-F164.
19. Russ A, Hand IL. Preterm brain injury: imaging and neurodevelopmental outcome. Am J Perinatol 2004;21:167-72.
20. Whitaker AH, Feldman JF, Van Rossem R, Schonfeld IS, Pinto-Martin JA, Torre C *et al*. Neonatal Cranial Ultrasound Abnormalities in Low Birth Weight Infants: Relation to Cognitive Outcomes at Six Years of Age. Pediatrics 1996;98:719-29.
21. O'Brien F, Roth S, Stewart A, Rifkin L, Rushe T, Wyatt J. The neurodevelopmental progress of infants less than 33 weeks into adolescence. Arch Dis Child 2004;89:207-11.
22. Hille ET, den Ouden AL, Bauer L, van den OC, Brand R, Verloove-Vanhorick SP. School performance at nine years of age in very premature and very low birth weight infants: perinatal risk factors and predictors at five years of age. Collaborative Project on Preterm and Small for Gestational Age (POPS) Infants in The Netherlands. J Pediatr 1994;125:426-34.
23. Ment LR, Vohr B, Allan W, Katz KH, Schneider KC, Westerveld M *et al*. Change in Cognitive Function Over Time in Very Low-Birth-Weight Infants. JAMA 2003;289:705-11.
24. van Zeben-van der AA T, Verloove-Vanhorick SP, Brand R, Ruys J. Morbidity of Very Low Birthweight Infants at corrected age of two years in a geographically defined population: Report from Project On Preterm and Small for Gestational Age Infants in the Netherlands. The Lancet 1989;333:253-5.
25. Van Zeben-van der AA, D. M. C. B. Outcome at two years of age in very preterm and very low birthweight infants in the Netherlands. Thesis. Leiden University. 1989.
26. Hempel MS. The neurological examination technique for toddler-age. Thesis. University of Groningen. 1993.
27. Olsen P, Vainionpaa L, Paakko E, Korkman M, Pyhtinen J, Jarvelin MR. Psychological Findings in Preterm Children Related to Neurologic Status and Magnetic Resonance Imaging. Pediatrics 1998;102:329-36.
28. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992;49:1-6.
29. Wezel-Meijler G, van der Knaap MS, Oosting J, Sie LT, de G, Huisman J *et al*. Predictive Value of Neonatal MRI as Compared to Ultrasound in Premature Infants with Mild Periventricular White Matter Changes. Neuropediatrics 1999;231-8.
30. Maalouf EF, Duggan PJ, Rutherford MA, Counsell SJ, Fletcher AM, Battin M *et al*. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants .J Pediatr 1999;135:351-7.
31. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. J Pediatr 2003;143:171-9.
32. Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White Matter Injury in the Premature Infant:

A Comparison between Serial Cranial Sonographic and MR Findings at Term. Am J Neuroradiol 2003;24:805-9.
33. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. Lancet 1983;1:1356-8.
34. Walsh MC, Yao Q, Horbar JD, Carpenter JH, Lee SK, Ohlsson A. Changes in the Use of Postnatal Steroids for Bronchopulmonary Dysplasia in 3 Large Neonatal Networks. Pediatrics 2006;118: e1328-e1335.
35. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver RG. Randomized Placebo-controlled Trial of a 42-Day Tapering Course of Dexamethasone to Reduce the Duration of Ventilator Dependency in Very Low Birth Weight Infants: Outcome of Study Participants at 1-Year Adjusted Age. Pediatrics 1999;104:15-21.
36. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC *et al.* Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics 1998;101:E7.
37. Shinwell ES, Karplus M, Bader D, Dollberg S, Gur I, Weintraub Z *et al.* Neonatologists are using much less dexamethasone. Arch Dis Child Fetal Neonatal Ed. 2003;88:F432-F433.
38. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB, and the DART Study Investigators. Low-Dose Dexamethasone Facilitates Extubation Among Chronically Ventilator-Dependent Infants: A Multicenter, International, Randomized, Controlled Trial. Pediatrics 2006;117:75-83.
39. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB, and the DART Study Investigators. Outcome at 2 Years of Age of Infants From the DART Study: A Multicenter, International, Randomized, Controlled Trial of Low-Dose Dexamethasonef. Pediatrics 2007;119:716-21.
40. Nixon PA, Washburn LK, Schechter MS, O'Shea TM. Follow-up Study of a Randomized Controlled Trial of Postnatal Dexamethasone Therapy in Very Low Birth Weight Infants: Effects on Pulmonary Outcomes at Age 8 to 11 Years. J Pediatr 2007;150:345-50.
41. Watterberg KL. Postnatal Steroids for Bronchopulmonary Dysplasia: Where Are We Now? J Pediatr 2007;150:327-8.
42. Grier D, Halliday H. Management of Bronchopulmonary Dysplasia in Infants: Guidelines for Corticosteroid Use. Drugs 2005;65:15-29.
43. Heide-Jalving M, Kamphuis PJGH, Laan MJ, Bakker JM, Wiegant VM, Heijnen CJ *et al.* Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatr. 2003;92:827-35.
44. Rademaker KJ, Uiterwaal CS, Groenendaal F, Venema MM, van Bel F, Beek FJ *et al.* Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children. J Pediatr 2007;150:351-7.
45. Lodygensky GA, Rademaker K, Zimine S, Gex-Fabry M, Lieftink AF, Lazeyras F *et al.* Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease. Pediatrics 2005;116:1-7.
46. Karemaker R, Heijnen CJ, Veen S, Baerts W, Samsom J, Visser GH *et al.* Differences in behavioral outcome and motor development at school age after neonatal treatment for chronic lung disease with dexamethasone versus hydrocortisone. Pediatr Res 2006;60:745-50.
47. Watterberg KL, Shaffer ML, Mishefske MJ, Leach CL, Mammel MC, Couser RJ *et al.* Growth and Neurodevelopmental Outcomes After Early Low-Dose Hydrocortisone Treatment in Extremely Low Birth Weight Infants. Pediatrics 2007;120:40-8.
48. Forsblad K, Kallen K, Marsal K, Hellstrom-Westas L. Apgar score predicts short-term outcome in infants born at 25 gestational weeks. Acta Paediatrica 2007;96:166-71.
49. Shankaran S, Johnson Y, Langer JC, Vohr BR, Fanaroff AA, Wright LL *et al.* Outcome of extremely-low-birth-weight infants at highest risk: Gestational age <=24 weeks, birth weight <=750 g, and 1-minute Apgar <=3. Am J Obstet Gynecol 2004; 191:1084-91.

CHAPTER 11

Summary

In **chapter 1**, increased survival in very preterm infants, related to some new interventions in perinatology is reported. Long-term outcome of the infants is summarised and discussed. The objective and methods of the Leiden Follow-Up Project on Prematurity (LFUPP), subject of the thesis, are described.

The purpose of **chapter 2** was to analyse mortality and outcome at 2 years of age in extremely preterm infants (with a gestational age (GA) < 27 weeks). An extensive neurological examination according to Hempel was performed; mental and psychomotor development were assessed by using the Bayley Scales of Infant Development I. Mortality was 35% (16/46) in infants < 27 weeks GA, compared to 6% (14/220) in infants with GA 27–32 weeks. In infants with GA < 27 weeks, mortality was higher after extra-uterine transport or pregnancy induction. Postnatal use of dexamethasone and still being hospitalised at term age, were associated with an abnormal neurological outcome at 2 years of age. Adverse outcome, defined as dead or an abnormal neurological, psychomotor or mental development was 92% (11/12) in infants of 23–24 weeks GA, 64% (7/11) in infants born at 25 weeks and 35% (8/23) in infants born at 26 weeks, compared to 18% (40/220) in infants born between 27–32 weeks GA.

Chapter 3 reviews survival rates and outcome of infants under 26 weeks of gestation, born in most European Countries along with some examples from the United States of America and Australia and discusses the role of parents and the influence of condition at birth, gender and birth weight in ethical decision-making on behalf of these infants. Survival at 22 weeks of gestation has not improved over the last decades and surviving infants born at 23–24 weeks of gestation show high rates of disabilities. Most European guidelines propose an active approach at 25 and 26 weeks, and a flexible approach at 23 and 24 weeks, depending on the opinion of the parents and the condition of the infant at birth. In the Netherlands an active approach is taken from 26 weeks and onwards and a flexible approach at GA 25 weeks. A table in this chapter illustrates the guidelines according to the Dutch Paediatric Association.

Chapter 4 presents growth of 160 of the 192 (82%) surviving infants of the LFUPP until the corrected age of 2 years. Infants from one of the three health regions (Delft) were excluded because a high percentage of missing growth data. The relationship between perinatal risk factors and growth was also stud-

ied. Furthermore, we analysed the relation between growth and neurodevelopmental outcome at 2 years of age. Length, weight and head circumference were measured. Standard Deviation Scores (SDS) were calculated and based on Dutch growth references. Besides, length SDS was corrected for target height SDS. Birth weight (BW)-SDS for GA was calculated according to Swedish references. Length, weight and weight-for-length were equally impaired in males and females at 2 years of age, compared to the Dutch reference group. Head circumference at 1 and 2 years of age was comparable with the reference group. The use of postnatal dexamethasone was associated with shorter length, lower weight, lower weight-for-length and smaller head circumference; this effect remained after adjusting for GA. Growth retardation in length and weight was associated with an abnormal neurological examination; smaller head circumference also with mental and psychomotor delay.

The purpose of **chapter 5** was to examine if preterm growth restraint (PGR), meaning extra-uterine growth restriction of preterm infants who suffered from medical complications in the neonatal period, had a similar effect on growth at the corrected age of 2 years, compared to intrauterine growth restriction in preterm born infants. PGR was defined as length or weight at term age below -1.3 SDS. We compared various growth parameters (the same as in chapter 4) until 2 years of age in three LFUPP-subgroups: preterm infants born small-for-gestational-age (SGA, defined as birth weight for GA < -1.3 SDS according to Swedish reference curves), preterm infants born appropriate-for-gestational-age with PGR (AGA-PGR) and preterm AGA-infants without PGR (AGA-nonPGR). Of the 158 included infants, 23 (14%) were SGA, 61 (39%) AGA-PGR and 74 (47%) AGA-nonPGR. From term age till 2 years of age, SGA-infants had the lowest growth parameters. At 2 years of age, length and head circumference were comparable in SGA- and AGA-PGR-infants; weight and weight-for-length were smaller in the SGA-infants. The AGA-nonPGR-infants displayed growth comparable to the Dutch reference group. After correction for confounders, PGR remained the most important predictor for length at 2 years.

In **chapter 6** we investigated the influence of perinatal risk factors, especially hypotension, on neurological outcome at term age according to Prechtl in the LFUPP-infants. Hypotension was defined as a mean arterial blood pressure < 30 mmHg on at least 2 occasions. Fifty percent of the infants (106/211) were

classified as neurologically normal, 44% (92/211) as mildly abnormal and 6% (13/211) as definitely abnormal. The odds ratio of hypotension for neurological morbidity was 1.90 (95% CI 1.06 – 3.40); after adjustment for gestational age, birth weight, SGA and gender, it was 1.96 (95% CI 1.02 – 3.77). Other risk factors for major neurological morbidity at term age were gestational age, cystic periventricular leucomalacia and bronchopulmonary dysplasia.

The aim of **chapter 7** was to describe the incidence of bronchopulmonary dysplasia (BPD) in the LFUPP-cohort. Data about the incidence of BPD in the Netherlands are scarce. Besides, we wanted to analyse associations between BPD and respiratory problems and developmental outcome at 2 years of age. At 36 weeks postmenstrual age, 49 infants (21% of the survivors at that time, 18.5% of all live born infants) suffered from BPD. Respiratory problems were the cause of death in 50% within this group. At 2 years of age, BPD-children had more respiratory problems and used more lung medication than children without BPD. Mean MDI and PDI were lower in BPD-children compared to children without BPD (88 an 87 compared to 101 and 99). Only 38% of the children with BPD had a normal neurological examination compared to 80% of the children without BPD.

Chapter 8 presents the mental and psychomotor developmental outcome in the LFUPP-cohort at 18 and 24 months corrected age, according to the Bayley Scales of Infant Development I. Developmental Indices were defined as normal (> -1 SD), moderate delay (-2 to -1 SD) and severe delay (< -2 SD). At 18 months 168 children (71%) and at 24 months 151 children (64%) of 235 survivors were assessed. Moderately to severely delayed mental and/or psychomotor development occurred in 40% of the children at both ages. Postnatal treatment with dexamethasone was associated with an increased risk of delayed development. Other independent predictors of delayed development were BPD at 18 months and ethnicity, maternal age at birth, birth weight and gender at 24 months.

Finally, in **chapter 9** we compared mortality and neonatal morbidity as well as changes in perinatal and neonatal management in two cohorts of very preterm infants: the Leiden Follow-Up Project on Prematurity (LFUPP) and the Project On Preterm and Small for gestational age (POPS) infants. The absolute number of preterm births in the study-region increased from 102 in 1983 to on average

133 in 1996/1997. In-hospital mortality decreased from 30% in the nineteen eighties to 11% in the nineteen nineties. Mortality of the extremely preterm infants with gestational age < 27 weeks decreased form 76% to 33%. Equal percentages (40%) of adverse outcome (dead or an abnormal condition at discharge) were found. The incidence of BPD increased from 6 to 19%. Improvements in peri- and neonatal care resulted in an increased survival but also in more morbidity, mainly BPD, at the moment of discharge from the hospital.

