8807276

PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE INFANTS IN THE NETHERLANDS 1983: A COLLABORATIVE SURVEY

Verloove-Vanhorick, Susanne Pauline, Ph.D.
Verwey, Robert Anton, Ph.D.

Leiden University(The Netherlands), 1987

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE INFANTS IN THE NETHERLANDS 1983

a collaborative survey

proefschrift ter verkrijging van de graad van Doctor aan de Rijksuniversiteit te Leiden, op gezag van de Rector Magnificus Dr. J.J.M. Beenakker, hoogleraar in de faculteit der Wiskunde en Natuurwetenschappen, volgens besluit van het college van dekanen te verdedigen op donderdag 11 juni 1987

te klokke 15.15 uur

door

Susanne Pauline Verloove-Vanhorick

geboren te Amsterdam in 1946

en te klokke 16.15 uur

door

Robert Anton Verwey

geboren te Amsterdam in 1946

Gezien de verwevenheid van de obstetrische en neonatologische aspecten in de beschreven patientengroep, zijn de hoofdstukken 1, 3, 4, 13, 14 en 15 gezamenlijk door S.P. Verloove-Vanhorick en R.A. Verwey geschreven.

De onderwerpen in de hoofdstukken 2, 8, 10, 11 en 12 werden voornamelijk bewerkt door S.P. Verloove-Vanhorick, de hoofdstukken 5, 6, 7 en 9 door R.A. Verwey.

Hoofdstuk 13 zou in zijn huidige vorm niet tot stand zijn gekomen zonder de inbreng van Dr. R. Brand, vakgroep Medische Statistiek van de Rijksuniversiteit Leiden. Wij hebben gemeend dit hoofdstuk in deze vorm op te moeten nemen teneinde de toegepaste statistische technieken zo volledig mogelijk te verantwoorden.

The Project On Preterm and Small for gestational age is supported by the Praeventiefonds, the Hague.

Printed by drukkerij J.H. Pasmans B.V., 's-Gravenhage

ISBN 90-9001620-1

PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE INFANTS IN THE NETHERLANDS 1983

a collaborative survey

Promotiecommissies

S.P. Verloove-Vanhorick:

Promotoren:	Prof. dr. J.H. Ruys Prof. dr. J. Bennebroek Gravenhorst
Co-promotor:	Dr. R. Brand
Referent:	Dr. C. Versluys, Rijksuniversiteit Utrecht
Overige leden:	Prof. dr. H.H. van Gelderen Prof. dr. M.J.N.C. Keirse Prof. dr. J.P. Vandenbroucke

R.A. Verwey:

Promotoren:	Prof. dr. J. Bennebroek Gravenhorst Prof. dr. J.H. Ruys
Co-promotor:	Dr. R. Brand
Referent:	Prof. dr. H.J. Huisjes, Rijksuniversiteit Groningen
Overige leden:	Prof. dr. M.J.N.C. Keirse Prof. dr. H.H. van Gelderen Prof. dr. J.P. Vandenbroucke

Abbreviations

AGA = appropriate for gestational age
BPD = bronchopulmonary dysplasia
CBS = Centraal Bureau voor de Statistiek
CI = confidence interval
CNS = central nervous system
CPAP = continuous positive airway pressure
CT = computerized tomography scan
CTG = cardiotocography
ELBW = extremely low birthweight
FIGO = Fédération Internationale de Gynécologie et d'Obstétrique
IC = intensive care
ICH = intracranial haemorrhage
IPPV = intermittent positive pressure ventilation
IRDS = idiopathic respiratory distress syndrome
IUGR = intrauterine growth retardation
LBW = low birthweight
LGA = large for gestational age
L/S = lecithine-sphingomyeline ratio
NICU = neonatal intensive care unit
OR = odds ratio
PFC = persistent fetal circulation
PG = prostaglandine
POPS = Project on Preterm and Small for gestational age
RR = relative risk
SGA = small for gestational age
VLBW = very low birthweight
WBC = white blood count
WHO = World Health Organization

PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE IN THE NETHERLANDS 1983

Definitions

The following definitions and recommendations have been given by the World Health Organization (WHO, 1977) and have been adopted by FIGO (1976, 1982):

Live birth

Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.

Gestational age

The duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (e.g. events occurring 280 to 286 days after the onset of the last normal menstrual period are considered to have occurred at 40 weeks of gestation).

Birthweight

The first weight of the newborn obtained after birth. This weight should be measured preferably within the first hour of life before significant postnatal weight loss has occurred.

Preterm

Less than 37 completed weeks (less than 259 days).

Low birthweight

Less than 2500 g (up to, and including 2499 g).

Early neonatal death

Death of a liveborn infant during the first seven completed days (168 hours) of life.

Late neonatal death

Death of a liveborn infant after 7 completed days but before 28 completed days of life. (WHO-Approved by FIGO with the modification of "completed days".

Neonatal death
Death of a liveborn infant before 28 completed days of life.

In addition to these, FIGO (1976; 1986) issued the following recommendations:

Low birthweight (LBW)
500 g to less than 2500 g (up to and including 2499 g).

Very low birthweight (VLBW)
500 g to less than 1500 g (up to and including 1499 g).

Extremely low birthweight (ELBW)
500 g to less than 1000 g (up to and including 999 g).

The above mentioned definitions do not adequately cover all circumstances. In the absence of recommendations by WHO or FIGO, we use the following additional definitions:

Postneonatal death
Death from 28 completed days to less than 1 year from birth (i.e. up to and including 364 days) (Pharoah, 1976; Hack, 1980; Chiswick, 1986).

In-hospital death
Death of a liveborn infant during the hospital stay following birth and before discharge home, irrespective of transferral between hospitals within this period.

Very preterm
Less than 32 completed weeks of gestation (less than 224 days).

Chapter 1 Introduction

1.1 Historical perspective

Since the beginning of this century, attention has been given to "low birthweight" (LBW) infants. In the past, the reported neonatal mortality in this group was very high (table 1.1.1.), even though some authors excluded "abortions, i.e. fetuses less than 1500 g in weight and less than 32 cm in length" (Peckham, 1938). Death was generally ascribed to "debilitas vitae", weakness of life. Follow-up was scanty, due to the high infant mortality rate and the large number of patients lost to follow-up for other reasons. Yet, substantial numbers of handicapped survivors were found in some studies (Wallich & Fruhinsholz, 1911; Ylppö, 1919; Capper, 1928a; Looft, 1928; Mohr & Bartelme, 1930; Brander, 1935; Duyzings, 1935; Hess & Lundeen, 1949). Other authors, however, saw the outcome as more favourable (Wall, 1913; Hess et al, 1934; Drillien, 1948; Koenig, 1950).

With the introduction of intensive care, the possibilities for treatment of very low birthweight infants increased considerably; neonatal mortality decreased, but from then on the quality of life in the surviving infants became a matter of growing concern, and the discussion still continues (Rawlings et al, 1971; Calame & Prod'hom, 1972; Francis-Williams & Davies, 1974; Stewart & Reynolds, 1974; Davies & Stewart, 1975; Davies, 1976; Hommers & Kendall, 1976; Sabel et al, 1976; Alberman, 1977; Saint-Anne Dargassies, 1977; Reynolds, 1978; Stewart et al, 1978; Brown & Taeusch, 1979; Dunn et al, 1979; Gamsu et al, 1979; Gordon, 1979; Jones et al, 1979b; Nelson et al, 1979; Philip, 1979; Reynolds & Stewart, 1979; Roberton, 1979; Bennett-Britton et al, 1981; Chalmers & Mutch, 1981; Jones & Davies, 1981; McDonald, 1981; Stewart et al, 1981; Alberman et al, 1982a,b; Fledelius, 1982; Noble-

Table 1.1.1. Evaluative studies on "low birth weight", 1913-1953.

author	year of publication	location	period	definition LBW	number of patients	mortality* rate (%)	follow-up n	duration (years)	infant** mortality %	handicaps*** rate (%)
Wallich	1911	France	1849-1909	900-1500 g			17	2-62		(3)
				1500-2000 g			25	2-26		(3)
Wall	1913	Breslau	1892-1910	Frühgeburt	691	29	183	3-20	16	1
Ylppö	1919	Berlin	1909-1918	<2500 g	598	53	278			6
				600-1000 g	37	84			7	
				1001-1500 g	178	49			15	
Looft	1928	Bergen	1910-1916	<2500 g	91	91	8	4-11		8
Capper	1928a,b	Vienna	1911-1926	<2500 g	437	45		1-16		majority
Mohr	1930	Chicago	±1920	<2500 g			113	1- 7		(35)
Brander	1935	Helsingfors		1000-2000 g			78	7-15		(27)
Duyzings	1935	Rotterdam	1907-1927	28-38 wks	1450	49	712	6-26		3.4
				<1500 g	193	94	12	6-26		2
Baedorf	1937	Frankfurt	1919-1929	<1700 g	434	77	27			(5)
Tyson	1946	Philadelphia	1930-1944	<2500 g	2960	25				
				1000-1500 g	331	80				
Hess	1949	Chicago	1922-1947	735-1260 g			216	0-17		(31)
Koenig	1950	New York	±1940-1950	<2500 g			650	2-10		(19)
Howard	1952	Detroit	1930-1942	<1820 g			22	8		(6)
Blegen	1953	Oslo	1930-1939	400-2500 g	893	17	541	10-20	5	(27)
				<1000 g	11	100				
				1001-1500 g	89	61			9	
				1501-2000 g	201	24			6	
				2001-2500 g	592	7			3	

*deaths in hospital, expressed as percentage of admitted infants

**deaths after discharge, expressed as percentage of admitted infants

***expressed as percentage of liveborn infants or (between parentheses) actual number

Jamieson et al, 1982; Shapiro et al, 1983; Kiely et al, 1984; McCormick et al, 1985a; McCormick 1985b; Mitchell, 1985; Allen & Jones, 1986; Bax, 1986).

