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

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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**).

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