CHAPTER 12

Samenvatting

In **hoofdstuk 1** wordt een toegenomen overleving gerapporteerd van zeer vroeggeboren kinderen, gerelateerd aan enkele nieuwe interventies in de perinatologie. Uitkomsten op de lange termijn van de kinderen worden samengevat en bediscussieerd. Het doel en de methoden van het Leidse Follow-Up Project van Prematuren (LFUPP), onderwerp van dit proefschrift, worden beschreven.

Hoofdstuk 2 beschrijft de mortaliteit en de uitkomsten op 2 jaar in extreem vroeggeboren kinderen (met een zwangerschapsduur van < 27 weken). Een uitgebreid neurologisch onderzoek volgens de methode van Hempel werd uitgevoerd; de mentale en psychomotorische ontwikkeling werd beoordeeld door middel van de Bayley ontwikkelingsschalen I. De mortaliteit bedroeg 35% (16/46) in kinderen < 27 weken zwangerschapsduur, vergeleken met 6% (14/220) in kinderen met een zwangerschapsduur tussen 27 – 32 weken. In kinderen met een zwangerschapsduur < 27 weken was de mortaliteit hoger na extra-uterien transport en na zwangerschapsinductie. Postnataal gebruik van dexamethason en het nog steeds opgenomen zijn op de à terme leeftijd, was geassocieerd met een abnormale neurologische uitkomst op 2 jaar. Een zeer slechte uitkomst, gedefinieerd als overleden of een afwijkende neurologische, psychomotorische of mentale ontwikkeling, kwam voor in 92% (11/12) van de kinderen geboren na 23-24 weken, in 64% (7/11) van de kinderen geboren na 25 weken en in 35% (8/23) van de kinderen geboren na 26 weken, vergeleken met 18% (40/220) van de kinderen geboren tussen 27 – 32 weken zwangerschapsduur.

Hoofdstuk 3 geeft een overzicht van overlevingspercentages en uitkomsten van kinderen geboren vóór 26 weken zwangerschapsduur, geboren in de meeste Europese landen samen met enkele voorbeelden uit de Verenigde Staten en Australië. De rol van de ouders en de invloed van de conditie bij de geboorte, het geslacht en het geboortegewicht in relatie tot het maken van ethische beslissingen rondom de geboorte, worden besproken. De overleving bij 22 weken zwangerschapsduur is niet verbeterd gedurende de laatste decaden en overlevende kinderen geboren na 23 – 24 weken zwangerschapsduur laten hoge percentages beperkingen (in het functioneren) zien. De meeste Europese richtlijnen stellen een actieve benadering voor bij 25 en 26 weken en een flexibele benadering bij 23 en 24 weken, afhankelijk van de mening van de ouders en de conditie van het kind bij de geboorte. In Nederland wordt een actieve benadering gehanteerd vanaf 26 weken en een flexibele benadering bij 25 weken. Een tabel in

dit hoofdstuk illustreert de richtlijnen volgens de Nederlandse Vereniging voor Kindergeneeskunde.

In **hoofdstuk 4** wordt de groei van 160 van de 192 (82%) overlevende kinderen van de LFUPP tot de gecorrigeerde leeftijd van 2 jaar gepresenteerd. Kinderen van één van de drie gezondheidsregio's (Delft) werden geëxcludeerd vanwege een hoog percentage ontbrekende groei data. De relatie tussen perinatale risicofactoren en groei werd ook bestudeerd. Tevens analyseerden wij de relatie tussen de groei en de ontwikkeling op 2 jaar. Lengte, gewicht en schedelomvang werden gemeten. Standaard Deviatie Scores (SDS) werden berekend en de gemiddelden werden vergeleken met de Nederlandse groei referenties. Daarnaast werd de gemiddelde SDS voor lengte gecorrigeerd voor de gemiddelde SDS voor target height (eindlengte in relatie tot lengte ouders). Geboortegewicht-SDS naar zwangerschapsduur werd berekend volgens Zweedse referentiecurven. Lengte, gewicht en gewicht naar lengte waren lager (evenveel in jongens als meisjes) op 2-jarige leeftijd, vergeleken met de Nederlandse referentiegroep. Schedelomvang op 1 en 2 jaar was vergelijkbaar met de referentiegroep. Het gebruik van postnataal dexamethason was geassocieerd met kortere lengte, lager gewicht, lager gewicht naar lengte en een kleinere hoofdomvang; dit verschil bleef bestaan na correctie voor zwangerschapsduur. Groeiretardatie wat betreft lengte en gewicht was geassocieerd met een afwijkend neurologisch onderzoek; een kleinere hoofdomvang ook met een mentale en psychomotorische ontwikkelingsachterstand.

Het doel van de in **hoofdstuk 5** beschreven studie was om te onderzoeken of "preterm growth restraint (PGR)", hiermee bedoelende extra-uteriene groei vertraging, van te vroeggeboren kinderen die te lijden hebben gehad van medische complicaties in de neonatale periode, een vergelijkbaar effect op de groei had als intra-uteriene groeivertraging bij te vroeggeboren kinderen. PGR was gedefinieerd als lengte of gewicht op de à terme leeftijd kleiner dan -1.3 SD. We vergeleken verschillende groei parameters (dezelfde als in hoofdstuk 4) tot de leeftijd van 2 jaar in 3 LFUPP-subgroepen: te vroeggeboren kinderen die ook small-for-gestational-age geboren zijn ("SGA", gedefinieerd als geboortegewicht voor zwangerschapsduur < -1.3 SD volgens Zweedse referentiecurven), te vroeggeboren kinderen die appropriate-for-gestational-age geboren zijn mét PGR ("AGA-PGR") en te vroeggeboren AGA-kinderen zónder PGR ("AGA-

nonPGR"). Van de 158 geïncludeerde kinderen waren er 23 (14%) SGA, 61 (39%) AGA-PGR en 74 (47%) AGA-nonPGR. De SGA-kinderen hadden op alle leeftijden de laagste groeiparameters. Op 2 jarige leeftijd waren lengte en schedelomvang vergelijkbaar in de SGA- en AGA-PGR-kinderen; gewicht en gewicht naar lengte waren kleiner in de SGA-kinderen. De AGA-nonPGR-kinderen lieten vergelijkbare groei zien vergeleken met de Nederlandse referentiegroep. Na correctie voor confounders bleef PGR de belangrijkste voorspeller voor lengte op de leeftijd van 2 jaar.

In **hoofdstuk 6** onderzochten we de invloed van perinatale risicofactoren, in het bijzonder hypotensie, op de neurologische uitkomst volgens Prechtl op de à terme leeftijd in de LFUPP-kinderen. Hypotensie was gedefinieerd als een gemiddelde arteriële bloeddruk < 30 mm Hg op minimaal 2 momenten. Vijftig procent van de kinderen (106/211) werd geclassificeerd als neurologisch normaal, 44% (92/211) als mild abnormaal en 6% (13/211) als definitief abnormaal. De odds ratio voor neurologische morbiditeit was 1.90 (95% CI 1.06 – 3.40). Na correctie voor zwangerschapsduur, geboortegewicht, SGA en geslacht bedroeg deze 1.96 (95% CI 1.02 – 3.77). Andere risicofactoren voor ernstige neurologische morbiditeit op de à terme leeftijd waren zwangerschapsduur, cysteuze periventriculaire leucomalacie en bronchopulmonale dysplasie.

In **hoofdstuk 7** wordt de incidentie van bronchopulmonale dysplasie (BPD) in het LFUPP-cohort beschreven. Data betreffende de incidentie van BPD in Nederland zijn schaars. Bovendien wilden we analyseren of er associaties waren tussen BPD en respiratoire problemen en ontwikkelingsproblemen op de leeftijd van 2 jaar. Op 36 weken postmenstruele leeftijd hadden 49 kinderen (21% van de overlevenden op dat moment, 18.5% van alle levendgeborenen) BPD. Van de overleden kinderen was in 50% respiratoire problematiek de doodsoorzaak. Op 2 jarige leeftijd hadden BPD-kinderen meer respiratoire problemen en gebruikten ze meer medicatie voor de longen dan kinderen zonder BPD. De gemiddelde mentale en psychomotorische ontwikkelingsindex was lager in de BPD-kinderen vergeleken met de kinderen zonder BPD (88 en 87 vergeleken met 101 en 99). Slechts 38% van de kinderen met BPD had een normaal neurologisch onderzoek vergeleken met 80% van de kinderen zonder BPD.

Hoofdstuk 8 presenteert de mentale en psychomotorische ontwikkelingsuitkomsten van het LFUPP-cohort op 18 en 24 maanden gecorrigeerde leeftijd, volgens de Bayley Ontwikkelings-Schalen I. Ontwikkelingsindexen werden gedefinieerd als normaal (> -1 SD), matige achterstand (-2 tot -1 SD) of ernstige achterstand (< -2 SD). Van de 235 overlevende kinderen werden op de leeftijd van 18 maanden 168 kinderen (71%) onderzocht en op 24 maanden 151 kinderen (64%). Matige tot ernstige mentale of psychomotorische ontwikkelingsachterstand werd gevonden in 40% van de kinderen op beide leeftijden. Postnatale behandeling met dexamethason was geassocieerd met een verhoogd risico op een vertraagde ontwikkeling. Een andere onafhankelijke voorspeller van een ontwikkelingsachterstand op de leeftijd van 18 maanden was BPD; etniciteit, leeftijd van de moeder bij de geboorte, geboortegewicht en geslacht waren op de leeftijd van 24 maanden andere onafhankelijke prediktoren voor een ontwikkelingsachterstand.

Tot slot vergeleken we in **hoofdstuk 9** zowel de mortaliteit en neonatale morbiditeit als ook veranderingen in perinataal en neonataal handelen, in twee cohorten van zeer vroeggeboren kinderen: het Leidse Follow-Up Project van Prematuren (LFUPP; 1996/1997) en het Project On Preterm en Small for gestational age infants (POPS; 1983). Het absolute aantal premature geboorten (< 32 weken) in de studieregio nam toe van 102 in 1983 tot gemiddeld 133 in 1996/1997. De mortaliteit gedurende de eerste ziekenhuisopname daalde van 30% in de 80er jaren tot 11% in de 90er jaren. Sterfte van de extreem vroeggeboren kinderen met een zwangerschapsduur onder de 27 weken daalde van 76% naar 33%. Gelijke percentages (40%) van een zeer ernstige uitkomst (overleden of een abnormale conditie bij ontslag) werden gevonden. De incidentie van BPD nam toe van 6% naar 19%. Verbeteringen in peri- en neonatale zorg hebben geresulteerd in een toegenomen overleving, maar ook in meer morbiditeit, voornamelijk BPD, op het moment van ontslag uit het ziekenhuis.

Abbreviations

AGA : appropriate for gestational age
BMI : body mass index
BPD : bronchopulmonary dysplasia
BW : birth weight
CI : confidence interval
DA : definitely abnormal
GA : gestational age
HC : head circumference
IVH : intraventricular haemorrhage
L : length
Lcorr : length corrected for target height
LFUPP : Leiden Follow-Up Project on Prematurity
MA : mildly abnormal
MD : moderate delay
MDI : mental developmental index
N : normal
NEC : necrotising enterocolitis
NICU : neonatal intensive care unit
OR : odds ratio
PDA : patent ductus arteriosus
PDI : psychomotor developmental index
PGR : preterm growth restraint
PMA : postmenstrual age
POPS : Project On Preterm and Small for gestational age infants
PVL : periventricular leucomalacia
RDS : respiratory distress syndrome
SD : severe delay
SDS : standard deviation score(s)
SES : socioeconomic status
SGA : small for gestational age
TH : target height
W : weight
W/L : weight-for-length

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Publications

Rijken M, Wit JM, Le Cessie S, Veen S. The effect of perinatal risk factors on growth in very preterm infants at 2 years of age: the Leiden Follow-Up Project on prematurity. Early Human Development 2007; 83:527-534

Rijken M, Veen S, Walther FJ. Ethics of maintaining extremely preterm infants. Paediatrics and Child Health 2007; 17(2): 58-63

Boom ML de, *Rijken M,* Walther FJ. Postnataal dexamethason bij prematuren met ernstige ademhalingsproblemen: laatste redmiddel of niet? Tijdschr Kindergeneesk 2007; 75(2):62-67

Wit JM, Finken MJ, *Rijken M*, de Zegher F. Preterm growth restraint: a paradigm that unifies intrauterine growth retardation and preterm extrauterine growth retardation and has implications for the small-for-gestational-age indication in growth hormone therapy. Pediatrics 2006, 117(4): e793-795.

Benders MJ, Bos AF, Rademaker CM, *Rijken M*, Torrance HL, Groenendaal F, van Bel F. Early postnatal allopurinol does not improve short term outcome after severe birth asphyxia. Arch Dis Child Fetal Neonatal Ed. 2006; 91(3): F163-165.