It must be kept in mind, however, that the selection criteria for the different study populations and the definition of intensive care have changed enormously, especially in the last few decades.

1.2 Very low birthweight

1.2.1 History

Usually, low birthweight (LBW) is defined as a weight of less than 2500 g at birth (WHO, 1977) and very low birthweight (VLBW) as less than 1500 g. A few years ago, the concept of extremely low birthweight (ELBW) was introduced, the upper limit being taken at 1000 or 800 g (Bavikatte et al, 1980; Egan et al, 1980; Nelson et al, 1980; Yu et al, 1981; Orgill et al, 1982b). Recently, FIGO defined ELBW as 500 to less than 1000 g (FIGO, 1986). Some authors refer to such infants as very very low birthweight (VVLBW) (Vidyasagar, 1986).

1.2.2 Incidence

The reported incidence of VLBW ranges from 0.2 to 2.0 per 100 liveborn infants (table 1.2.1).

Although this might be interpreted as a small number of infants, it accounts for a large proportion (30-50%) of the total neonatal mortality (Usher, 1977; Stewart et al, 1981; Kitchen et al, 1982d; Goldenberg et al, 1983b; Alberman, 1984; McCormick, 1985b). Thus, variations in the incidence of VLBW have a strong impact on the total neonatal mortality rate (Davies, 1980; Lee et al, 1980a; MacFarlane, 1981; Miller, 1983). Lee at al (1980b) reported little or no change in the incidence of LBW in the USA over the last 30 years, whereas David & Siegel (1983b) described a positive birthweight shift. In Australia the same shift in birthweight distribution towards heavier babies was noted between 1968 and 1975, accounting for 22% of the fall in total neonatal mortality during this period (Stanley & Hobbs, 1980). In England and Wales a decrease in the incidence of VLBW (Gordon, 1977a,b;) was followed by indications of an increase (Stewart et al, 1981).

Birthweight shifts within the VLBW range are less distinct. For a long time, the extremely low birthweight group has been considered virtually "non viable" (Drillien, 1947; Smallpeice & Davies, 1964; Alden et al, 1972; Usher, 1977; Haesslein & Goodlin, 1979; Amiel-Tison et al, 1981a), and has therefore been underreported (Weatherall, 1977; Alley & Terry,

Table 1.2.1 Incidence of very low birthweight (as percentage of liveborn infants) in various countries and cities

author	country or city	%
Blegen, 1953	Oslo (Norway)	1.1
Lee et al, 1980a	Japan	0.3
	Norway	0.5
	Canada	0.8
	U.S.A.	1.1
	Denmark	0.6
	Austria	1.0
	Poland	1.5
	Hungary	2.0
Wallace & Goldstein, 1975	Sweden	0.6
Usher, 1977	Quebec (Canada)	0.8
Stanley & Hobbs, 1980	Western Australia	0.78
	Tasmania	0.67
Milligan & Shennan, 1980	Toronto (Canada)	0.9
Amiel-Tison et al, 1981a	Paris (France)	1.0
Mutch et al, 1981	England	0.7
Saigal et al, 1982	Hamilton (Canada)	0.78
Goldenberg et al, 1983a	Alabama (USA)	1.2
David, 1983a	USA (1965)	1.0
	(1976)	0.9
McCormick, 1985b	USA (1982)	1.1
Erjavec et al, 1984	Yugoslavia (1980)	0.7
Papiernik et al, 1985a	France (1975-1978)	0.5
	(1979-1982)	0.2

1979). Presently attention has focused on this group (Nars, 1976; Stewart AL et al, 1977; Bhat et al, 1978; Pape et al, 1978; Yu & Hollingworth, 1979a,b; Nelson et al, 1980; Bennett-Britton et al, 1981; Hernandez et al, 1981; Ruiz et al, 1981; Campbell, 1982; Cohen RS et al, 1982; Driscoll et al, 1982; Nickel et al, 1982; Orgill et al, 1982b; Bennett et al, 1983; Hirata et al, 1983; Hoskins et al, 1983; Hutson et al, 1983; Rothberg et al, 1983; Buckwald et al, 1984; Saigal et al, 1984; Walker et al, 1984; Goldenberg et al, 1985a; Hack & Fanaroff, 1986; Raju, 1986; Yu et al, 1986a,b) due to the simultaneously growing interest of obstetricians and paediatricians and due to technological advances in perinatology, that have pushed the limit of viability down

to 750 g (Hein & Brown, 1981) or even 500 g (Koops et al, 1982; Stahlman, 1984).

When countries or populations are compared, it should be kept in mind that, in comparable gestational age groups, the mean birthweight can show considerable variation (Macfarlane, 1980; Priolisi, 1980; Rooth, 1980) because of different ethnic factors and socio-economic conditions. The various birthweight distributions of the studied groups or populations and the accompanying mortality risks should be taken into account in the interpretation of the results.

1.3 Preterm birth

1.3.1 History

Both birthweight and gestational age are strongly correlated with mortality and handicap rate (Lubchenco et al, 1972; Keirse & Kanhai, 1981a; Philip et al, 1981; Bennett et al, 1982; Field et al, 1982; Orgill et al, 1984).

Traditionally, paediatricians tended to classify newborn infants by birthweight, because this measurement is generally readily available and reasonably accurate. Gestational age was considered to be unreliable in at least 10-15% of all pregnancies (Keirse, 1979). This percentage was subject to wide variations in subpopulations depending on their ethnic and cultural background (Kloosterman, 1977).

The tendency to classify by birthweight was encouraged by the WHO. In their final report in 1950, the expert group on prematurity recommended to apply the term "prematurity" to all infants with a birthweight of 2500 g or less (WHO, 1950). At that time, van Gelderen (1954) reported an incidence of "prematurity" (birthweight $\leq$ 2500 g) in the Netherlands of 3-4 %. Soon after, researchers felt the restraints of this definition, for a considerable proportion of infants with a birthweight of less than 2500 g were born at term or even postterm.

In 1961, the WHO recommended to apply the term "prematurity" to infants born before 37 completed weeks after the beginning of the last menstrual period. Infants with a birthweight of less than 2500 g were referred to as "low birthweight infants" (WHO, 1961).

Although these definitions improved mutual understanding, confusion remained omnipresent. Some authors continued to apply the term "premature" to infants with low birthweight, while others restricted its use to infants born too early in terms of gestational age. Furthermore some distinguished obstetricians and neonatologists raised objections to relate an infant's "maturity" to gestational age only.

The "Committee on Fetus and Newborn" of the American Academy of Pediatrics had a meeting in Chicago on October 22, 1966, to consider

standard terms for the classification of newborn infants (American Academy of Pediatrics, 1967). Adhering to the WHO recommendation to calculate gestational age in "completed weeks", the participants agreed that duration-of-gestation categories should be indicated by words that refer unequivocally to time and time alone. Therefore, "pre-term", "term", and "post-term" were recommended as being appropriate, simple, and time oriented. No agreement could be reached as to where the cutoff point for preterm gestational age in completed weeks should be made.

During the Second European Congress of Perinatal Medicine in 1970, a "Working party to discuss nomenclature based on gestational age and birthweight" recognised the need "to group babies in terms of gestational age". Among other things, the working party suggested the following definitions (Working Party, 1970):

1. Pre-term : less than 259 days (37 completed weeks)
2. Term : 259-293 days (37-41 completed weeks)
3. Post-term: 294 days (42 weeks) or more

No lower limit of gestation was provided. Birth was defined as the delivery of an infant with a weight of 500 g or more; consequently, preterm birth applies to infants born with a weight of 500 g or more and a gestational age of less than 259 days.

The International Federation of Gynecology and Obstetrics (FIGO), in 1976, and the World Health Organization (WHO) in 1977, formally recommended these definitions for use in statistical tables relating to the perinatal period (FIGO, 1976; WHO, 1977a,b).

A better understanding of the physiology of pregnancy and the introduction of modern diagnostic tools (ultrasound) in obstetrics greatly improved the obstetrician's possibilities to determine accurately gestational age. In modern, highly developed countries the percentage of pregnancies with uncertain gestational age continues to fall. When gestational age remains uncertain, the paediatrician's scoring of physical and neurological characteristics of the newborn infant can help to estimate gestational age (Dubowitz et al, 1970; Finnström, 1977; Ballard et al, 1979). In prospective surveys, adequate information about gestational age can be obtained if the following information is included: last menstrual period, menstrual cycle, last use of oral contraceptives, pregnancy test by means of urine analysis, first trimester ultrasound examination, and growth of fundal height. If circumstances prevent the recording of complete information, at least the last menstrual period, menstrual cycle, and the results of a first trimester ultrasound examination are needed.

In this study, we strictly adhere to WHO and FIGO definitions of low birthweight and preterm birth. However, with advancing perinatal care the need for a more detailed classification of preterm infants becomes

apparent. In the absence of an official subclassification, various authors used different subclassifications of preterm birth in recent papers, e.g. less than 28 weeks, 28-33 weeks, and 34-36 weeks, with or without mentioning whether the last week has been completed or not.

In this study, gestational age will be referred to in days and, if necessary, in completed weeks, i.e. 30 weeks = 210-216 days (postmenstrual age, taking into consideration cycle irregularities or ultrasound examinations whenever appropriate). The term "very preterm" is applied to infants born with a gestational age of less than 32 completed weeks (from 112 up to and including 223 days).

1.3.2 Incidence

Contrary to the large amount of data on the incidence of (very) low birthweight, information on the incidence of preterm or very preterm birth is scarce and often unreliable. Only few countries routinely record gestational age of all live births (chapter 9.1).

In the absence of a national registration system in the Netherlands, the only available data are provided by the "Nederlands Huisartsengenootschap" (Dutch Society of General Practitioners). Their estimate of the incidence of preterm birth in the Netherlands is 5.4% (Kloosterman, 1977).

In the United States of America in 1983, the birth certificates of 49 States and the District of Columbia included the first day of the mother's last menstrual period (New Mexico did not require this information). The length of gestation for a given pregnancy can be determined by calculating the interval between the onset of the last menstrual period and the date of birth. If one takes into account possible irregularities in the menstrual cycle, it becomes plausible that calculated incidences of preterm birth are minimum estimates. In 1983, 9.6 percent of all infants were born preterm (prior to 37 completed gestational weeks). This percentage has risen slowly since 1981: 9.4% and 1982: 9.5% (National Center for Health Statistics, 1983).

In Norway, the Medical Birth Registry records all live births and fetal deaths with a gestational age of 16 weeks or more since 1967. The registry includes information on birthweight, gestational age, mother's health during pregnancy as well as complications and interventions during labour and delivery. During the years 1967 and 1968 a total of 135,731 live births were studied by Bjerkedal et al (1973). They reported on the distribution of male and female, singleton live births in specific gestational age categories. The results are presented in table 1.3.2.1.

Table 1.3.2.1 Distribution of singleton live births according to gestational age in completed weeks (Norway, 1967-1968)

gestational age (weeks)	male n	female n	total n	total %
28-31	411	273	684	0.5
31-33	516	406	922	0.7
34-35	1277	1031	2300	1.8
36-37	3860	3066	6926	5.5
38-39	18845	16587	35432	28.3
40-41	30817	30665	61482	49.0
≥42	8856	8875	17731	14.1
total	64582	60903	125485	100.0

From data on the 1972-1973 cohort (total number of infants 124,584), Hoffman & Bakketeig (1984) calculated the cumulative percentage distribution of gestational age in completed weeks for singleton births. The results are presented in table 1.3.2.2.

Table 1.3.2.2 Cumulative percentage distribution of gestational age in completed weeks for singleton births (Norway, 1972-1973)

gestational age (weeks)	cumulative percentage
22-23	0.16
24-26	0.42
27-29	0.77
30-32	1.50
33-35	3.68
36-38	17.08
39-41	84.20
42-44	98.73
>44	99.97
unknown	100.00

In the United Kingdom, the incidence of preterm birth was 5.3% in 1958 and 5.2% in 1970 (Alberman, 1977). A national survey in France showed in 1972 that 8.8% of all infants were born with a gestational age of less than 37 weeks (Melchior & Berna rd, 1977). Creasy & Liggins (1979) reported for New Zealand in 1975 an incidence of preterm birth of 6.7% . More recently, in Finland, Piekkala et al (1986) found an incidence of preterm birth of 6.6% (gestational age < 37 weeks).

In the Haguenau Perinatal Study in France, Papiernik et al (1985a,b) demonstrated a decrease in the incidence of preterm birth as a result of a prevention program. The incidence of preterm birth had fallen from 6.3% in 1971 to 4.2% in 1982.

Even less data on the incidence of live births are available for "very preterm" infants (born with less than 32 gestational weeks). In the United Kingdom, the incidence of very preterm birth was 0.7% in 1958 and 0.8% in 1970 (Alberman, 1977). In Norway, the incidence of very preterm birth attained at least 0.5% in 1967 (table 1.3.2.1). In the United States of America, 64,593 out of 3611,316 infants, liveborn in 1983, had a gestational age of less than 32 weeks, resulting in an incidence of very preterm birth of 1.78% (Nat. Center for Health Statistics, 1985).

Only studies based on the total population of a geographically well defined area have been presented for comparison because hospital based reports are hampered by selection of cases. For instance, the highest "incidences" of preterm births are reported by centres for in vitro fertilisation and embryo transfer techniques. Lancaster (1985) reported 7% very preterm births (9 out of 138 infants born < 32 weeks) and 22% preterm births (30 out of 138 cases born < 37 weeks).

1.4 Intrauterine growth retardation

It has long been recognised that not all low birthweight infants are born too early (WHO, 1970), since birthweight depends on both the rate of intrauterine growth and the duration of pregnancy. Although the use of ultrasound has now made it possible to study intrauterine growth in a longitudinal fashion, this tool has hitherto not been fully exploited for epidemiological studies of intrauterine growth retardation. Virtually all data on both epidemiology and causes of intrauterine growth retardation are based on "growth charts" that are in fact weight-for-gestational-age charts. Nevertheless, these charts have been very helpful in understanding the tremendous range of variation in growth and weight in and between various populations.

In the Netherlands, the "Amsterdam growth charts" made by Kloosterman and Huidekoper (1969), are commonly used. These curves are based on the birthweights of babies born between 1931 and 1965 in Amsterdam. Gestational age was calculated in completed weeks (40 weeks is 281-287 days).

Corrections have been made for parity, infants' sex, and multiple pregnancy. The growth charts start at 25 gestational weeks and have the shortcoming of containing only limited numbers of infants in the lower gestational age categories. However, no new growth charts have been made and hence the Amsterdam growth charts are the best available for the Dutch population.

Infants born with a weight below the 10th percentile, are said to be small for gestational age (SGA), and those with a birthweight below the 2,3 percentile are considered very small for gestational age (VSGA). Both groups are believed to have suffered from intrauterine growth retardation and carry an increased risk for perinatal mortality and morbidity (Huisjes, 1981).

1.5 Intensive care

In 1922, a "premature infant station" was opened in Chicago (Hess, 1953), the objective being "to provide care for premature infants born in homes or hospitals not equipped with the necessities for their complete care". Stewart et al (1981) described this as phase I: in the absence of special treatment, few VLBW infants survived and almost none weighing less than 1000 g; most of the survivors were said to be healthy (Douglas & Gear, 1976).

In 1951, a new unit was opened. Now, a permanent, well-trained nursing staff, aseptic nursing techniques, maintenance of body temperature, careful and minimal handling, oxygen, use of breast milk, and careful feeding regulation were seen as significant factors in neonatal care (Stewart et al, phase II, 1950s and early 1960s; Rider et al, 1957; Stewart et al, 1981). This led to a gradual decrease in the mortality, initially accompanied by an increase in the number of handicapped survivors. Technical progress was provided by the incubator, humidifier, skin temperature monitor, glucose infusion, and tube feeding.

After 1965 (Reynolds, 1978) intensive care was introduced successively in centres all over the world (Vapaavuori & Räihä, 1970; Rawlings et al, 1971; Fitzhardinge & Ramsay, 1973; Fitzhardinge, 1975; Fitzhardinge et al, 1976a, 1978; Kitchen et al, 1978, 1979; Jones et al, 1979b; Kumar et al, 1980; Koppe & Treffers, 1981; Verloove & Ruys, 1982; Stahlman, 1984; Jivani, 1986): phase III had begun, characterized by a falling mortality rate achieved "by more rational use of modern knowledge and increasing sophistication of obstetric and neonatal care", without an increase in the proportion of handicapped infants (Stewart et al, 1981). Cerebral palsy, one of the handicapping conditions associated with very low birthweight, even showed a significantly decreasing incidence, when calculated per 1000 liveborn infants (Hagberg et al, 1975; Jarvis et al, 1985).

In the years since then, the care has gradually been intensified:- cardio-respiratory monitoring, IPPV, intravascular P_aO_2 monitoring, exchange transfusion, orogastric feeding, and servo-controlled incubators were followed by CPAP, transcutaneous P_tO_2 monitoring, phototherapy, transpyloric tube feeding, total parenteral nutrition, radiant heater, and ultrasound detection of intracranial haemorrhage and patent ductus arteriosus. The results of this type of care, as far as mortality and handicap rate are concerned, will be discussed in chapter 2.

1.6 Situation in the Netherlands

In the absence of a national registration of birthweight and gestational age of liveborn infants in the Netherlands, no data are routinely available on incidence, morbidity or mortality by gestational age or birthweight. Collecting data on all high risk newborns in the Netherlands would have involved 10,000 or more infants per year. We therefore decided to collect data only on the smallest and least mature infants with the highest risk of mortality and morbidity: the very low birthweight and very preterm infants.

Assuming an incidence of VLBW of between 0.5 and 0.7% (Lee et al, 1980a; Stewart et al, 1981) and a stable number of live births of approximately 180,000 per year, this would imply a total of 900 to 1270 VLBW infants per year in the Netherlands. Only some 500 VLBW infants per year are admitted to the 8 university hospital neonatal intensive care units (NICU). Several of these units (Versluys, 1977; van Doornik et al, 1980; Koppe & Treffers, 1981; Hein et al, 1982; Sporken et al, 1982; Verloove & Ruys, 1982; Dubois & Koppe, 1984; Kollée et al, 1984; Koppe et al, 1984; Fetter et al, 1986) have recently published the results of their intensive care treatment, including data on long term outcome. Therefore, a similar number of infants per year must have been admitted to general hospitals. No appropriate data were available about these infants.

Evaluation of care of the high risk newborn is a necessity, particularly regarding quality control and management of perinatal care at the hospital, regional, and national level (Mitchell, 1985). Both in the report on regionalization of neonatal care by the "Commissie Neonatologie van de Nederlandse Vereniging voor Kindergeneeskunde" (Working Party on Neonatology of the Dutch Paediatric Association) (1978) and in the recommendations on neonatal intensive care of the "Gezondheidsraad" (Health Council) (1983) a plea was made for regional or national (follow-up) studies of high risk newborns, as well as a national registration of perinatal data.