Wit JM, Finken MJ, *Rijken M*, Walenkamp MJ, Oostdijk W, Veen S. Confusion around the definition of small for gestational age. Pediatr Endocrinol Rev. 2005; 3(1):52-53

Stoelhorst GMSJ, *Rijken M*, Martens SE, Brand R, den Ouden AL, Wit JM, Veen S. Changes in neonatology: comparison of two cohorts of very preterm infants (gestational age < 32weeks): the Project on Preterm and Small for Gestational Age Infants 1983 and the Leiden Follow-Up Project on Prematurity 1996-1997. Pediatrics 2005; 115(2):396-405

Martens SE, *Rijken M*, Stoelhorst GMSJ, van Zwieten PHT, Zwinderman AH, Wit JM, Hadders-Algra M, Veen S; Leiden Follow-Up Project on Prematurity. Is hypotension a major risk factor for neurological morbidity at term age in very preterm infants? Early Hum Dev. 2003; 75(1-2):79-89

Rijken M, Stoelhorst GMSJ, Martens SE, van Zwieten PHT, Brand R, Wit JM, Veen S. 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. Pediatrics 2003; 112(2):351-358

Stoelhorst GMSJ, Martens SE, *Rijken M*, van Zwieten PHT, Zwinderman AH, Wit JM, Veen S; Leiden Follow-Up Project on Prematurity. Behavior at 2 years of age in very preterm infants (gestational age < 32 weeks). Acta Paediatr. 2003; 92(5):595-601

Stoelhorst GMSJ, *Rijken M*, Martens SE, van Zwieten PHT, Feenstra J, Zwinderman AH, Wit JM, Veen S; Leiden Follow-Up Project on Prematurity. Developmental outcome at 18 and 24 months of age in very preterm children: a cohort study from 1996 to 1997. Early Hum Dev. 2003; 72(2):83-95

Ouden LA den, *Rijken M*, Brand R, Verloove-Vanhorick SP, Ruys JH. Is it correct to correct? Developmental milestones in 555 "normal" preterm infants compared with term infants, J Pediatr. 1991; 118(3):399 – 404.

Appendices

Appendix 1.
Consensus on treatment of extremely premature infants at birth in the Netherlands (Dutch Paediatric Association, November 2005)

Appendix 2.
Registration forms up to and including 2 years corrected age

Appendix 1. Consensus on treatment of extremely premature infants at birth in the Netherlands (Dutch Paediatric Association, November 2005)

Gestational age in weeks & days	Intrauterine referral to level 3 perinatal center	Antenatal steroids	Caesarean section	Neonatal treatment in the delivery room
$< 24^{+0}$	No	No	Only on maternal indication	Family-centred comfort care
$24^{+0} – 24^{+6}$	Indicated	Can be considered	Only on maternal indication	Family-centred comfort care, unless an active approach seems justified
$25^{+0} – 25^{+6}$	Indicated	Yes	Rarely on foetal indication	Active approach, unless comfort care seems more justified
$\geq 26^{+0}$	Indicated	Yes	Yes, unless an active approach does not seem justified	Active approach, unless this does not seem justified

If a child weighs less than 500 grams at birth, neonatal treatment will be withheld, except for family-centred comfort care.

18-04-96

FOLLOW-UP STUDIE VAN ZEER VROEGGEBOREN KINDEREN
IN DE GEZONDHEIDSREGIO'S
DEN HAAG, LEIDEN EN DELFT

Samenwerkingsproject kinderartsen, Juliana Kinderziekenhuis Den Haag,
Diaconessenhuis Leiden, Rijnland Ziekenhuis Leiderdorp, Reinier de Graaf Gasthuis Delft,
't Langeland Ziekenhuis Zoetermeer, St. Antoniushove Leidschendam, Diaconessenhuis Voorburg,
TNO-Preventie en Gezondheid Leiden, Academisch Ziekenhuis Leiden

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FORMULIER 1: PERINATALE FACTOREN EN GEGEVENS TOT EN MET ONTSLAG EERSTE ZIEKENHUIS OPNAME

NAAM.....GEBOORTE DATUM.....

01 IDENTIFICATIE Regionaal Follow-up Project (RFP)	registratienummer	[ ]]]]
02 Regionaal ziekenhuis	registratienummer	[ ]]]]]]]
03 NICU AZL	registratienummer	[ ]]]]]]]
04 NICU JKZ	registratienummer	[ ]]]]]]]
05 Andere NICU	registratienummer	[ ]]]]]]]

codeerinstructie: onbekend alle beschikbare hokjes coderen met 99, niet van toepassing coderen met 88.

GEGEVENS MOEDER

06 geboortedatum (dg/mnd/jr)		[ ]]]]]]
07 postcode (woonplaats)		[ ]]]]]]
OBSTETRISCHE GEGEVENS		
08 zwangerschapsinductie		
nee=0 medicamenteus=1 IVF=2		
ICSI=3 (intra-cytoplasmatische sperma injectie)		[ ]
09 ziekten vóór de zwangerschap		
hartaandoening	nee=0 ja=1	[ ]
cara	nee=0 ja=1	[ ]
epilepsie	nee=0 ja=1	[ ]
diabetes mellitus	nee=0 ja=1	[ ]
nierziekte	nee=0 ja=1	[ ]
hypertensie		
(diastolische bloeddruk $ 90 mm Hg)	nee=0 ja=1	[ ]
overige	nee=0 ja=1	[ ]
indien ja beschrijf.....		
10 ziekten tijdens de zwangerschap	nee=0 ja=1	[ ]
diabetes mellitus gravidarum	nee=0 ja=1	[ ]
actief bloedgroep antagonisme	nee=0 ja=1	[ ]
hypertensie		
(2x diastolische bloeddruk $ 90 mm Hg)	nee=0 ja=1	[ ]
pre-eclampsie	nee=0 ja=1	[ ]
eclampsie	nee=0 ja=1	[ ]
HELPP-syndroom	nee=0 ja=1	[ ]
overige	nee=0 ja=1	[ ]

indien ja beschrijf.....

11 intoxicaties tijdens de zwangerschap

nee=0, roken #10 sig/dg=1, roken >10 sig/dg=2 [ ]

alcoholgebruik [ ]

geen=0, 1-2glazen/wk=1, 2-7glazen/wk=2, >7 glazen/wk=3 [ ]

incidenteel excessief drankgebruik (>10 gl) nee=0 ja=1 [ ]

indien ja, frequentie (keer p/jr).....

harddrugs nee=0 ja=1 [ ]

indien ja, welke.....

12 medicijngebruik tijdens de zwangerschap

(geen ijzer vitaminen en fluor vermelden)

diuretica nee=0 ja=1 [ ]

antihypertensiva nee=0 ja=1 [ ]

tranquillizers nee=0 ja=1 [ ]

anti-epileptica nee=0 ja=1 [ ]

antibiotica nee=0 ja=1 [ ]

gestagenen nee=0 ja=1 [ ]

cara therapie nee=0 ja=1 [ ]

andere, namelijk..... nee=0 ja=1 [ ]

PARTUS, GEBOORTE KIND

13 geboortedatum (dg/mnd/jr) [ ]]]]]]

14 zwangerschapsduur (wk + dg)

zoals opgegeven door obstetricus, (op grond van amennorrhoe duur

en/of echografie en/of zwangerschapstesten) [ ]] + [ ]

15 betrouwbaarheid termijn

zeker=0, dubieus=1, onbetrouwbaar=2 [ ]

16 geslacht

vrouw=1, man=2, onduidelijk=3 [ ]

17 gebruik weeënremmende middelen, langer dan 24 uur

ß-mimetica nee=0 ja=1 [ ]

prostaglandine synthetase remmers nee=0 ja=1 [ ]

18 antenataal toedienen glucocorticoïden

nee=0, éénmalig=1, volledige kuur=2 (2 giften) [ ]

datum toediening eerste gift [ ]]]]]]

datum toediening tweede gift [ ]]]]]]

indicatie beschrijf.....

19 wijze van geboorte

vaginaal hoofdligging spontaan=0, hoofdligging kunstverlossing=1,

stuit Bracht=2, stuit extractie=3, versie en extractie=4,

sectio caesarea=5 [ ]

20 gebroken vliezen bij het begin van de partus

nee=0, < 24 uur=1, 1-7 dg=2, langer dan 7 dg=3 [ ]

KIND

21 geboortegewicht (gram) [ ]]]]

22 geboortelengte (cm) [ ]]

23 schedelomtrek (cm, gemeten na minstens 24 uur en binnen 7 dagen) [ ]]

24 apgarscore na 5 minuten [ ]]

25 apgarscore na 10 minuten [ ]]

26 Ph Navelstreng arterieel (2 decimalen) [ ],[ ][ ]

base excess (mmol/l) bv min 10.5, afronden [-] [1]1] [ ] [ ]]

27 Ph Navelstreng veneus (2 decimalen) [ ],[ ][ ]

base excess (mmol/l) bv pos 10.4, afronden [+] [1]0] [ ] [ ]]

28 eerste Ph capillair na de geboorte (2 decimalen) [ ],[ ][ ]

base excess (mmol/l) [ ] [ ]]

tijd na de geboorte bv 20 min [0]0].[2]0] [ ]].[ ]]

3 uur [0]3].[0]0]

29 meerling

nee=0, tweeling 1e kind=1, tweeling 2e kind=2, drieling 1e kind=3,

drieling volgende kind=4, vierling eerste kind=5,

vierling volgende kind=6, vijf of zesling 1e kind=7,

vijf of zesling volgende kind=10 [ ]]

30 plaats van geboorte

Regio Den Haag=0, Diaconessenhuis Leiden=1,

Rijnland Ziekenhuis Leiderdorp=2, Reinier de Graaf Gasthuis Delft=3,

't Langeland Ziekenhuis Zoetermeer=4, St. Antoniushove Leidschendam=5,

Diaconessenhuis Voorburg=6, Academisch Ziekenhuis Leiden=7,

universitair met NICU=10, algemeen ziekenhuis buiten onderzoeksregio=11 [ ]]

31 hypotensie RR mean <30 mmHg nee=0 ja=1 [ ]

indien ja is therapie gegeven nee=0 ja=1 [ ]

wat was de laagste RR (mean) bv 25 [2]5] [[ ]

32 navelarterielijn nee=0 ja=1 [ ]

trombusvorming (diagnose mbv echo) nee=0 ja=1 [ ]

33 navelvenelijn nee=0 ja=1 [ ]

trombusvorming (diagnose mbv echo) nee=0 ja=1 [ ]

34 longafwijkingen (radiologisch zie definitielijst)

IRDS nee=0, IRDS graad 1=1,

IRDS graad 2=2, IRDS graad3=3,IRDS graad4=4 [ ]

verdenking longhypoplasie nee=0 ja=1 [ ]

longbloeding nee=0 ja=1 [ ]

wet lung nee=0 ja=1 [ ]

(cong) pneumonie nee=0 ja=1 [ ]

interstitieël emphyseem nee=0 ja=1 [ ]

pneumothorax (mediastinum) nee=0 ja=1 [ ]

chronisch longbeeld (zie definitielijst) nee=0 ja=1 [ ]

O2 behoefte op leeftijd > 28 dagen nee=0 ja=1 [ ]

meconiumaspiratie nee=0 ja=1 [ ]

35 Continuous Positive Airway Pressure (CPAP), aantal dagen bv 006 [ ]]

36 Intermittent Positive Airway Pressure (IPPV), aantal dagen bv 012 [ ]]

37 High Frequency Ventilation (HFV), aantal dagen bv 003 [ ]]

38 maximale inspiratoire druk (cm H2O) [ ]]

39 maximale peep (cm H2O,IPPV) [ ]

40 maximale FiO2 (%) [ ]]

41 pulmonale hypertensie

(persisterende foetale circulatie zie definitielijst) nee=0 ja=1 [ ]

tolazoline nee=0 ja=1 [ ]

flolan nee=0 ja=1 [ ]

NO-inhalatie therapie (aantal uren bv 048) [ ]]

effect ingestelde NO therapie ja=0, matig=1, geen effect=3 [ ]

42 Open Ductus Botalli (van haemodynamisch belang)

nee=0, ja bewezen (echo)=1 [ ]

indien ja therapie nee=0, medicamenteus=1, chirurgisch=2

beiden=1+2=3 [ ]

43 apnoe's (minstens 15 sec) en/of **bradycardieën** (<100/min) nee=0 ja=1 [ ]

44 congenitale infecties

bacterieël nee=0 ja=1 [ ]

(bewezen door bloedkweek en/of sputumkweek, contaminatie uitgesloten)

indien ja verwekker.....

viraal nee=0 ja=1 [ ]

(bewezen door urine en/of serologie)

indien ja, verwekker.....