With the first objective in mind, the members of the "Sectie Perinatologie van de Nederlandse Vereniging voor Kindergeneeskunde" (Division of

Perinatology of the Dutch Paediatric Association) decided to collaborate on collecting information on very low birthweight and very preterm infants in their departments. Thus, the Project On Preterm and Small for gestational age infants (POPS) was started.

1.7 Scope of the study

Evaluation of neonatal mortality alone is insufficient for the assessment of care. Postneonatal mortality and outcome in terms of later morbidity and handicaps must be reported, based on data collected during follow-up. For several reasons this is difficult to achieve: the infants generally belong to younger families who change their residence frequently (Mercer et al, 1978). When the infant appears normal, parents (and physicians outside the field of perinatology) are not motivated to continue control visits. When the infant is not normal, the same problem may occur, e.g. with respect to developmental disorders and family problems (Kiely & Paneth, 1981). In addition to these "avoidable" losses, there are "unavoidable" ones (death and emigration, Douglas & Blomfield, 1955). In both categories, information about infants lost to follow-up should be obtained from family physicians, health clinics, school physicians, etc. in order to estimate a possible selection bias. Like mortality and handicaps, the rate of "lost to follow-up" should be reported as a percentage of liveborn infants. A follow-up of 80 % of survivors is considered reasonably successful (Dunn, 1986).

The duration of follow-up will depend on feasibility and cost factors. More than half a century ago, Ylppö (1919) and Capper (1928b) were convinced that a rather long follow-up period (8 and 18 years respectively) was needed for the recognition of subsequent disorders that might hamper normal functioning in society, and most authors still favour this point of view (Dunn, 1986).

However, little is known about the etiology of such disorders, and in addition to perinatal factors other influences seem to play an important role (Cohen SE et al, 1982; Sameroff, 1975). In order to estimate the influence of perinatal factors without too much interference from other sources, a shorter follow-up period may be preferable (Fitzhardinge, 1976b; Shapiro et al, 1980; Ross et al, 1982). Furthermore, a shorter follow-up period requires less financial support, and the results are up to date and therefore more useful to the perinatal practice.

In agreement with such considerations, the follow-up period in POPS was limited initially to two years of age.

1.8 Outline of this thesis

In these combined theses, the obstetric and paediatric features of the study population will be discussed as far as pregnancy, delivery, birth and hospital stay after birth are concerned.

The final outcome of the study population, i.e. the total mortality, morbidity, and handicaps at two years of age (corrected for gestational age) will be reported at a later date.

Part 1 (chapters 2-4) contains an outline of the study. Chapter 2 presents a review of the extensive literature on intensive care for very low birthweight and very preterm infants. In chapter 3, the objectives of the present study are given, and in chapter 4, the methodology of collecting, processing and analysis of the data is described and discussed.

In Part 2, chapters 5-8, descriptive data are presented concerning incidences, frequencies and distributions of various factors in the perinatal period. Chapter 9 compares this study to data from other sources available in the Netherlands.

In chapter 10, mortality rates are reported, while in chapter 11 the causes of death are discussed. Chapter 12 deals with morbidity during the neonatal and postneonatal hospital stay, and the short term outcome of the surviving infants at the time of discharge home.

In Part 3, chapters 13-15, inferential statistics are presented. Chapter 13 explains the methodology of the applied statistical techniques. In chapter 14 and 15, a number of perinatal factors and events are related to outcome in terms of mortality and short term morbidity.

In chapter 16 conclusions are drawn from the first part of this study project.

PART 1 GENERAL ASPECTS OF THE STUDY

Chapter 2 Review of evaluative studies of intensive care for very low birthweight and very preterm infants

2.1 Introduction

Traditionally, perinatal care has mainly been evaluated by observational studies in small hospital-based populations (Chalmers & Sinclair, 1985). Only a few regional surveys, free of the selection bias adherent to a hospital study, have been accomplished, and trials are scarce in perinatal medicine (Bryce & Enkin, 1985; Chalmers & Sinclair, 1985).

In this chapter a review is presented of the current literature on these subjects.

2.2 Trials

A controlled trial to assess intensive care versus routine care in infants weighing 1000-1500 g, performed in Melbourne between 1966 and 1969, (Kitchen et al, 1978; 1979) showed a distinct improvement of survival in the intensive care group (table 2.5.3), especially during the second half of the study. Follow-up results indicated in both groups a considerable reduction in the percentage of survivors with "serious" handicap, as compared with an earlier period in the same hospital, but "severe" handicaps were more common among the intensively managed children than in the routine care group.

In Buffalo (N.Y.), distinct differences were found in the mortality rate before and after a program of neonatal intensive care was instituted (Egan et al, 1980): aggressive neonatal intensive care for the smallest viable infants (600-800 g) improved survival tenfold (from 5% to 52%), the handicap rate (13% of live births) was acceptable (Buckwald et al, 1984) (table 2.5.7).

A randomized trial of the efficiency of immediate intubation and stabilization of the airway in very low birthweight infants was effected

in Melbourne in 1978 and 1979 (Drew, 1982). In the electively intubated infants, survival was improved, (77 versus 51%), without a rise in early or late complications. Long term results were not yet available.

2.3 Regional studies

A few regional studies in which bias due to sample selection was minimized have been reported. In New York, a regional survey (Paneth et al, 1982b) showed considerable differences between the neonatal mortality rates of low birthweight infants born in three kinds of hospitals: "those with newborn intensive care units (level 3), those with capabilities for the care of most premature infants (level 2), and those without any special facilities for premature newborns (level 1)". Across the entire range of birthweights of 501 to 2250 g, but especially in infants over 1250 g, the neonatal mortality rate (adjusted for birthweight, gestational age, race and sex) was significantly lower for level-3 hospitals (12.8%) than for both level-2 (16.3%) and level-1 units (16.3%). The association between level of care and mortality could not be accounted for by differences between groups.

With regionalization of perinatal services (as done in the Nova Scotia Reproductive Care Program) (Peddle et al, 1983) the overall perinatal mortality rate fell in the central tertiary unit as well as in the regional and the community hospitals; the mortality rates of the other hospitals approximated those of the tertiary unit.

Other regionalization programs for perinatal intensive care have also been reported to be effective. In Columbus (Georgia) for example, after institution of such a program, neonatal mortality in all birthweight groups decreased considerably in the regional perinatal centre as well as in the whole region (Thompson et al, 1976). In Alabama (Goldenberg et al, 1983a, b; 1985d) and Colorado (Bowes, 1981) neonatal mortality in the 500-2000 g birthweight group had clearly decreased in the same way throughout the area after the regionalization of perinatal services. Birthweight specific neonatal mortality rates were still lowest in the regional perinatal centre, compared with the rest of the region.

In the Hamilton-Wentworth Region Study (Horwood et al, 1982) mortality decreased after the introduction of intensive care, but there was no significant change in later morbidity. The outcome of unreferred babies was also included in a follow-up report (Saigal et al, 1982), thus containing an unselected population, which gave a more realistic picture of the total developmental pattern of VLBW infants (table 2.5.2). The improved survival rate was not associated with an increase in the incidence of handicapping conditions.

A later study (Saigal et al, 1984) in a bigger area showed once more improved survival rates in the 501-1000 g infants, with a comparable

handicap rate (table 2.5.5). Unreferred infants all died (not implying that referral could have saved them), and similar survival rates occurred in referred and inborn infants.

In eight geographically defined populations in the United States where a regionalization program was evaluated, a decrease in neonatal mortality rate was found at all birthweights including the VLBW group. This decrease was accompanied by a slightly lower handicap rate (Shapiro et al, 1983; McCormick et al, 1985a). In comparison areas the same kind of shift of high risk pregnancies to tertiary centres appeared to have taken place, and neonatal mortality had fallen as well. Similar results were reported from North Carolina (Siegel et al, 1985; 1986): declines in fetal and neonatal mortality rates as well as in birthweight specific mortality rates were observed in both pilot and control regions. No differences were reported in developmental and neurological outcomes of the infants at 1 year except in language development and mother-infant interaction.

2.4 Reviews

Evaluation of the efficacy of perinatal and neonatal intensive care must be based mainly on careful assessment of reported results of neonatal intensive care units, because further controlled clinical trials of perinatal care are not considered feasible or morally acceptable (Usher, 1977) and geographically defined population studies are scarce (Pharoah & Alberman, 1981). Furthermore, comparison of studies and units can be very difficult, due to differences in criteria, definitions, selection of patients, and practices (Davies, 1976; Harper et al, 1979; Pharoah & Alberman, 1981).

Even when such a comparison was made in the course of a collaborative study (Bajuk et al, 1981; Kitchen et al, 1982a, b; 1983) in which criteria and definitions were meant to be identical, differences in neonatal management (early ventilatory support and parenteral feeding for extremely preterm infants) led to differences in mortality rates, and different perinatal factors appeared to affect survival. Unfavourable outcome in survivors was correlated with different perinatal factors in the two Melbourne hospitals, and none of the factors (e.g. short gestation; birthweight below 10th percentile; ventilatory support) were shared (Kitchen et al, 1983).

In an appreciable number of reviews, surveys, and editorials, attempts have been made to sort out the reported data.

Davies and Stewart (1975) reviewed papers dealing with infants born since 1960 and found that the prognosis for survival and normal development of LBW infants had improved in that period, compared with similar infants born during the preceding 20 years. In survivors, an improvement

of mean IQ of the VLBW group was accompanied by a reduction in major handicaps.

Versluys (1977) provided data from 4 neonatal intensive care units in the Netherlands and compared their results with international data. He concluded that neonatal intensive care is worthwhile (though not necessarily the only or the highest priority in perinatal care).

Hack et al (1979) thought that the prevailing optimistic attitude on the immediate and long-term outcome of VLBW infants appeared to be justified.

An editorial in The Lancet (Anonymous, 1980) stated that neonatal mortality in VLBW infants had improved remarkably, and that the handicap rate, expressed as a proportion of live VLBW births, was approximately constant.

Jones and Davies (1981) reported a gradual decrease in neonatal mortality in many parts of the world and, starting with the 1970's also a decline of morbidity in reports from centres with adequate technological facilities. However, evidence that intensive care, besides saving lives, also improved the quality of survival, was deemed more difficult to come by. It was postulated, not only that further and more widespread application of intensive care would not lead to any marked change in the number of handicaps but also that the degree of handicap might even increase.

Stewart et al (1981) reviewed 16 studies dealing with infants weighing up to 1500 g at birth, and assigned all infants to one of four categories: "died, survived handicapped, lost to follow-up or survived healthy". These authors found the chances of survival to have trebled, whereas the handicap rate had remained stable and relatively low at 6-8% of VLBW live births. After phases I, II and III, the beginning of phase IV was predicted: objective techniques such as computerized tomography and real-time ultrasound will permit controlled trials covering procedures designed to prevent death and brain damage, and will make it possible to arrive at an ethically justifiable decision about withholding of further intensive care.

In a review of some of the above mentioned studies, Amiel-Tison and Lebrun (1981b) also concluded that the mortality rate had dropped considerably; the difficulty of assessing major handicap induced them to plead for regular analysis of fetal and neonatal death as well as severe sequelae by every perinatal team.

Sinclair et al (1981) reviewed the evaluation of special programs, in an attempt to assess efficacy (does it work under ideal conditions), effectiveness (does it work under normal "field" conditions), efficiency (are the resources needed for the program spent usefully) and availability (are the services accessible to babies who may benefit from them). They found that efficacy had been tested in a number of randomized controlled trials of specific elements and of "packages" of

neonatal intensive care, mainly with the use of neonatal mortality and morbidity as measure of outcome. About effectiveness they reported "a continuing controversy, spawned by the lack of randomized controlled studies and regional population studies". However, the decline in birthweight specific mortality rates was thought to be most plausibly explained by the steady improvement in perinatal medical care. The effect on morbidity, reported in hospital studies as handicap rate in survivors, was also considerable, but in population-based data no such proof of effectiveness could be found. Availability had not yet been studied at that time, and the same held for efficiency, which was investigated later by the same group (Boyle et al, 1983).

Kitchen et al (1982d) gave a carefully balanced answer, based on a large sample of inborn infants from two maternity hospitals in the preceding 13 years: on the credit side decreasing mortality, higher psychological test scores, and lower incidence of severe sensory handicap at two years of age in survivors; on the debit side a substantial increase of all forms of spastic cerebral palsy.

Allen and Jones (1986) concluded that, as the survival of extremely low birthweight infants improves, these infants remain vulnerable to a wide spectrum of morbidity. Although the data on the incidence of spastic diplegia are controversial, the number of major handicaps seems to decrease.

2.5 Reports from neonatal intensive care units

Consensus between studies from NICUs will remain impossible, especially regarding overall outcome of VLBW infants, as long as results are expressed in different ways. For example, the handicap rate is still usually calculated as a percentage of survivors, sometimes even without mention of the mortality rate in the original sample, but on this basis no conclusions can be drawn concerning total "poor", "adverse" or "not satisfactory" outcome.

Since "death is indeed a major handicap" (Knobloch et al, 1982), the only way that the outcome of liveborn infants can be properly evaluated is by the inclusion of not only the neonatal mortality, but also the postneonatal mortality due to perinatal problems (Kulkarni et al, 1978; Harper et al, 1979; Hack et al, 1980; Keirse & Kanhai, 1981a; Philip et al, 1981; Haas et al, 1983; Kraybill et al, 1984; Yu et al, 1984b; Goldenberg et al, 1985c; Beckwitt Turkel et al, 1986) and the handicap rate, all three as a percentage of total liveborn infants. Recently, this has been done in few papers (Stewart et al, 1978; Kitchen et al, 1979; Bennett-Britton et al, 1981; Koppe & Treffers, 1981; Kitchen et al, 1982c; Orgill et al, 1982b; Haas et al, 1983; Milligan et al, 1984; Saigal et al, 1984).

Tables 2.5.1-2.5.7 show data from a number of papers published since 1970, arranged according to birthweight and year(s) of study samples; in addition, postneonatal mortality[1] and handicap rate[2] have been (re)calculated as percentages of total liveborn infants. A large number of other publications could not be included, because such recalculation was impossible due to lack of information about either the follow-up (Wallace & Goldstein, 1975; Thompson et al, 1976; Kopelman, 1978; Reynolds, 1978; Stanley & Alberman, 1978; Bowes et al, 1979; Dunn et al, 1979; Gamsu et al, 1979; Haesslein & Goodlin, 1979; Hughes-Davies, 1979; Jones et al, 1979b; Riegel et al, 1979; Roberton, 1979; Bowes & Simmons, 1980; Lee et al, 1980a,b; Milligan & Shennan, 1980; Stanley & Hobbs, 1980; Amiel-Tison et al, 1981a; Hernandez et al, 1981; Mutch et al, 1981; Perkins, 1981; Cordero et al, 1982; Drew, 1982; Koops et al, 1982; Moriette et al, 1982; Paneth et al, 1982b; Yu et al, 1982; Goldenberg et al, 1983a,b; Gray et al, 1983; Rhodes et al, 1983; Brans et al, 1984; Kollée et al, 1984; Teberg et al, 1984; Gérard et al, 1985; Goldenberg et al, 1985a; Thompson & Khot, 1985) or about the original sample of liveborn infants and the corresponding neonatal mortality (Teberg et al, 1977; Stave & Ruvalo, 1980; Hertzig, 1981; Rothberg et al, 1981; Bennett et al, 1982; Fledelius, 1982; McCartonDaum, 1983).

2.6 Discussion

Trials, preferably randomized controlled double blind trials, are the instrument of choice for evaluation of effectiveness of new procedures.

In perinatal care, there is a growing awareness that such trials should be performed directly at the introduction of new treatments or practices, and a number of multicentral or even multinational trials are being undertaken. However, trials do not register trends over time, or differences between hospitals or countries. For such purposes, epidemiological surveys will still be needed.

Regional studies can be very useful in that respect as for instance the Hamilton-Wentworth study (Horwood et al, 1982; Saigal et al, 1982; 1984) has shown. Most regional studies however have been undertaken with

[1] deaths on day 29-364, or "first year", due to perinatal problems

[2] includes so-called major, profound, severe, and serious handicaps, according to Stewart and Reynolds' (1974) definition: "an abnormality sufficiently severe to interfere with present or future normal function in society"

Table 2.5.1 Outcome in infants 1000-2000 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	neonatal mortality (0-28 days)		postneonatal mortality (29-365 days)	total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
							% of live births						
Eaves	1970	Vancouver	1958-1965	<2041		502	16.3		2.8	19		3-4	lost to follow-up: 14%
Sabel	1976	Göteborg	1969-1970	1500-2000		55	16		13	29			
Michelsson	1983	Helsinki	1971-1974	1510-2000	I	208	13		5	18		5	
Shennan	1980	Toronto (WCH)	1976-1977	1000-2000		124	9	0.8	5.6	15		1-2	
Smith	1982	Oslo	1976-1977	<2000	10% R	62	18	5.0	19	42			cross-section of the population

Table 2.5.2 Outcome in infants ≦1500 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	neonatal mortality (0-28 days)	postneonatal mortality (29-365 days)	total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
							% of live births					
Wright, FH	1972	Chicago	1952-1956	<1500	I	159	55.7		±20	±75	10	
Koppe	1981	Amsterdam (WG)	1959-1964	501-1500		245	75		9	84		
Jones	1979a	London (Ham.)	1961-1965	501-1500			59.5	1.6	12.7	74		
Steiner	1980	Mansfield	1963-1971	501-1500		236	49.6	0.4	5.5	55	8	no intervention, no intens. care; general hospital
Hunt	1982	San Francisco (Un. Cal.)	1965-1969	≦1500	I + R	100	52	3	20	75	8-11	chromos. abn. excl.
Stewart	1978	London (UCH)	1966-1967	<1500	49% I	39	55		4.0	59	1.5-8	
Calame	1972	Lausanne	1966-1968	≦1500	admitted	185	58		3.6	62	1-4	
Rawlings	1971	London (UCH)	1966-1969	<1500	68% I	149	47	0.6	3	51	3	
Kitchen	1980	Melbourne(RWH)	1966-1969	<1500	I	456	62.9		5.5	68	8	
Stewart	1974	London (UCH)	1966-1970	<1500	62% I	197	45	5.5*	4.5	55	3-8	
Jones	1979a	London (Ham.)	1966-1970	501-1500			63.0	2.4	7.0	72		
Hunt	1982	San Francisco (Un. Cal.)	1970-1975	≦1500		128	35.9	4.6	20.3	61	4-8	
Michelsson	1984	Helsinki	1971-1974	≦1500	I	116	51		6	57	9	
Jones	1979a	London (Ham.)	1971-1975	501-1500			51.9	0	13.4	65		
Mercer	1978	Sydney	1971-1975	≦1500		188	44.7	1.0	1.6	47	2-6	
Bosch	1981	Bonn	1971-1977	<1500		138	51.4	1.4	0.7	53	1-7	<24 w. excluded lost to follow up: 16%
Lam	1978	Singapore	1971-1977	<1500	admitted	140	53		3.6	57		lost to follow-up: 6%
Hommers	1976	Coventry	1973-1974	<1500	admitted	103	54	4	2	60	1-2	
Klein	1985	Cleveland	1976	<1500	admitted	153	27		10	37	5	lost to follow-up: 21%