45 sepsis

aantal malen volledige kuur antibiotica/mycotica [ ]

aantal malen op grond van bloedbeeld en/of kliniek [ ]

aantal malen bewezen bloedkweek [ ]

46 meningitis

nee=0, ogv celaantal liquor en/of kliniek=1, bewezen liquor kweek=2 [ ]

47 necrotiserende enterocolitis

nee=0, klinisch zeer verdacht=1 röntgenologisch duidelijk=2

operatief behandeld =3 [ ]

48 serum bilirubine hoogste waarde (capillair, in micromol/l)]]]

datum waarop deze waarde werd bereikt bv 17-12-96 [1]7]1]2]9]6] [ ]]]]]]

wisseltransfusie (aantal, exclusief partiële wissel ivm hyperviscositeit) [ ]

fototherapie (aantal uren ivm afwisselende FT) [ ]]]

49 intracraniële bloeding

(diagnose mbv echo schedel;zie definitielijst)

A) rechts nee=0 ja=1 [ ]

graad 1 nee=0 ja=1 [ ]

graad 2 nee=0 ja=1 [ ]

graad 3 nee=0 ja=1 [ ]

graad 4 nee=0 ja=1 [ ]

flaring (zie def.lijst) nee=0 ja=1 [ ]

periventriculaire leucomalacie nee=0 ja=1 [ ]

andere afwijkingen nee=0 ja=1 [ ]

beschrijf.....

B) links nee=0 ja=1 [ ]

graad 1 nee=0 ja=1 [ ]

graad 2 nee=0 ja=1 [ ]

graad 3 nee=0 ja=1 [ ]

graad 4 nee=0 ja=1 [ ]

flaring (zie def. lijst) nee=0 ja=1 [ ]

periventriculaire leucomalacie nee=0 ja=1 [ ]

andere afwijkingen nee=0 ja=1 [ ]

beschrijf.....

50 Sarnat-score (zie definitie lijst, alleen bij asfyxie)

binnen 24 uur normaal=0 score 1=1 score 2=2 score 3=3 [ ]

24 tot 72 uur normaal=0 score 1=1 score 2=2 score 3=3 [ ]

meer dan 72 uur normaal=0 score 1=1 score 2=2 score 3=3 [ ]

51 multiorgan failure

(lever en/of nierfunctiestoornissen, zie definitielijst) nee=0 ja=1 [ ]

52 convulsies nee=0 ja=1 [ ]

Electroencephalogram normaal=0 afwijkend=1 niet verricht=2 [ ]

53 hydrocefalie nee=0 ja=1 [ ]

posthaemorrhagische ventrikeldilatatie nee=0 ja=1 [ ]

frequente lumbaal puncties nee=0 ja=1 [ ]

ventriculo-peritoneale of andere drainage nee=0 ja=1 [ ]

54 afwijkingen centrale zenuwstelsel

(tonus, motoriek (neonatale) reflexen)

normaal=0, dubieus=1, afwijkend=2 [ ]

55 retinopathie van de prematuur (zie definitielijst)

nee=0, graad I =1, graad II=2, graad III=3, graad IV=4, graad V=5 [ ]

therapie nee=0 ja=1 [ ]

56 medicamenteuze behandeling (uitgezonderd vitamines, fe)

surfactant nee=0 ja=1 [ ]

positieve inotropica (dopamine, dobutamine) nee=0 ja=1 [ ]

antibiotica nee=0 ja=1 [ ]

systemische antimycotica nee=0 ja=1 [ ]

allopurinol nee=0 ja=1 [ ]

diuretica nee=0 ja=1 [ ]

anti-convulsiva nee=0 ja=1 [ ]

57 corticosteroïden kuur (kuren) aantal bv 2=02 [ ]

datum start eerste kuur [ ]]]]]]

datum eind eerste kuur [ ]]]]]]

datum start tweede kuur [ ]]]]]]

datum eind tweede kuur [ ]]]]]]

datum start derde kuur [ ]]]]]]

datum eind derde kuur [ ]]]]]]

58 aangeboren afwijkingen

geen=0, met het leven verenigbaar=1, niet met het leven verenigbaar=2 [ ]

59 soort aangeboren afwijking (max 6, zie definitie lijst) [ ]]

[ ]]

60 overleden aan nee=0 ja=1 [ ]

aangeboren afwijking nee=0 ja=1 [ ]

pulmonale problematiek nee=0 ja=1 [ ]

cerebrale problematiek nee=0 ja=1 [ ]

congenitale infectie nee=0 ja=1 [ ]

infectieuze problemen nee=0 ja=1 [ ]

cardiale problemen nee=0 ja=1 [ ]

necrotiserende enterocolitis nee=0 ja=1 [ ]

andere nee=0 ja=1 [ ]

beschrijf.....

61 datum overlijden [ ]]]]]]

62 wijze van overlijden

spontaan=1, niet (verder) behandelbaar geacht=2,

fout en/of accident=3, [ ]

63 obductie

ja=0, nee=1 [ ]

heeft de obductie nieuwe diagnose(n) opgeleverd [ ]

nee=0, ja=1 [ ]

zo ja welke.....

64 datum ontslag neonatologisch centrum (dg/mnd/jr) [ ]]]]]]

65 datum ontslag naar huis of gezinsvervangend tehuis [ ]]]]]]

66 transmurale verpleegkundige nee=0 ja=1 [ ]

67 monitorbewaking thuis nee=0 ja=1 [ ]

68 zuurstof therapie thuis nee=0 ja=1 [ ]

69 toestand kind bij ontslag

normaal nee=0 ja=1 [ ]

neurologische stoornis nee=0 ja=1 [ ]

longproblemen nee=0 ja=1 [ ]

cardiale problemen nee=0 ja=1 [ ]

voedingsproblemen nee=0 ja=1 [ ]

ROP nee=0 ja=1 [ ]

gehoorstoornis nee=0 ja=1 [ ]

psychosociale problemen nee=0 ja=1 [ ]

andere problemen nee=0 ja=1 [ ]

indien ja beschrijf.....

DEFINITIELIJST

A. Radiological stages of severity of RDS according to Giedion

Stage I very fine reticulo-granular pattern, normal lucency, air bronchogram within the cardiac border

Stage II generalized typical reticulo-granular pattern, slightly diminished lucency, air bronchogram extending the cardiac border

Stage III confluent reticulo-granular densities, marked reduction of lucencywith indistinct cardiac border

Stage IV total opafication, "white lungs"

Giedion, Pediatr Radiol 1973;1:145-152.

B. Bronchopulmonale Dysplasie, Chronisch longbeeld:

Zuurstof afhankelijkheid > 36 weken postconceptionele leeftijd

Shennan, Pediatrics 1988;82(4):527-32

C. Persisterende foetale circulatie, Persisterende pulmonale hypertensie:

Beademingsafhankelijkheid; 'optimale' ademhalings,- circulatoire- en biochemische ondersteuning; zoals sedering, paralyse, synchronisatie (SIMV/assist control;alkalose)

paCO2 < of gelijk 6.5 kPa

paO2 < 7.5 kPa (ongeveer 55 mmHg) met een FiO2 ≥ 0.8

vitium cordis uitgesloten; tekenen van pulmonale hypertensie op echo

D. IVH (Intra ventricular hemorrhage)

GRAAD 1: geisoleerde subependymale bloeding (SEH)

GRAAD 2: SEH with IVH no ventricular dilatation

GRAAD 3: SEH with IVH with ventricular dilatation

GRAAD 4: SEH with IVH and intraparenchymal hemorrhage

(Papile, J.Pediatr. 1978;92(4):529-34)

FLARING: toegenomen periventriculaire echodensiteit

Echodensities which are present in both coronal and parasagittal planes and which irrespective of duration, size or location resolved without the subsequent development of cysts, irregular shaped ventrikels other abnormal findings seen on ultrasound scan.

Appleton, Arch. Dis. Child 1990; 65: 27-29.

E. Hypoxic-ischaemic encephalopathy indeling volgens Sarnat en Sarnat

F. MULTIORGAN FAILURE

THE MULTIPLE EFFECTS OF PERINATAL ASPHYXIA (MULTIORGAN FAILURE)

CNS: Hypoxic-ischaemic encephalopathy, cerebral edema, neonatal seizures, long-term neurologic sequelae

Pulmonary: Pulmonary hypertension, surfactant disruption, meconium aspiration

Renal: Oliguria, acute renal failure

Cardiovascular: Tricuspid insufficiency, myocardial necrosis, shock/hypotension

Metabolic: Metabolic acidosis, hypoglycemia, hypocalcemia, hyponatremia

Gastrointestinal: Necrotizing enterocolitis, hepatic dysfunction

Haematologic: Thrombocytopenia, disseminated intravascular coagulopathy

Death

G. CLASSIFICATION OF RETINOPATHY OF PREMATURITY (ROP)

Stage	Proliferative-Phase Fundus Changes
I	Demarcation line (thin, nonelevated white line at junction between vascularized and avascular retina)
II	Ridge (elevated demarcation line)
III	Ridge with extraretinal fibrovascular proliferation
IV	Retinal detachment (partial)
V	Complete retinal detachment
Grade	**Cicatricial-Phase Fundus Changes**
I	Small areas of retinal pigment irregularities; small peripheral retinal scars
II	Disk distorsion
III	Retinal fold
IV	Incomplete retrolental mass; partial retinal detachment
V	Complete retrolental mass; total retinal detachment

"Plus" disease indicates dilatation of posterior veins and tortuosity of posterior arterioles.

Three zones of retinal involvement centered on the optic disk are recognized. They are consecutively numbered from posterior to anterior. International classification of proliferative ROP and Reese classification of cicatricial RLF.

Referenties

1. Szewczyk TS, A Classification of Retrolental Fibriplasia. American Journal of Ophthalmology, vol 36, no.10, October 1953:1333-1361.
2. An International Classification of Retinopathy of Prematurity. Pediatrics vol. 74, no.1 July 1984:127-133.
3. Avery, Neonatology, third edition 1987:1308.
4. Taylor D., Pediatric Ophtalmology. Blackwell Scientific Publications 1990.

H. LIJST AANGEBOREN AFWIJKINGEN (ZIE VRAAG 59)

00 geen aangeboren afwijkingen

zenuwstelsel

01 anencefalie

02 microcefalie

03 spina bifida occulta

04 spina bifida aperta

05 hydrocefalie

06 meningomyelocele

07 encefalocele

09 andere cong. afw. centr. zenuwstel.

zintuigen

10 microphtalmie

11 andere cong. afw. ogen

12 cong. afw oren

hartvaatstelsel

20 vitium cordis

21 ontbreken van een navelarterie

29 andere cong. vaatanomalieen

ademhalingswegen

30 choanaal atresie

39 overige cong. afw. tr. resp

spijsverteringsstelsel

40 gehemeltespleet

41 lipspleet

42 oesofago-tracheale fistel

urogenitaalstelsel

50 hypospadie en epispadie

59 andere cong. afw. tr. urogenitalis

huid

60 naevus pigmentosus

61 haemangioma cavernosum

69 andere cong. huidafwijkingen

bewegingstelsel

70 polydactylie

71 syndactylie

72 focomelie en amelie

73 congenitale heupluxatie

74 pes equinovarus

75 andere cong. afw. van de extremiteiten

76 cong. afw. van bot en skelet

79 andere cong. afw. van het bewegingsstelsel (incl. spierstelsel)

44 overige darmatresie incl. van de anus

45 hernia diafragmatica

49 andere cong. afw. tractus digestivus

43 oesofagus atresie

overige cong. afw.

80 struma congenita

81 syndroom van Down

82 andere chromosoom afwijkingen

83 situs inversus

84 multipele cong. afw.

89 overige cong. afw. (niet nader omschreven)

90 inborn error of metabolism

91 syndroom van Potter

18-04-96

FOLLOW-UP STUDIE VAN ZEER VROEGGEBOREN KINDEREN

IN DE GEZONDHEIDSREGIO'S

DEN HAAG, LEIDEN EN DELFT

Samenwerkingsproject kinderartsen, Juliana Kinderziekenhuis Den Haag,

Diaconessenhuis Leiden, Rijnland Ziekenhuis Leiderdorp, Reinier de Graaf Gasthuis Delft,

't Langeland Ziekenhuis Zoetermeer, St. Antoniushove Leidschendam, Diaconessenhuis Voorburg,

TNO-Preventie en Gezondheid Leiden, Academisch Ziekenhuis Leiden

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FORMULIER 2: POLIKLINISCHE NACONTROLE OP DE A TERME LEEFTIJD

NAAM.....GEBOORTEDATUM.....