Table 2.5.2 (continued)

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	neonatal mortality (0-28 days) % of live births		postneonatal mortality (29-365 days) % of live births	total major handicap % of live births	total adverse outcome (0-365 days) % of live births	duration of follow-up (years)	remarks
van Doornik	1980	Amsterdam (VU)	1973-1977	<1500		114	44.7		17.0	62			
Saigal	1982	Hamilton-Wentw.	1973-1978	501-1500	I + R	294	32.2	5.3	10.2	48		2.5	regional study
Galloway	1981	Inverness	1973-1978	VLBW	15% R	102	53		2	55		4	lost to follow-up: 24%
Fitzhardinge	1978	Toronto (HSCh)	1974	≦1500	R	250	34		17.6	52		2	
Bucci	1979	Rome	1974-1977	≦1500	admitted	177	51		2	53		1-3	
Paludetto	1979	Naples	1975-1977	≦1500	admitted	68	65		1.5	66		1	
Westgren	1982	Lund	1975-1978	<1500	I	72	26.4		8.3	35		2-5	singletons only
Knobloch	1982	Albany	1975-1978	<1501	I	159	47		12.6	60		2-5	
Koppe	1981	Amsterdam (WG)	1975-1979	501-1500	I + R	243	32		2	34			
Lloyd	1984	Wolverhampton	1975-1979	≦1500		158	54	3	6.3	63			general hospital
Ouden den	1984	Utrecht	1976-1978	≦1500	R	170	30.6		5.3	36		1.5-3.5	
Kitchen	1982	Melbourne	1977-1978	500-1500	86% I	440	29.5		12.3	42		2	prospective collaborative
	(a,b)	RWH				258	28.7		12.4	41			study
		QVMC				182	30.8		12.0	43			
Haas	1983	Tübingen	1977-1981	501-1500		245	29.8		8.2	38			
Orgill	1982a	Melbourne (QVMC)	1979-1980	≦1500	81% I	149	17	3	9.3	29		1	delivery-room-death included
Astbury	1983	Melbourne (QVMC)	1979	≦1500		102	21	3	11	35		2	lost to follow-up: 11%
Urrutia	1984	Toledo (Ohio)	1979-1981	VLBW	admitted	376	25		4.8	30		1.5-3	lost to follow-up: 41%
Konstantinou	1984	Athens	1980-1982	≦1500	I	326	55.8		5.2	61			lost to follow-up: 10%
Fetter	1986	Rotterdam	1979-1983	<1500	admitted	491	27	3	9.0	39		1	lost to follow-up: 10%

*1-25 months

Table 2.5.3 Outcome in infants 1000-1500 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	% of live births: neonatal mortality (0-28 days)	% of live births: postneonatal mortality (29-365 days)	% of live births: total major handicap	% of live births: total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
Kitchen	1978 1979	Melbourne (RWH)	1966-1969	1000-1500	I, admitted nursery	238						contr. trial: i.c. vs. routine care; cong. malf. and hydrops excl.
					intensive care		26.0	1.6	14*	42*	8	comparison group: 2% handicaps
					routine care		36.1	0.4	5*	41*	8	43% lost to follow-up
Sabel	1976	Göteborg	1969-1970	1000-1500		24	40		8	48		
Kitchen	1983	Melbourne (RWH + QVMC)	1977-1978	1000-1500	I, RWH	156	14.1		16.6	31	2	collaborative study
					I, QVMC	94	19.1		10.6	30	2	
Orgill	1982a	Melbourne (QVMC)	1979-1980	1001-1500	I + R	112	9		8.9	18	1	

*profound and severe handicap; "significant" handicap excluded

Table 2.5.4 Outcome in infants ≦1250 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	neonatal mortality (0-28 days)	postneonatal mortality (29-365 days)	total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
							% of live births					
Hatt	1972	Besançon	1953-1969	≦1250		368	82.6		3.0	86	0.5-10	
Fitzhardinge	1973	Montreal (RVH)	1960-1966	<1251,	AGA	118	67	1	18.6	87	5	SGA excluded
Vapaavuori	1970	Helsinki	1966-1967	850-1250	admitted	49	55		4	59	2	congenital malformations excluded
Dweck	1973	Birmingham (Ala)	1968-1970	≦1100	I + R	82	81.7		3.6	85	1-3	
Kumar	1980	Philadelphia	1974-1977	≦1250	I	132	54.5		5.3	60	1	majority black females (selection bias)
Minkowski	1983	Paris	1976-1977	≦1250		76	43.4	3.9	6.6	54	4-5	lost to follow-up: 8%

Table 2.5.5 Outcome in infants ≦1000 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	neonatal mortality (0-28 days)	postneonatal mortality (29-365 days)	total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
							% of live births					
Nickel	1982	Seattle	1960-1972	≦1000			83.1	1.7	5.4	90	6-18	
Nars	1976	Basel	1963-1975	<1000		74	73.0	2.7	2.7	78	1	lost to follow-up: 8%
Alden	1972	Seattle	1965-1970	<1000	admitted	161	87	1.2	5.0	93	1-6	
Stewart, AL	1977	London (UCH)	1966-1975	<1000	47% I	148	68	6	4	78	1-8	56% of deaths after elective withdrawal of i.c.
Grassy	1976	Madison	1968-1972	≦1000 (680-1000)	admitted	98	71		8.1	79	2-4	
Sabel	1976	Göteborg	1969-1970	500-1000		7	57		0	57		
Rothberg	1983	Hershey (Pennsylv.)	1973-1976	≦1000	24% I	69	64		10.1	74		
Pape	1978	Toronto (HSCh)	1974	≦1000	R	97	53		13	66	2	
Bhat	1978	Chicago	1974-1976	<1000	62% R		69	8	5.8	83		
Ruiz	1981	Syracuse (N.Y.)	1976-1978	≦1000	I + R	134	64.9	5.2	13.4	83		
Bavikatte	1980	Indianapolis	1977	≦1000	85% R	56	55.3	5.3	5.3	66	1-1.5	
Kitchen	1982	Melbourne	1977-1978	<1000								
	(a,b)	RWH			I	79	65.8		5.1	71	2	collaborative study
	1983	QVMC			I	48	54.2		14.5	69	2	
Driscoll	1982	New York (Col. Un.)	1977-1978	≦1000	55% I	54	51.8	4.0	13.0	69	1.5-3	

Table 2.5.5 Continued

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	neonatal mortality (0-28 days)	postneonatal mortality (29-365 days)	total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
							% of live births					
Yu	1979a	Melbourne (QVMC)	1977-1978	≦1000	25% R	55	40	2	3.6	46	1	
Orgill	1982b	Melbourne (QVMC)	1977-1980	<1000	83% I	107	44		11	55		
Orgill	1982a	Melbourne (QVMC)	1979-1980	501-1000	81% I	37	43		10.8	54	1	
Hoskins	1983	Toronto (WCH)	1979-1980	≦1000	I,78% MT	106	32	0	8.5	40	1-2	
Saigal	1984	McMaster Health Region	1977-1978	501-1000		255	54*		10.2	64	2	regional study
Walker	1984	Providence	1977-1981	500- 999	admitted	247	68		7.3	75	0.3-5	lost to follow-up: 4%
Kraybill	1984	Chapel Hill	1980	<1001	admitted	56	46	2	7.1	55	1-3	
Skouteli	1985	London (Ham.)	1979-1981	<1001	admitted	67	57		3	60	1-3	lost to follow-up: 7%
Yu	1986a	Melbourne (QVMC)	1979-1983	500- 999	inborn	186	53		13	66		
Yu	1986b	Melbourne (QVMC)	1977-1982	500- 999	inborn	196	51.5	3.6	12.2	67	2	

*in-hospital mortality.

Table 2.5.6 Outcome in infants 750-1000 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	% of live births: neonatal mortality (0-28 days)	% of live births: postneonatal mortality (29-365 days)	% of live births: total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
Nelson	1980	Gainsville (Florida)	1974-1979	801-1000	admitted	98	50		4	54		developmental evaluation only
Orgill	1982b	Melbourne (QVMC)	1977-1980	751-1000	83% I	81	39	1	10	50	2	
Cohen, RS	1982	Stanford	1961-1976	751-1000	admitted	229	63	4	7.4	70		lost to follow-up: 6%
Hoskins	1983	Toronto (WCH)	1979-1980	751-1000		67	21	0	4.5	25		

Table 2.5.7 Outcome in infants ≦750/800 g

author	year of publication	city (hospital)	study sample	sample criteria	inborn (I), referred (R), maternal transfer (MT)	number of liveborn infants	% of live births: neonatal mortality (0-28 days)		postneonatal mortality (29-365 days)	total major handicap	total adverse outcome (0-365 days)	duration of follow-up (years)	remarks
Bennett-Britton	1981	Toronto (HSCh)	1974-1977	700-800	R		65		13.8	79	1.5		no intensive-care-transport system
				<700	R		88.7		11.3	100			
Nelson	1980	Gainsville (Florida)	1974-1979	≦800	admitted	70	84		4	88	1-4.5		developmental evaluation only
Egan	1980	Buffalo (N.Y.)	1975-1977	600-800	I + R	44	95*		2.5	97	3-5		before aggressive management
Hirata	1983	San Francisco (Ch. Hosp.)	1975-1980	501-750	42% I	60	53.3	8.3	3.3	65	2-4		
Kitchen	1982 (a,b)	Melbourne (RWH+QVMC)	1977-1978	<800	I RWH	43	83.7		4.7	88			
					I QVMC	19	57.9		10.5	68			
Egan	1980	Buffalo (N.Y.)	1977-1979	600-800	I + R	58	48*		8.6	55	1-3		after aggressive management
Bennett	1983	Seattle	1977-1980	<800	I + R	95	80		3.1	83	0.5-3		
Orgill	1982b	Melbourne (QVMC)	1977-1980	501-750	83% I	26	58		15.4	73	1-2		
Hoskins	1983	Toronto (WCH)	1979-1980	≦750	I,78% MT	39	51	0	15.0	66			
Buckwald	1984	Buffalo (N.Y.)	1977-1981	500-800	I + R	147	56*		3.0	59	1		

*postneonatal death included.

the aim of showing effects of regionalization programs, or effects of different levels of care. Actually a randomized controlled trial would be the proper means of finding the answer to such questions, but factors like place of birth, antenatal transport or adherent level of neonatal care are not easy to randomize, and impossible to blind. Therefore a regional study before and after the institution of a specific regionalization program is the usual way to evaluate such procedures (Chiswick, 1982). All of these studies (chapter 2.2) show the beneficial effect of concentrating high risk deliveries at the tertiary units.

At the same time, these regional surveys can be used to follow trends in mortality and handicap rate in certain groups of infants, for instance the very low birthweight infants. Since regional studies contain unselected populations, comparisons between them are often possible.

This is not the case in reports from neonatal intensive care units. Due to differences in selection mechanism, infants born in or admitted to one unit will differ widely from those in another unit, with respect to such factors as gestational age, birthweight, maternal disorders during pregnancy, antenatal or neonatal transfers and condition on admission to the unit. Nevertheless, after arranging all such reports chronologically and recalculating them to render mortality and handicap rates more or less comparable (chapter 2.4), trends can be discerned.

All birthweight groups show a distinct gradual decline of the mortality rate, even the group below 750 g. Postneonatal mortality is steady at about 1-5 % . The handicap rate shows some fluctuation, probably mainly due to differences in the definition of handicap and duration of follow-up. However, no tendency of the handicap rate to increase or decrease can be discerned, not even among the smallest infants. Inevitably there will always be a "buffer zone" of patients who survive with some degree of handicap, wedged between those who survive intact and those who die (Roberton, 1979).

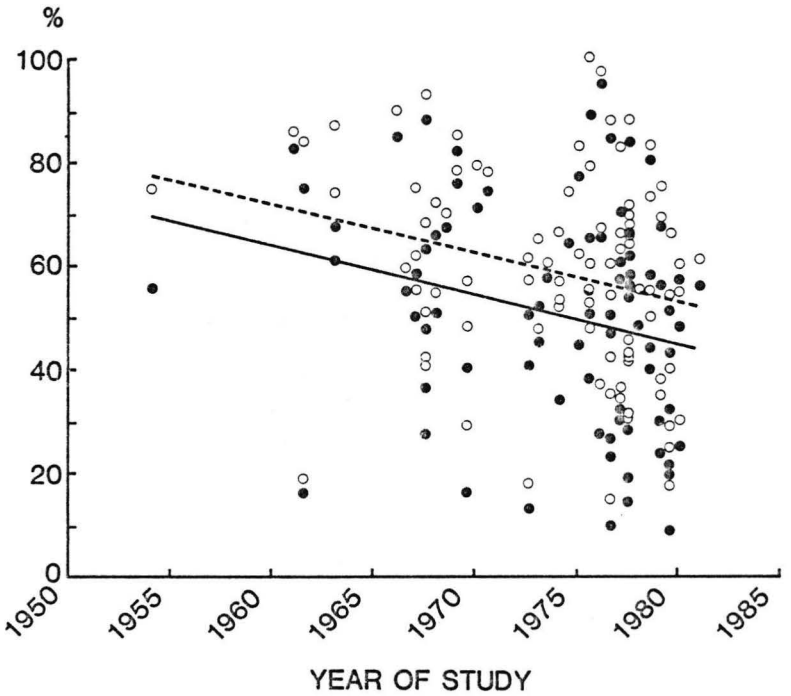
For reasons of comparability, the handicap rate is best expressed as a percentage of liveborn infants, because handicap rate, calculated as a percentage of surviving infants, depends on survival rates. In table 2.6.1, this phenomenon is illustrated: in addition to the handicap rates stated in tables 2.5.1-2.5.7 (as a percentage of liveborn infants) we calculated the rates as a percentage of survivors, in the 14 largest study populations. These latter rates show more variation, mostly due to differences in survival rates.

As a result of the changes in the three rates (neonatal mortality, postneonatal mortality and handicap rate), the "total adverse outcome" is also decreasing steadily in all birthweight groups (figures 2.6.1-2.6.4). These figures show that the handicap rate has virtually not changed, while the mortality rate has decreased in all birthweight groups.

Table 2.6.1 Handicap rate in VLBW infants, as a percentage of liveborn infants and as a percentage of surviving infants

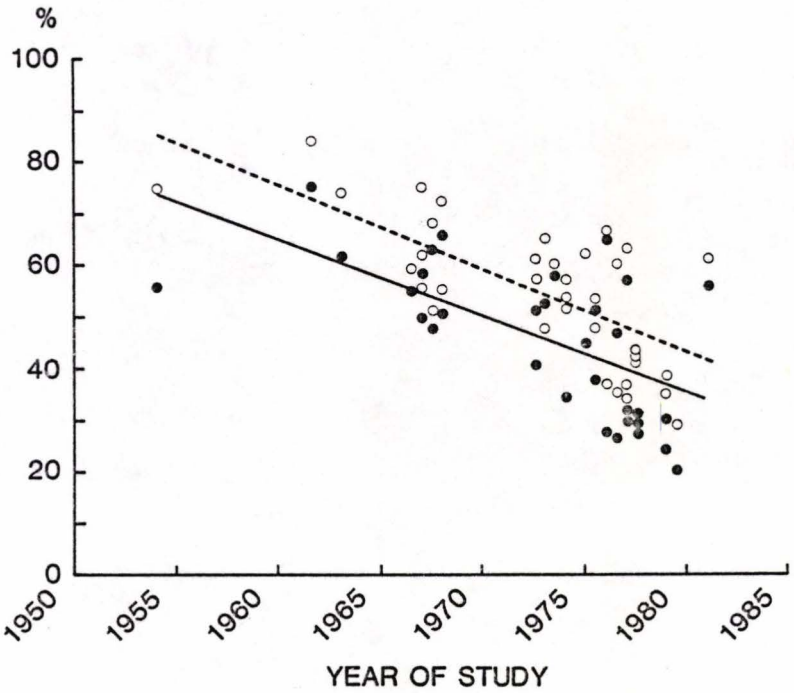
author year of publication	study sample	sample criteria	liveborn infants n	surviving infants			major handicaps		
				n	(follow-up)	%	n	% of liveborn	% of surviving
Kitchen, 1980	1966-1969	500-1499	456	169		37	25	5	15
Saigal, 1982	1973-1978	501-1500	294	184		63	30	10	17
Kitchen, 1982b	1977-1978	500-1500	440	297		68	54	12	18
Urrutia, 1984	1979-1981	VLBW	376	281	(127)	75	18	5	14
Konstantinou, 1984	1980-1982	≦1500	326	144	(112)	44	17	5	15
Fetter, 1986	1979-1983	<1500	491	341	(307)	69	44	9	14
Alden, 1972	1965-1970	<1000	161	20		12	8	5	40
Stewart, 1977	1966-1975	<1000	148	39		26	6	4	15
Saigal, 1984	1977-1980	501-1000	255	117	(110)	46	26	10	24
Walker, 1984b	1977-1981	500- 999	247	78	(68)	32	18	7	26
Yu, 1986b	1977-1982	500- 999	196	88		45	24	12	27
Nelson, 1980	1974-1979	≦800	70	11		16	3	4	27
Bennett, 1983	1977-1980	<800	95	19	(16)	20	3	3	16
Buckwald, 1984	1977-1981	500- 800	147	65	(53)	44	5	3	9

Figure 2.6.1 In-hospital mortality ● and total adverse outcome ○ (percentage of liveborn infants) in all studies described in tables 2.5.1-2.5.7



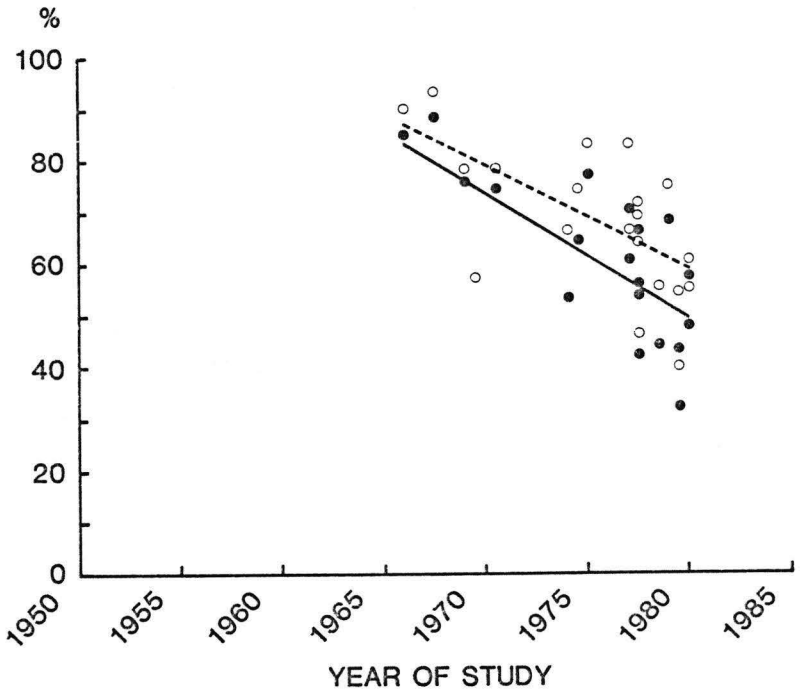
Except for a general impression of the total outcome, as mentioned above, the picture given by the findings is very difficult to interpret. Sometimes the different outcomes in seemingly comparable studies cannot be explained. One of the most obvious reasons for this problem is the lack of gestational age data. Most reports mention only a mean gestational age, but sometimes not even that. This precludes proper classification of the infants in categories related to the pathophysiology, e.g. intrauterine growth retardation. Uneven distribution of gestational age