01 IDENTIFICATIE Regionaal Follow-up Project (RFP)	registratienummer	[ ] [ ] [ ]
02 Regionaal ziekenhuis	registratienummer	[ ] [ ] [ ] [ ] [ ] [ ]
03 NICU AZL	registratienummer	[ ] [ ] [ ] [ ] [ ] [ ]
04 NICU JKZ	registratienummer	[ ] [ ] [ ] [ ] [ ] [ ]
05 Andere NICU	registratienummer	[ ] [ ] [ ] [ ] [ ] [ ]
06 onderzoek in ziekenhuis (zie definitielijst voor nummer)		[ ]
07 kinderarts.....		[ ]
08 patient nog opgenomen op de gecor. à terme leeftijd nee=0 ja=1		[ ]
09 STREEFDATUM CONTROLE		[ ] [ ] [ ] [ ] [ ] [ ]
10 DATUM CONTROLE		[ ] [ ] [ ] [ ] [ ] [ ]

codeerinstructie: onbekend alle beschikbare hokjes coderen met 99, niet van toepassing coderen met 88

11 NIET VOOR NACONTROLE BESCHIKBAAR WEGENS

wel beschikbaar=0

overleden tussen ontslag en controle=1 (datum.../.../...) [ ]]]]]]

diagnose.....

verhuisd=2 (nl naar.....

controle aldaar door.....

verdere medewerking door de ouders geweigerd ivm goede toestand kind=3

verdere medewerking door de ouders geweigerd ivm slechte toestand kind=4

andere reden weigering medewerking=5 geef aan..... [ ]

12 SOCIO-ECONOMISCHE GROEP

moeder: beroep.....

opleiding.....

vader: beroep.....

opleiding.....

13 BEVOLKINGSGROEP

beide ouders kaukasisch (exclusief Turkse allochtonen) nee=0 ja=1 [ ]

één van beide of beide ouders niet kaukasisch nee=0 ja=1 [ ]

beide ouders niet kaukasisch nee=0 ja=1 [ ]

14 LENGTE MOEDER (in centimeters) [ ]]]

15 LENGTE VADER (in centimete [ ]]]

CENTRAAL ZENUWSTELSEL

16 Convulsies nee=0 ja=1 [ ]

indien ontslagen beantwoorden voor de periode tussen ontslag en a terme controle

indien nog opgenomen invullen niet van toepassing [9]

17 EEG afwijkingen nee=0, ja=1, niet verricht=2 [ ]

indien ontslagen beantwoorden voor de periode tussen ontslag en a terme controle

indien nog opgenomen invullen niet van toepassing [8]

18 Echo-schedel intracraniële bloeding (zie definitielijst)

A) rechts	nee=0 ja=1	[ ]
graad 1	nee=0 ja=1	[ ]
graad 2	nee=0 ja=1	[ ]
graad 3	nee=0 ja=1	[ ]
graad 4	nee=0 ja=1	[ ]
periventriculaire leucomalacie	nee=0 ja=1	[ ]
resorptie bloeding	nee=0 ja=1	[ ]
pseudocyste(n)	nee=0 ja=1	[ ]
posthaemorhagische hydrocephalus	nee=0 ja=1	[ ]
externe benigne hydrocephalus	nee=0 ja=1	[ ]
andere afwijkingen	nee=0 ja=1	[ ]

beschrijf.....

A) links	nee=0 ja=1	[ ]
graad 1	nee=0 ja=1	[ ]
graad 2	nee=0 ja=1	[ ]
graad 3	nee=0 ja=1	[ ]
graad 4	nee=0 ja=1	[ ]
periventriculaire leucomalacie	nee=0 ja=1	[ ]
resorptie bloeding	nee=0 ja=1	[ ]
pseudocyste(n)	nee=0 ja=1	[ ]
posthaemorhagische hydrocephalus	nee=0 ja=1	[ ]
externe benigne hydrocephalus	nee=0 ja=1	[ ]

andere afwijkingen nee=0 ja=1 [ ]

beschrijf.....

19 ventriculo peritoneale drainage nee=0 ja=1 [ ]

20 Neurologisch onderzoek volgens Prechtl

Stability of states	stable=0	mod unstable=1	very unstable=2			[ ]
Facial innervation	sym=0	asym=1				[ ]
Twitching face, convulsions	absent=0	present=1				[ ]
Fontanelles, consistency	normal=0	full=1	bulging=2			[ ]
Lip reflex	++=0	+=1	neg=2	+++=3		[ ]
Glabella reflex	normal=++=0	+=1	neg=2	+++=3		[ ]
Resting posture in crib	normal=0	abnormal=1				[ ]
Posture in supine position	zie ad a codering					[ ]
Spontaneous motor activity, type	normal GMS=0	abnorm GMS =1				[ ]
Spontaneous motor actvity, amount	normal=++=0	+=1	neg=2	+++=3		[ ]
Clonus	absent=0	few beats occas=1	often=2			[ ]
Overshooting movements	absent=0	present=1				[ ]
Athetoid movements	normal=+/++=0	neg=1	+++=2			[ ]
Tremor, frequency	medium=0	low=1	high=2			[ ]
Tremor, amplitude	medium=0	low=1	high=2			[ ]
Abdominal skin reflex	normal=+=0	++=1	neg=2	+++=3		[ ]
Position of eyes	normal=0	occas strab=1	constant abnorm=2			[ ]
Nystagmus	normal=-=0	+=1	++=2			[ ]
Pupils size, light reaction	normal=0	abnormal=1				[ ]
Optical blink	normal=++=0	+=1	neg=2			[ ]
Acoustical blink	normal=++=0	+=1	neg=2			[ ]
Posture of arms in supine suspension	(semi)flex=0	extension=1				[ ]
Posture of legs in supine suspension	(semi)flex=0	extension=1				[ ]
Doll's eyes phenomenon	normal=++=0	+=1	neg=2	asym=3		[ ]
Tonic neck reflexes	variable present=0	consistantly present=1	absent=2			[ ]
Resistance against passive movement	zie ad b codering					[ ]
Active power	normal=0	decreased=1	increased=2	strongly increased =3		[ ]
Range of movements	normal=0	abnormal=1				[ ]
Recoil of arms	normal=++=0	+=1	neg=2	+++=3	asym=4	[ ]
Muscle consistency	normal=0	abnormal=1				[ ]
Biceps reflex	normal=++=0	+=1	neg=2	+++=3	asym=4	[ ]
Knee jerk	zie ad c codering					[ ]
Threshold tendon reflexes	medium=0	low=1	high=2			[ ]
Palmar grasp	normal=++=0	+=1	neg=2	asym=3		[ ]
Plantar grasp	normal=++=0	+=1	neg=2	asym=3		[ ]

Footsole response	normal=0	decreased=1	neg=2	abn increased =3	abn decreased =4	asym=5	[ ]
Withdrawal reaction	normal=++=0	+=1	neg=2	asym=3			[ ]
Rooting	normal=++=0	+=1	neg=2	+++=3			[ ]
Sucking	normal=++=0	+=1	neg=2	+++=3			[ ]
Posture of arms during traction test	flexion=0	semiflexion=1	extension=2	asym=3			[ ]
Posture of head during traction test	head follows in line=0	head lags a bit=1	head lags=2	active retroflex=3			[ ]
Head balance during sitting	balancing head " 3 sec=0	little head balance =1	collapses=2	balancing head > 3 sec=3			[ ]
Moro reaction threshold	medium=0	low=1	high=2				[ ]
Moro reaction amplitude of abduction and extension	normal=++=0	+=1	neg=2	+++=3	asym=4		[ ]
Moro reaction intensity	normal=++=0	+=1	neg=2	+++=3			[ ]
Tremor during Moro reaction frequency	medium=0	low=1	high=2				[ ]
Tremor during Moro reaction amplitude	medium=0	low=1	high=2				[ ]
Spine	normal=0	abnormal=1					[ ]
Spontaneous head movements in prone position	normal=++=0	+=1	neg=2	+++=3			[ ]
Crawling movements	normal=++=0	+=1	neg=2				[ ]
Bauer response	normal=++=0	+=1	neg=2	+++=3	asym=4		[ ]
Ankle jerk	normal=+==0	+=1	neg=2	+++=3	asym=4		[ ]
Galant response	normal=++=0	+=1	neg=2	+++=3	asym=4		[ ]
Posture in prone suspension	normal=0	=1	=2	=3			[ ]

Rotation test	normal=++=0	+=1	neg=2	asym=3	[ ]
Placing reaction	normal=++=0	+=1	neg=2	asym=3	[ ]
Stepping movements	normal=++=0	+=1	neg=2		[ ]
Type of crying	normal=0	abnormal=1			[ ]
Head circumference (cm)					[ ]]
Overriding	normal=0	+=1			[ ]

ad a

normal sym=0

mild hyperextension neck/trunk=1

mild head preference=2

1+2=3

marked hyperextension=4

marked head preference=5

4+5=6

otherwise abnormal=7

ad b

normal=0

mild decreased neck trunk=1

mild diffuse decreased=2

marked diffuse decreased=3

mild increased=4

marked increased=5

changing increased=6

decreased asym=7

ad c

normal=++=0

+=1

neg=2

+++=3

asym=4

followed by leg extension=5

CONCLUSIE PRECHTL

normaal=0 normaal, echter sub-optimaal=1 abnormaal=2 [ ]

21 fysiotherapie nee=0 ja=1[bobath,voyta] alleen hanteringsadvies=2 [ ]

22 gewicht (gram) [ ]]]]

23 lengte (cm) [ ]]

24 bloeddruk (Dynamap in mm Hg, van de drie metingen meest betrouwbare)

rechter arm systole [ ]]

rechterarm diastole [ ]]

mean rechts [ ]]

toestand van het kind tijdens meting

slapend=0, rustig wakker=1, huilend=2 [ ]

AFWIJKINGEN TRACTUS RESPIRATORIUS

25 anamnese

roken vader en/of moeder	nee=0 ja=1	[ ]
kortademigheid	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]
piepen op de borst	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]
kortademigheid met piepen	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]
hoesten	nooit=0 éénmaal in maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]

26 afwijkingen samenhangend met pulmonale problematiek

bronchopulmonale dysplasie

(chronisch longbeeld zie definitielijst)	nee=0 ja=1	[ ]
pneumonie (X-thorax)	nee=0 ja=1	[ ]
cap PCo2 (Kp) bv 7.6 [7].[6]		[ ].[ ]
rechterventrikel hypertrofie (ECG)	nee=0 ja=1	[ ]
cor pulmonale (ECG)	nee=0 ja=1	[ ]
pulmonale hypertensie (Echo)	nee=0 ja=1	[ ]
O2 therapie thuis	nee=0 ja=1	[ ]
indien ja aantal l/min bv 0.2 l/min [0].[2]		[ ].[ ]
RS-virus infectie (bewezen dmv neusspoelsel)	nee=0 ja=1	[ ]

27 medicatie voor pulmonale problemen

onderhoud dexamethason	nee=0 ja=1	[ ]
indien ja, dagelijks	nee=0 ja=1	[ ]
indien ja, om de dag	nee=0 ja=1	[ ]
inhalatie anticholinergica	nee=0 ja=1	[ ]
inhalatie beta-mimetica	nee=0 ja=1	[ ]
systemische anticholinergica	nee=0 ja=1	[ ]
systemische beta-mimetica	nee=0 ja=1	[ ]
inhalatie steroiden	nee=0 ja=1	[ ]
diuretica	nee=0 ja=1	[ ]

28 AFWIJKINGEN TRACTUS DIGESTIVUS

voedingsproblemen	nee=0 ja=1 sondevoeding=2	[ ]
andere	nee=0 ja=1	[ ]

beschrijf.....

29 GEHOORSAFWIJKINGEN

twijfel ouders en/of arts	nee=0 ja=1	[ ]
afwijkend audiologisch onderzoek	nee=0 ja=1	[ ]

noise stick 60 db

normaal=0, rechts afwijkend=1, links afwijkend=2, beiderzijds afwijkend=3 [ ]

noise stick 90 db

normaal=0, rechts afwijkend=1, links afwijkend=2, beiderzijds afwijkend=3 [ ]

30 OOGAFWIJKINGEN

retinopathie van de prematuur (zie definitielijst)

rechts nee=0 graad I =1 graad II=2 graad III=3 graad IV=4 [ ]

links nee=0 graad I =1 graad II=2 graad III=3 graad IV=4 [ ]

andere oogafwijkingen nee=0 ja=1 [ ]

beschrijf.....

31 PSYCHOSOCIALE PROBLEMEN

huilen (aantal uren per dag)

0-3 uur=0, 3-6uur=1, 6-9uur=2, 9-12uur=3, 12-15uur=4, 15-18uur=5,

18-21uur=6, 21-24uur=7 [ ]

hoeveel dagen per week [ ]

slaappatroon (aantal uren wakker per dag zonder huilen)

0-3 uur=0, 3-6uur=1, 6-9uur=2, 9-12uur=3, 12-15uur=4, 15-18uur=5,

18-21uur=6, 21-24uur=7 [ ]

hoeveel dagen per week [ ]

verdenking mishandeling nee=0 ja=1 [ ]

HET ONDERZOEK OP A TERME LEEFTIJD HEEFT PLAATSGEVONDEN IN ZIEKENHUIS

AZL =1

JKZ =2

ZOETERMEER =3

VOORBURG =4 [ ]

Mei 97

FOLLOW-UP STUDIE VAN ZEER VROEGGEBOREN KINDEREN
IN DE GEZONDHEIDSREGIO'S
DEN HAAG, LEIDEN EN DELFT

Samenwerkingsproject kinderartsen, Juliana Kinderziekenhuis Den Haag, Diaconessenhuis Leiden,
Rijnland Ziekenhuis Leiderdorp, Reinier de Graaf Gasthuis Delft,
't Langeland Ziekenhuis Zoetermeer, St. Antoniushove Leidschendam, Diaconessenhuis Voorburg,
TNO-Preventie en Gezondheid Leiden, Academisch Ziekenhuis Leiden

---

FORMULIER 3: POLIKLINISCHE NACONTROLE OP DE GECORRIGEERDE LEEFTIJD VAN 1 JAAR.

NAAM..... **GEBOORTEDATUM**.....

01 IDENTIFICATIE Regionaal Follow-up Project (FUP) registratienummer [ ]]]]

02 Diaconessenhuis Vb registratienummer [ ]]]]]]]
03 't Lange Land ziekenhuis Zm registratienummer [ ]]]]]]]
04 Juliana Kinderziekenhuis DH registratienummer [ ]]]]]]]
05 AZL registratienummer [ ]]]]]]]

06 Onderzoek in ziekenhuis [ ]
AZL=1 JKZ=2 ZOETERMEER=3 VOORBURG=4

07 kinderarts..... [ ]

codeerinstructie: weigering 77 niet van toepassing coderen met 88 onbekend alle beschikbare hokjes coderen met 99

08 STREEFDATUM CONTROLE [ ]]]]]]

09 DATUM CONTROLE [ ]]]]]]

10 NIET VOOR NACONTROLE BESCHIKBAAR WEGENS [ ]
wel beschikbaar=0
overleden tussen a terme en 1 jaarscontrole=1 (datum..../..../....) [ ]]]]]]
diagnose.....
verhuisd=2 nl naar.....
controle aldaar door.....
verdere medewerking door de ouders geweigerd ivm goede toestand kind=3
verdere medewerking door de ouders geweigerd ivm slechte toestand kind=4
andere reden weigering medewerking=5
geef aan.....

11 AFWIJKINGEN TRACTUS RESPIRATORIUS

A) Anamnese

1- kortademigheid	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]
2- piepen op de borst	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]
3- kortademigheid met	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
piepen	1-4 maal per week=3 > driemaal per week=4	[ ]
4- hoesten	nooit=0 éénmaal in de maand=1 éénmaal per week=2	
	1-4 maal per week=3 > driemaal per week=4	[ ]
5- roken vader en/of moeder	nee=0 ja=1	[ ]
B) Afwijkingen samenhangend met pulmonale problematiek	nee=0 ja=1	[ ]
1- bronchopulmonale dysplasie		
(chronisch longbeeld, zie definitielijst)	nee=0 ja=1	[ ]
2- pneumonie (X-thorax)	nee=0 ja=1	[ ]
indien ja, datum		[ ]]]]]]
3- O2 therapie thuis	nee=0 ja=1	[ ]
indien ja aantal l/min bv 0.2 l/min [0].[2]		[ ].[ ]

indien ja tot wanneer [ ] [ ] [ ] [ ]

4- RS-virus infectie (bewezen dmv neusspoelsel) nee=0 ja=1 [ ]

C) Medicatie voor pulmonale problemen nee=0 ja=1 [ ]

1- onderhoud corticosteroiden (systematisch) nee=0 ja=1 [ ]

2- indien ja, dagelijks nee=0 ja=1 [ ]

3- indien ja, om de dag nee=0 ja=1 [ ]

4- inhalatie anticholinergica nee=0 ja=1 [ ]

5- inhalatie beta-mimetica nee=0 ja=1 [ ]

6- systemische anticholinergica nee=0 ja=1 [ ]

7- systemische beta-mimetica nee=0 ja=1 [ ]

8- inhalatie steroiden nee=0 ja=1 [ ]

9- diuretica nee=0 ja=1 [ ]

12 AFWIJKINGEN TRACTUS DIGESTIVUS nee=0 ja=1 [ ]

A) voedingsproblemen nee=0 ja=1 sondevoeding=2 [ ]

B) andere nee=0 ja=1 [ ]

zo ja, beschrijf.....

C) (pre)logopedie nee=0 ja=1 [ ]

13 GEHOORAFWIJKINGEN nee=0 ja=1 [ ]

A) twijfel ouders en/of arts nee=0 ja=1 [ ]

B) afwijkend audiologisch onderzoek nee=0 ja=1 [ ]

C) afwijkende Ewingtest nee=0 ja=1 [ ]

D) KNO problemen nee=0 ja=1 [ ]

zo ja, beschrijf.....

14 OOGAFWIJKINGEN nee=0 ja=1 [ ]

A) ROP nee=0 ja=1 [ ]

B) restverschijnselen ROP nee=0 ja=1 [ ]

zo ja, beschrijf.....

C) blindheid door ROP nee=0 ja=1 [ ]

D) corticale blindheid nee=0 ja=1 [ ]

E) andere oogafwijkingen nee=0 ja=1 [ ]

zo ja, beschrijf.....

15 MONITORING THUIS nee=0 ja=1 [ ]

A- bradiecardieen (<70 per minuut) nee=0 ja=1 [ ]

B- apnoe's (> 15 sec) nee=0 ja=1 [ ]

apnoe delay =.....sec.

C- coffeine medicatie nee=0 ja=1 [ ]

16 VERDENKING MISHANDELING nee=0 ja=1 [ ]

17 KWALITEIT VAN LEVEN - vragenlijst nee=0 ja=1 [ ]

18 ALGEMEEN LICHAMELIJK ONDERZOEK normaal=0 afwijkend=1 [ ]

A- KNO nee=0 ja=1 [ ]

B- Cor nee=0 ja=1 [ ]

C- Pulmonen nee=0 ja=1 [ ]

D- Abdomen nee=0 ja=1 [ ]

E- Huid nee=0 ja=1 [ ]

F- Extremiteiten nee=0 ja=1 [ ]

Zo ja bij A t/m F, beschrijf.....

19 GEWICHT (gram) [ ] [ ] [ ]

20 LENGTE (cm) [ ]]

21 SCHEDELOMTREK (cm) [ ]],[ ]

22 BLOEDDRUK (Dynamap in mm Hg, van de drie metingen meest betrouwbare)

A) rechter arm systole [ ]]

B) rechterarm diastole [ ]]

C) mean rechts [ ]]

D) toestand van het kind tijdens meting

slapend=0, rustig wakker=1, huilend=2 [ ]

CENTRAAL ZENUWSTELSEL

23 Convulsies nee=0 ja=1 [ ]

in de periode tussen a terme controle en controle op 1 jaar

anti-epileptica nee=0 ja=1 [ ]

24 EEG afwijkingen nee=0, ja=1, niet verricht=2 [ ]

voor de periode tussen a terme controle en controle op 1 jaar

25A) NEUROLOGISCH ONDERZOEK volgens TOUWEN

(items en criteria voor neurologische optimaliteit)

1- Stability of states [ ]

0= optimal

1= moderate unstable

2= very unstable

2- Facial innervation [ ]

0= optimal

1= asymmetrical

3- Twitching face, convulsions [ ]

0= absent

1= present

4- Glabella reflex [ ]

0= optimal=+

1= negative

2= exaggerated response

5- Biceps reflex [ ]

0= optimal=+ or ++

1= negative

2= +++

3= asymmetrical

6- Knee jerk [ ]

0= optimal=+ or ++

1= negative

2= +++

3= asymmetrical

7- Ankle jerk [ ]

0= optimal=+ or ++

1= negative

2= +++

3= asymmetrical

8- Treshold of arm reflexes [ ]

0= optimal=medium

1=low

2= high

3= asymmetrical

9- Treshold of leg reflexes [ ]

0= optimal

1= low

2= high

3= asymmetrical

10- Footsole response [ ]

0= optimal= variable dorsi-or plantar flexion, or indifferent

1= stereotyped dorsiflexion

2= stereotyped plantar flexion

3= asymmetrical response

11- Resistance against passive movements of neck and trunk [ ]

0= optimal = normal

1= slightly decreased

2= markedly decreased

3= slightly increased

4= markedly increased

5= changing from + to +++

12- Resistance against passive movements - arms [ ]

0= optimal = normal

1= symmetrical slightly decreased

2= symmetrical markedly decreased

3= symmetrical slightly increased

4= symmetrical markedly increased

5= changing from + to +++
6= asymmetrical

13- Resistance against active movements - arms [ ]
0= optimal = normal
1= symmetrical slightly decreased
2= symmetrical markedly decreased
3= symmetrical slightly increased
4= symmetrical markedly increased
5= asymmetrical

14- Resistance against passive movements - legs [ ]
0= optimal = normal
1= symmetrical slightly decreased
2= symmetrical markedly decreased
3= symmetrical slightly increased
4= symmetrical markedly increased
5= asymmetrical

15- Resistance against active movements - legs [ ]
0= optimal = normal
1= symmetrical slightly decreased
2= symmetrical markedly decreased
3= symmetrical slightly increased
4= symmetrical markedly increased
5= asymmetrical

16- Amount of movements [ ]
0= optimal = symmetrical, medium
1= symmetrical, medium abnormal

17- Range of movements of the arms [ ]
0= optimal (symmetrical, medium)
1= abnormal

18- Range of movements of the legs [ ]
0= optimal (symmetrical, medium)
1= abnormal

19- Muscle consistency [ ]
0= optimal
1= abnormal

20- Position of eyes [ ]
0= optimal = normal
1= changing convergent strabism
2= consistent convergent strabism
3= otherwise abnormal

21-Sunset [ ]
0= optimal = no
1= +
2= ++

22- Eye movements [ ]
0= optimal = conjugated eye movements
1= non-conjugated eye movements

23- Nystagmus [ ]
0= optimal = absent
1= present, horizontally
2= present, vertically or rotatory

24- Pupilsize, light reaction [ ]
0= optimal
1= abnormal

25- Posture neck and trunk in supine position [ ]
0= optimal= symmetrical, normal
1= hyperextension +
2= hyperextension ++
3= floppy +
4= floppy ++

26- Posture arms in supine position [ ]
0= optimal = symmetrical, normal
1= mildly abnormal, symmetrically
2= R mildly abnormal,L normal
3= L mildly abnormal,R normal

4= definitely abnormal, symmetrically
5= R definitely abnormal
6= L definitely abnormal

27- Posture legs in supine position [ ]
0= optimal = symmetrical, normal
1= mildly abnormal, symmetrically
2= R mildly abnormal, L normal
3= L mildly abnormal, R normal
4= definitely abnormal, symmetrically
5= R definitely abnormal
6= L definitely abnormal

28- Posture arms in sitting position [ ]
0= optimal = symmetrical, normal
1= mildly abnormal, symmetrically
2= R mildly abnormal, L normal
3= L mildly abnormal, R normal
4= definitely abnormal, symmetrically
5= R definitely abnormal
6= L definitely abnormal

29- Posture legs in sitting position [ ]
0= optimal = symmetrical, normal
1= mildly abnormal, symmetrically
2= R mildly abnormal, L normal
3= L mildly abnormal, R normal
4= definitely abnormal, symmetrically
5= R definitely abnormal
6= L definitely abnormal

30- Spontaneous motor activity arms (supine) [ ]
0= optimal = sym. variable and fluent motility
1= sym. rather variable but non-fluent motility
2= sym. stereotyped motility
3= asym, stereotyped motility

31- Spontaneous motor activity legs [ ]
0= optimal = sym. variable and fluent motility
1= sym. rather variable but non-fluent motility
2= sym. stereotyped motility
3= asym, stereotyped motility

32- Head lift in supine [ ]
0= optimal = + or sits up independently
1= no lifting

33- Traction test - Head [ ]
0= optimal, normal performance, anteflexion
1= 'en bloc'
2= active retroflexion +
3= active retroflexion ++
4= head lag +
5= head lag ++

34- Traction test - Arms [ ]
0= optimal, normal performance
1= R normal, L abnormal
2= L normal, R abnormal

35- Traction test - Hips [ ]
0= normal hipflexion (++)
1= hipflexion +
2= hipflexion -

36- Headbalance during sitting [ ]
0= optimal, adequate headbalance
1= active head retroflexion
2= head collapses

37- Sitting posture and balance [ ]
0= optimal, symmetrical, straight back, good balance
1= sits collapsed
2= sits on lumbosacral spine
3= sits asymmetrically
4= cannot sit without help

38- Rotation during sitting [ ]

0= optimal adequate symmetrical rotation possible

1= looses balance while rotating

2= unable to sit without help

39- Lateral supporting reaction [ ]

0= optimal = ++

1= +

2= -

3= asymmetrical

40- Palmar grasp reaction [ ]

0= none

1= +

2= ++

3= asymmetrical

41- Type of voluntary grasping [ ]

0= optimal pincet grasp

1= scissor grasp

2= radial palmair grasp

3= palmair grasp

4= grasp reflex

5= not able to grasp

42- Goal directed motility of arms and hands [ ]

0= one object in each hand or three objects

1= looking at the object, only playing with hands

2= grasping at objects

3= playing with feet

4= hold one object

5= no good directed motility

43- Quality of grasping [ ]

0= optimal= normal

1= symmetrically mildly abnormal, jerky

2= symmetrically mildly abnormal, stiff

3= mildly abnormal R, jerky

4= mildly abnormal R, stiff

5= mildly abnormal L, jerky

6= mildly abnormal L, stiff

7= symmetrically definitely abnormal

8= definitely abnormal R

9= definitely abnormal L

44- Handpreference during grasping [ ]

0= optimal, no preference or no grasping

1= clear preference R

2= clear preference L

45- Posture in prone position [ ]

0= supporting himself on hands and extended arms, begins to draw his knees under his abdomen symmetrical, no scoliosis

1= similar, support by extending the arms

2= lifts head and the upper part of the chest, supporting himself on hands/elbows

3= lifts head and upper part of the chest without supporting himself

4= lifts head for a few seconds

46- Locomotion in prone position [ ]

0= abdominal progression using arms and legs and/or creeping on all fours

1= abdominal progression using only arms

2= move only backwards, wriggle

3= no movement

47- Rolling supine to prone [ ]

0= symmetrical, trunk rotation

1= no rotation

2= axial rotation

3= asymmetrical

48- Rolling prone to supine [ ]

0= symmetrical, trunk rotation

1= no rotation

2= axial rotation

3= asymmetrical

49- Posture in supine suspension [ ]

0= symmetrical, not stif or floppy, no hyperextension

1= hyperextension

2= floppy

50- Vertical basculation, shoulders [ ]

0= normal

1= slips through +

2= slips through ++

3= stiff shoulders

51- Vertical basculation, legs [ ]

0= symmetrical flexion

1= symmetrical extension +

2= symmetrical extension ++

3= R ext, L flex

4= R flex, L ext

52- Optical placing reaction of hands [ ]

0= symmetrical, forward extension of arms, dorsiflexion of wrist and opening of hand

1= no forward extension of the arms, and or opening of the hands

2= asymmetrical

53- Optical placing of the feet [ ]

0= extension of feet, then placing of the feet

1= no extension and placing of the feet

2= asymmetrical

54- Posture in prone suspension (Landau) [ ]

0= smooth, complete movement, head lift upward, curvation of the spine and extension of the hips and knees or symmetrical and voluntary movements

1= no complete movement

55- Standing up [ ]

0= possible

1= not possible

56- Standing posture and balance [ ]

0= optimal, symmetrical posture of trunk, legs and feet

1= abnormal standing posture

2= not able to stand without help

57- Response to push while standing (sidestep) [ ]

0= optimal= +

1= not present

58- Walking [ ]

0= optimal, symmetrical posture of trunk, legs and feet

1= abnormal walking posture

2= not able to walk without help

59- Tremor during movements [ ]

0= absent

1= present

60- Tremor during responses [ ]

0= no

1= yes

25 B) CONCLUSIE TOUWEN [ ]

normaal=0 normaal, echter sub-optimaal=1 abnormaal=2

26 VAN WIECHEN ONTWIKKELINGSONDERZOEK 15 MAANDEN:

Fijne motoriek/Adaptatie/Persoonlijkheid en Sociaalgedrag:

1- Ogen fixeren		ja=0	nee=1	[ ]
2- Volgt met ogen en hoofd	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
3- Handen af en toe open	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
4- Kijkt naar eigen handen (M)		ja=0	nee=1	[ ]
5- Speelt met handen middenvoor		ja=0	nee=1	[ ]
6- Pakt in rugligging voorwerp binnen bereik	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
7- Pakt blokje over		ja=0	nee=1	[ ]
8- Houdt blokje vast, pakt er nog een in andere hand		ja=0	nee=1	[ ]
9- Speelt met beide voeten	Re	ja=0	nee=1	[ ]

	Li	ja=0	nee=1	[ ]
10- Pakt propje met duim en wijsvinger	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
11- Doet blokje in/uit de doos*	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
12- Speelt “geven en nemen”*	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
Communicatie:				
13- Reageert op toespreken (M)		ja=0	nee=1	[ ]
14- Lacht terug (M)		ja=0	nee=1	[ ]
15- Maakt geluiden terug (M)		ja=0	nee=1	[ ]
16- Maakt gevarieerde geluiden (M)		ja=0	nee=1	[ ]
17- Reageert op roepen bij naam (M)		ja=0	nee=1	[ ]
18- Zegt ‘dada-baba of gaga’ (M)		ja=0	nee=1	[ ]
19- Brabbelt bij zijn spel (M)		ja=0	nee=1	[ ]
20- Reageert op mondeling verzoek (M)		ja=0	nee=1	[ ]
21- Zwaait ‘dag, dag’(M)		ja=0	nee=1	[ ]
22- Zegt 2 geluidswoorden met begrip (M)*		ja=0	nee=1	[ ]
23- Begrijpt enkele dagelijks gebruikte zinnen (M)*		ja=0	nee=1	[ ]
Grove motoriek:				
24- Beweegt armen evenveel		ja=0	nee=1	[ ]
25- Beweegt benen evenveel		ja=0	nee=1	[ ]
26- Blijft hangen bij optillen onder de oksels		ja=0	nee=1	[ ]
27- Reacties bij optrekken tot zit		ja=0	nee=1	[ ]
28- Heft kin van de onderlaag		ja=0	nee=1	[ ]
29- Heft in buikligging tot 45 graden		ja=0	nee=1	[ ]
30- Kijkt rond met 90 graden geheven hoofd		ja=0	nee=1	[ ]
31- Benen gebogen of trappelen bij verticaal zwaaien	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
32- Rolt zich om van rug naar buik en omgekeerd (M)		ja=0	nee=1	[ ]
33- Kan hoofd goed ophouden in zit		ja=0	nee=1	[ ]
34- Zit op billen met gestrekte benen		ja=0	nee=1	[ ]
35- Zit stabiel los		ja=0	nee=1	[ ]
36- Kruipt vooruit, buik op de grond (M)		ja=0	nee=1	[ ]
37- Trekt zich op tot staan (M)		ja=0	nee=1	[ ]

38- Kruipt, buik vrij van de grond (M)*	ja=0	nee=1	[ ]
39- Loopt langs (M)*	ja=0	nee=1	[ ]

*** = voor 15 maanden**

27 FYSIOTHERAPIE nee=0 ja=1 [bobath,voyta] alleen hanteringsadvies=2 [ ]

Maart 98

FOLLOW-UP STUDIE VAN ZEER VROEG GEBOREN KINDEREN
IN DE GEZONDHEIDSREGIO'S
DEN HAAG, LEIDEN EN DELFT

Samenwerkingsproject kinderartsen, Juliana Kinderziekenhuis Den Haag, Diaconessenhuis Leiden,
Rijnland Ziekenhuis Leiderdorp, Reinier de Graaf Gasthuis Delft,
't Langeland Ziekenhuis Zoetermeer, St. Antoniushove Leidschendam, Diaconessenhuis Voorburg,
TNO-Preventie en Gezondheid Leiden, Academisch Ziekenhuis Leiden

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FORMULIER 4: POLIKLINISCHE NACONTROLE OP DE GECORRIGEERDE LEEFTIJD VAN 2 JAAR

NAAM..... GEBOORTEDATUM .....

01 IDENTIFICATIE Regionaal Follow-up Project (FUP) registratienummer [ ]]]]

02 Diaconessenhuis Vb registratienummer [ ]]]]]]]
03 't Lange Land ziekenhuis Zm registratienummer [ ]]]]]]]
04 Juliana Kinderziekenhuis DH registratienummer [ ]]]]]]]
05 AZL registratienummer [ ]]]]]]]
06 Onderzoek in ziekenhuis [ ]
AZL=1 JKZ=2 ZOETERMEER=3 VOORBURG=4
07 kinderarts..... [ ]

Codeerinstructie: weigering 77, niet van toepassing coderen met 88 onbekend alle beschikbare hokjes coderen met 99

08 STREEFDATUM CONTROLE [ ]]]]]]

09 DATUM CONTROLE [ ]]]]]]

10 NIET VOOR NACONTROLE BESCHIKBAAR WEGENS [ ]
wel beschikbaar=0
overleden tussen 1 jaar en 2 jaarscontrole=1 (datum.../..../....) [ ]]]]]]
diagnose.....
verhuisd=2 (nl naar.....
controle aldaar door.....
verdere medewerking door de ouders geweigerd ivm goede toestand kind=3
verdere medewerking door de ouders geweigerd ivm slechte toestand kind=4
andere reden weigering medewerking=5
geef aan.....

11 AFWIJKINGEN TRACTUS RESPIRATORIUS

A) Anamnese

1- kortademigheid nooit=0 wel eens=1 in de afgelopen 12 maanden=2 [ ]
2- piepen op de borst nooit=0 wel eens=1 in de afgelopen 12 maanden=2 [ ]
3- kortademigheid met piepen nooit=0 wel eens=1 in de afgelopen 12 maanden=2 [ ]
4- hoeveel aanvallen van piepen en/of kortademigheid in de afgelopen 12 mnd?
geen=0 1tot3=1 4 tot 12=2 meer dan 12=3 [ ]
5- hoestperioden (droge hoest, buiten verkoudheden)
nee=0 frequentie <1x per maand=1 frequentie>1x per maand=2 [ ]
6- roken vader en/of moeder nee=0 ja=1 [ ]

B) Afwijkingen samenhangend met pulmonale problematiek nee=0 ja=1 [ ]
1- O2 therapie thuis nee=0 ja=1 [ ]
indien ja aantal l/min bv 0.2 l/min [0].[2] [ ].[ ]
indien neen tot wanneer [ ]]]]]]
C) Medicatie voor pulmonale problemen nee=0 ja=1 [ ]
1- onderhoud corticosteroiden (systematisch) nee=0 ja=1 [ ]

2- indien ja, dagelijks nee=0 ja=1 [ ]
3- indien ja, om de dag nee=0 ja=1 [ ]
4- inhalatie anticholinergica nee=0 ja=1 [ ]
5- inhalatie beta-mimetica nee=0 ja=1 [ ]
6- inhalatie steroiden nee=0 ja=1 [ ]
7- diuretica nee=0 ja=1 [ ]
8- indien medicamenteuze therapie gehad maar nu niet meer nee=0 ja=1 [ ]
datum tot wanneer: [ ]]-[ ]]-[ ]]]]

12 AFWIJKINGEN TRACTUS DIGESTIVUS nee=0 ja=1 [ ]
A) voedingsproblemen nee=0 ja=1 sondevoeding=2 [ ]
B) andere nee=0 ja=1 [ ]
zo ja, beschrijf.....

13 GEHOORSAFWIJKINGEN nee=0 ja=1 [ ]
zo ja, beschrijf.....
A) KNO problemen nee=0 ja=1 [ ]
zo ja, beschrijf.....

14 OOGAFWIJKINGEN nee=0 ja=1 [ ]
Zoja, beschrijf.....

15 VERDENKING MISHANDELING nee=0 ja=1 [ ]

16 KWALITEIT VAN LEVEN - vragenlijst ja=0 nee=1 [ ]

17 BAYLEY ONTWIKKELINGSSCHALEN (BOS) 18 mnd ja=0 nee=1 [ ]

18 BAYLEY ONTWIKKELINGSSCHALEN (BOS) 24 mnd ja=0 nee=1 [ ]

19 CHILD BEHAVIORCHECKLIST (ACHENBACH) ja=0 nee=1 [ ]

20 ALGEMEEN LICHAMELIJK ONDERZOEK normaal=0 afwijkend=1 [ ]
A- KNO nee=0 ja=1 [ ]
B- Cor nee=0 ja=1 [ ]
C- Pulmonen nee=0 ja=1 [ ]
D- Abdomen nee=0 ja=1 [ ]
E- Huid nee=0 ja=1 [ ]
F- Extremiteiten nee=0 ja=1 [ ]
Zo ja bij A t/m F, beschrijf.....
21 GEWICHT (kg) [ ]],[ ]
22 LENGTE (cm) [ ]]
23 SCHEDELOMTREK (cm) [ ]],[ ]
24 BLOEDDRUK (Dynamap in mm Hg, van de drie metingen meest betrouwbare)
A) rechter arm systole [ ]]]
B) rechterarm diastole [ ]]
C) mean rechts [ ]]
D) toestand van het kind tijdens meting
slapend=0, rustig wakker=1, huilend=2 [ ]

CENTRAAL ZENUWSTELSEL
25 Convulsies nee=0 ja=1 [ ]
in de periode tussen controle op 1 jaar en 2 jaar
anti-epileptica nee=0 ja=1 [ ]
26 EEG afwijkingen nee=0, ja=1, niet verricht=2 [ ]
voor de periode tussen controle op 1 jaar en 2 jaar

27 NEUROLOGISCH ONDERZOEK volgens HEMPEL
(Observation motor functions)
0= optimaal, bij sommige items hoeft dit niet gescoord te worden op 2 jarige leeftijd
A. Prehension
1- Able to grasp [ ]
0= +
1= -
2- Mode of grasping [ ]
0= R+ L+

3- Handpreference [ ]
0= no handpreference
1= handpreference R / L
2= excl. handpreference R / L

4- Posture arm /shoulder R [ ]
0= normal L [ ]
1= mildly abnormal
2= abnormal

5-Yoke movements [ ]
0= -
1= + = soms
2= ++ = bij elke beweging komt het voor

6- Quality of arm / shoulder movements [ ]
0= smooth
1= non-fluent
2= stiff
3= dyskinetic

7- Posture hands / fingers R [ ]
0= normal L [ ]
1= mildly abnormal
2= abnormal

8- Adjustment handopening [ ]
0= good
1= poor
2= inability

9- Associated movements (hindering) [ ]
0= -
1= +

10- Quality of hand mobility [ ]
0= smooth
1= non fluent / block

B. Sitting

1- Sitting [ ]
0= can sit without help
1= can sit, but needs one hand for support
2= can sit only with help
3= cannot sit at all

2- Sitting up [ ]
0= can sit up without help
1= can sit up only with help
2= cannot sit up

3- Posture head [ ]
0= centered and well adapted
1= stereotyped, deviant

4- Posture trunk [ ]
0= normal
1= mildly abnormal
2= abnormal

5- Posture legs R [ ]
0= normal L [ ]
1= mildly abnormal
2= abnormal

6- Posture feet / toes R [ ]
0= normal L [ ]
1= mildly abnormal
2= abnormal

7- Trunk rotation, spontaneous [ ]
0= ++ (> 45 graden)
1= + (< 45 graden)
2= - (moet billen bijschuiven)

8- Trunk rotation, elicited [ ]
0= ++
1= +
2= -

9- Fluency of trunk movements [ ]

0= smooth

1= non-fluent

2= block

10- Lateral supporting reactions R [ ]

0= ++ L [ ]

1= +

2= -

11- Accelaration / Deceleration [ ]

0= smooth

1= abrupt

2= sluggish (vertraagd inzetten v.e. beweging)

C. Crawling

1- Ability to crawl [ ]

0= yes, on hands and knees

1= yes, other way

2= no

2- Symmetry of movements [ ]

0= no asymmetry

1= mild asymmetry

2= definitive asymmetry

3- Posture head [ ]

0= centered and well adapted

1= stereotyped, deviant

4- Coordination of arm-leg movements [ ]

0= +

1= -

5- Variability in speed (tijdens 1 kruiptraject) [ ]

0= +

1= -

6- Fluency of trunk movements [ ]

0= smooth

1= non-fluent

7- Fluency of leg movements [ ]

0= smooth

1= non-fluent

2= stiff

D. Standing

1- Standing up [ ]

0= can stand up without help with object in both hands

1= stands up without help

2= stands up with help only

3= cannot stand up

2- Standing free [ ]

0= stands free

1= stands with help

2= cannot stand

3- Variability in standing up [ ]

0= ++

1= +

2= -

4- Posture head [ ]

0= centred and well adapted

1= stereotyped, deviant

5- Posture arms R [ ]

0= normal L [ ]

1= mildly abnormal

2= abnormal

6- Posture trunk [ ]

0= normal

1= mildly abnormal

2= abnormal

7- Posture legs R [ ]
0= || L [ ]
1=)(
2= ()
3= mildly abnormal
4= abnormal

8- Posture feet / toes R [ ]
0= normal, good arch L [ ]
1= normal, no arch
2= mildly abnormal
3= abnormal

9- Distance between feet [ ]
0= medium
1= broad (buiten de heupbreedte)
2= narrow (scharen)

10- Balance without movements [ ]
0= +++
1= ++ (smalle correctiebewegingen zonder voeten te verplaatsen)
2= + (grove correctiebewegingen)
3= - (valt soms, valt aldoor)

11- Balance with movements [ ]
0= +++
1= ++
2= +
3= -

12- Trunk rotation, spontaneously [ ]
0= ++
1= +
2= -

13- Trunk rotation, elicited [ ]
0= ++
1= +
2= -

14- Fluency of trunk movements [ ]
0= smooth
1= non-fluent
2= block

15- Reaction to push against shoulders R [ ]
0= ++ L [ ]
1= +
2= -

16- Dyskinesia [ ]
0= -
1= +
2= ++ (echt hinderen in de beweging) Omschrijf:

E. Walking

1- Ability to walk [ ]
0= able to walk without help
1= able to walk with help
2= cannot walk

2- Toddling [ ]
0= -
1= +
2= ++ (bij elk stukje lopen aanwezig)

3- Fluency of trunk movements [ ]
0= smooth
1= non-fluent
2= stiff

4- Fluency of leg movements [ ]
o= smooth
1= non-fluent
2= stiff

5- Reciprocal arm swing [ ]
0= +
1= -

6- Posture head [ ]
0= centred and well adapted
1= stereotyped, deviant

7- Posture arms R [ ]
0= normal L [ ]
1= mildly abnormal
2= abnormal

8- Posture trunk [ ]
0= normal
1= mildly abnormal
2= abnormal

9- Posture legs R [ ]
0= || L [ ]
1=)(
2= ()
3= mildly abnormal
4= abnormal

10- Posture feet / toes R [ ]
0= normal, good arch L [ ]
1= good, no arch
2= mildly abnormal
3= abnormal

11- Gait width [ ]
0= medium
1= broad
2= narrow

12- Plantigrade walk [ ]
0= + (goed afwikkelen van je voet)
1= -

13- Balance during walking (loslopen is 7 passen lopen) [ ]
0= good
1= moderate (veel correctiebewegingen)
2= bad (omvallen)

14- Abduction shoulder [ ]
0= -
1= + (< 45 graden)
2= ++ (> 45 graden)

15- Walking on tip-toe [ ]
0= -
1= + (< ½ v.d. tijd)
2= ++ (> ½ v.d. tijd)
3= +++ (altijd)

16- Variability of speed (in 1 stukje lopen) [ ]
0= +
1= -

17- Manoeuvrability [ ]
0= ++ (kan slalom lopen)
1= + (moet grotere bochten maken)
2= - (moet eerst stilstaan voordat de richting kan veranderen)

18- Ability to avoid objects [ ]
0= ++
1= + (zo nu en dan erop stappen)
2= -

F. Head (kind zit op schoot bij moeder)

1- Eyes, position [ ]
0= symmetrical centered
1= latent strabism
2= deviant

2. Eyes, movements [ ]
0= smooth, symmetrical
1= limited range
2= abnormal quality

3- Nystagmus (spontaneous/direct) [ ]
0= absent
2= directional nystagmus
3= spontaneous nystagmus

4- Optokinetic nystagmus [ ]
0= symmetrical present
1= asymmetrical
2= absent

5- Pupils size/ shape [ ]
0= normal
1= deviation

6- Reaction to light, direct R [ ]
0= + L [ ]
1= -

7- Reaction to light, indirect R [ ]
0= + L [ ]
1= -

8- Visual fields [ ]
0= intact
1= doubts

9- Visual acuity [ ]
0= intact
1= doubts

10- Hearing acuity [ ]
0= intact
1= doubts

11- Localisation of sounds [ ]
0= intact
1= doubts

12- Facial expression/symmetrical [ ]
0= normal
1= asymmetrical
2= expression less

13- Drooling, continuous [ ]
0= -
1= +

14- Speech/ language [ ]
0= normal
1= doubts

G. Manipulative examination

1- Resistance against passive movements - arms R [ ]
0= ++ (normaal) L [ ]
1= +++ (hypertonie)
2= + (hypotonie)
3= - (volledige hypotonie)

2- Resistance against passive movements - legs R [ ]
0= ++ (normaal) L [ ]
1= +++ (hypertonie)
2= + (hypotonie)
3= - (volledige hypotonie)

3- Resistance against active power - arms R [ ]
0= + L [ ]
1= ++
2= -

4- Resistance against active power - legs R [ ]
0= + L [ ]
1= ++
2= -

5- Range of movements of the arms R [ ]
0= ++ (normaal) L [ ]
1= +++ (teveel laxiteit)
2= + (beperkt)
3= - (volledig beperking)

6- Range of movements of the legs R [ ]
0= ++ (normaal) L [ ]
1= +++ (teveel laxiteit)
2= + (beperkt)
3= - (volledig beperking)

7- Biceps jerk R [ ]
0= ++ (normaal) L [ ]
1= +++
2= +
3= -

8- Knee jerk R [ ]
0= ++ (normaal) L [ ]
1= +++
2= +
3= -

9- Ankle jerk R [ ]
0= ++ (normaal) L [ ]
1= +++
2= +
3= -

10- Treshold of the biceps jerk R [ ]
0= medium (normaal) L [ ]
1= high
2= low

11- Threshold of the knee jerk R [ ]
0= medium (normaal) L [ ]
1= high
3= low

12- Threshold of the ankle jerk R [ ]
0= medium (normaal) L [ ]
1= high
2= low

13- Footsole response R [ ]
0= optimal= variable dorsi-or plantar flexion, or indifferent L [ ]
1= stereotyped dorsiflexion
2= stereotyped plantar flexion
3= asymmetrical response

H- Summery of findings

1- Hand / arm function [ ]
0= normal
1= mildly abnormal
2= abnormal

2- Trunk / head / legfunction [ ]
0= normal
1= mildly abnormal
2= abnormal

Involving

1. Posture	N	MA	A
2. Coordination trunk	N	MA	A
3. Coordination extremities	N	MA	A
4. Fluency / adequacy of movements/ dyskinesia	N	MA	A
5. Sensorimotor apparatus	N	MA	A
6. Examination of the head			
Visuomotor function	N	MA	A
Auditory function	N	MA	A
Facial innervation	N	MA	A
7.(Neuro)development			
Manual	N	MA	A
Gross motor	N	MA	A

28- Conclusion [ ]
0= normal
1= suspect
2= abnormal

29- Stability of states [ ]
0= optimal
1= moderate unstable
2= very unstable

6 VAN WIECHEN ONTWIKKELINGSONDERZOEK 15-48 MAANDEN:

Fijne motoriek/Adaptatie/Persoonlijkheid en Sociaalgedrag:

11- Doet blokje in/uit de doos	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
12- Speelt “geven en nemen”	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
13- Stapelt 2 blokjes	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]

14- Gaat op onderzoek uit (M)		ja=0	nee=1	[ ]
15- Stapelt 3 blokjes	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
16- Doet anderen na (M)		ja=0	nee=1	[ ]
17- Stapelt 6 blokjes		ja=0	nee=1	[ ]
18- Plaatst ronde vorm in de stoof		ja=0	nee=1	[ ]
19- Trekt kledingstuk uit (M)		ja=0	nee=1	[ ]
20- Bouwt vrachtauto na		ja=0	nee=1	[ ]
21- Plaatst 3 vormen in de stoof		ja=0	nee=1	[ ]
22- Tekent verticale lijn na		ja=0	nee=1	[ ]
23- Bouwt brug na		ja=0	nee=1	[ ]
24- Plaatst 4 vormen in de stoof		ja=0	nee=1	[ ]
25- Trekt eigen kledingstuk aan (M)		ja=0	nee=1	[ ]
26- Houdt potlood met vingers vast		ja=0	nee=1	[ ]
27- Tekent cirkel na		ja=0	nee=1	[ ]
Communicatie:				
28- Zegt 2 geluidswoorden met begrip (M)		ja=0	nee=1	[ ]
29- Begrijpt enkele dagelijks gebruikte zinnen (M)		ja=0	nee=1	[ ]
30- Zegt 3 woorden (M)		ja=0	nee=1	[ ]
31- Begrijpt spelopdrachtjes (M)		ja=0	nee=1	[ ]
32- Zegt “zinnen “ van 2 woorden (M)		ja=0	nee=1	[ ]
33- Wijst 6 lichaamsdelen aan bij pop (M)		ja=0	nee=1	[ ]
34- Noemt zichzelf bij eigen naam of “ik” (M)		ja=0	nee=1	[ ]
35- Wijst 5 plaatjes aan in boek (M)		ja=0	nee=1	[ ]
36- Zegt “zinnen” van 3 of meer woorden (M)		ja=0	nee=1	[ ]
37- Is verstaanbaar voor bekenden (M)		ja=0	nee=1	[ ]
38- Praat spontaan over gebeurtenissen thuis/speelzaal (M)		ja=0	nee=1	[ ]
39- Stelt vragen naar “wie”,”wat”,”hoe”(M)		ja=0	nee=1	[ ]
40- Is goed verstaanbaar voor onderzoeker		ja=0	nee=1	[ ]
41- Stelt vragen naar “hoeveel”,”wanneer”,”waarom” (M)		ja=0	nee=1	[ ]
Grove motoriek:				
42- Kruipt, buik vrij van de grond (M)		ja=0	nee=1	[ ]
43- Loopt langs (M)		ja=0	nee=1	[ ]
44- Loopt los		ja=0	nee=1	[ ]
45- Gooit bal zonder om te vallen		ja=0	nee=1	[ ]
46- Raapt vanuit hurkzit iets op		ja=0	nee=1	[ ]
47- Loopt goed los		ja=0	nee=1	[ ]
48- Schopt bal weg	Re	ja=0	nee=1	[ ]
	Li	ja=0	nee=1	[ ]
41- Kan in zit soepel roteren		ja=0	nee=1	[ ]
42- Loopt soepel		ja=0	nee=1	[ ]
43- Fietst (op driewieler) (M)		ja=0	nee=1	[ ]
44- Springt met beide voeten tegelijk		ja=0	nee=1	[ ]

27 FYSIOTHERAPIE	nee=0	ja=1	[ ]