Figure 2.6.2 In-hospital mortality ● and total adverse outcome ○ (percentage of liveborn infants) in all studies on infants with birthweight ≤ 1500 g, described in table 2.5.2



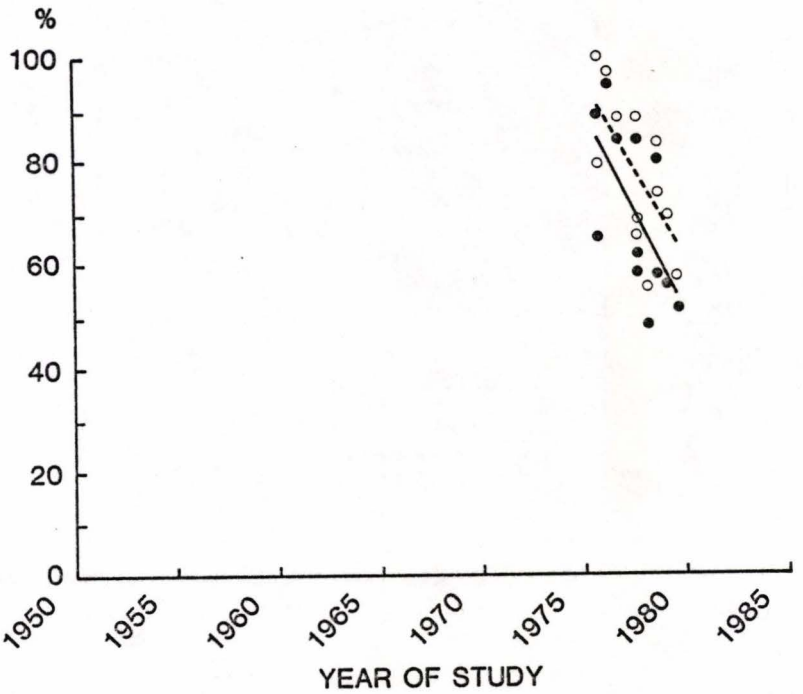
can introduce a considerable selection bias into the sample, as in the study done by Kopelman (1978), where the relatively low rate of mortality is probably due to a large proportion of infants with longer gestation. In some studies, gestational age was used as the primary criterion for the classification of infants (Perkins, 1981; Hein et al, 1982; Kitchen et al, 1982c; Smith et al, 1982; Verloove & Ruys, 1982; Koppe, 1983; Lamont et al, 1983; Koppe et al, 1984; Milligan et al, 1984; Yu et al, 1984a; Gilstrap et al, 1985; Shennan et al, 1985; Sporken, 1986).

Figure 2.6.3 In-hospital mortality ● and total adverse outcome ○ (percentage of liveborn infants) in all studies on infants with birthweight ≤ 1000 g, described in table 2.5.5



Other authors use both gestational age and birthweight in some form or other, mostly as appropriate for gestational age (AGA) or small for gestational age (SGA) infants (Fitzhardinge, 1975; Fitzhardinge & Pape, 1977; Commey & Fitzhardinge, 1979; Vohr et al, 1979; Kitchen et al, 1982c; Yu et al, 1982; Calame et al, 1983; Goldenberg et al, 1985b). Regrettably, the simultaneous use of gestational age and birthweight as such for classification of infants is a rare occurrence (Koops et al, 1982; Goldenberg et al, 1984).

Figure 2.6.4 In-hospital mortality ● and total adverse outcome ○ (percentage of liveborn infants) in all studies on infants with birthweight ≤ 800 g, described in table 2.5.7



This review of the literature demonstrates a very clear decrease in neonatal mortality during the last decades in all birthweight categories, coincident with the introduction and further perfection of neonatal intensive care. At the same time, the handicap rate, expressed as a percentage of liveborn infants, remained virtually unchanged. Consequently, the percentage of intact surviving infants increased almost threefold.

Chapter 3 Objectives of the study

3.1 Introduction

As stated in chapter 1.5, the purpose of the study was to collect, prospectively, data on a specific group of high risk newborn infants, those with the highest risk of mortality and later handicaps, in order to evaluate what happened to such infants in the perinatal period and subsequent years.

3.2 Choice of criteria for inclusion in the study

By investigating only VLBW infants (birthweight less than 1500 g) in accordance with international practice, regardless of gestational age, many authors have unwittingly mixed two basically different populations. On the one hand, there are the very preterm infants, of which the majority has a birthweight appropriate for their gestational age (AGA) and a minority is small for gestational age (SGA) or very small for gestational age (VSGA). On the other hand, there are the term or nearly term infants, who are all SGA or VSGA. These two groups differ in aetiology, neonatal morbidity and mortality, and may differ in outcome (Touwen, 1986). Therefore, VSGA infants are often considered separately, but still selected on birthweight criteria.

The study of such infants on the criteria of both birthweight and gestational age provides a more comprehensive approach that is useful to the paediatrician and the obstetrician alike. The sample selection bias mentioned above can be avoided, and comparability will be increased not only between centres and regions, but also in time (Battaglia & Lubchenco, 1967; Yerushalmy, 1970; Behrman et al, 1971; Lubchenco et al, 1972; Harris et al, 1978; Anonymous, 1980; Philip et al, 1981; Koops et al, 1982). Comparison of the figures published by Koops et al in 1982, with those of Lubchenco et al dating from 1972, shows an impressive overall decrease in neonatal mortality. The influence of birthweight at any given gestational age is unmistakable and the effect of gestational age at a given birthweight is also very clear.

With these considerations in mind, we decided to study not only birthweight, but also gestational age influences in high risk neonates.

3.3 General objectives

The main objectives of the POPS-study were to obtain epidemiological data (incidences, mortality and morbidity rates) on very low birthweight or very preterm infants in the Netherlands, and to investigate relationships of a variety of perinatal factors affecting these infants. Recently, recommendations to this effect have been published by the U.S. Department of Health and Human Services (Rosen, 1985).

Such data will then be available as a basis for health care planning, as a standard for quality control for individual hospitals, and as a historic control for future studies. Hypotheses can be generated on feasibility and efficacy of procedures in neonatal care; these will have to be tested in prospective trials.

Subsequently, the newly acquired knowledge will be put at the disposal of all clinicians for use in medical practice and as an aid for parental counseling. Finally, the data can be incorporated in teaching programs.

3.4 Specific objectives

Primarily, the study was meant to determine:

- incidence of liveborn very low birthweight infants
- incidence of liveborn very preterm infants
- demographic, geographic and obstetric backgrounds
- frequencies of perinatal procedures, including maternal and infant referral and backtransport
- mortality rates and causes of death
- neonatal morbidity (e.g. incidence of congenital malformations, idiopathic respiratory distress syndrome, intracranial haemorrhage and septicaemia)
- morbidity in the first two years of life (e.g. handicap rate and rehospitalization rate)
- resulting total adverse outcome

By analysis of the information collected on the pre-, peri- and postnatal periods, combined with the above mentioned outcome data, we hoped to elucidate relationships between perinatal factors and outcome.

Chapter 4 Methodology

4.1 Introduction

Since the objective of the study was to obtain information that would be relevant for the Netherlands as a whole, a survey in a geographically defined area was required on at least a regional basis. The Netherlands is a small, densely populated country (36,842 sq. km = 14,255 sq. miles, 14 million inhabitants) with 224 hospitals; nevertheless, there are small regional differences in e.g. urbanization, socio-economic situation and access to care. To avoid any bias from such unintentional selection, the survey was conducted throughout the country.

4.2 Study design

The optimal approach was thought to be a truly perinatal study, in which obstetricians and paediatricians would collect information on stillborn and liveborn infants from 16 weeks gestational age onwards; however, a study of such scope was not feasible.

Therefore, paediatricians were asked to collect, prospectively, information on liveborn infants with a gestational age of less than 32 completed weeks and/or a birthweight of less than 1500 g. The collected data included pre-, peri- and postnatal information (chapter 4.4.) that was entered on precoded forms by the attending paediatrician(s) during the hospital stay of the infant.

For the surviving infants, a follow-up period of 2 years ensued during which data were collected. At the age of 3, 6, 12 and 24 months (corrected for gestational age) information on health, growth, development, handicaps and psychosocial problems was recorded. The attending paediatrician completed the precoded forms during or shortly after the scheduled visits at the outpatient department, either in the hospital near the home of the infant, or in the referral hospital, according to local practice and the parents' preference.

The choice of an observational study, carried out with the cooperation of a great number of paediatricians, enabled us to collect currently available information on all study infants in a standardized manner, without implementing any new treatments. On the other hand, such a study poses problems of inter-observer variability (Bax, 1983); therefore, the information to be collected was restricted to conditions, diseases, and treatments that were either generally accepted and used (e.g. number of pregnancies, multiple pregnancy, infant's sex, pneumonia, intermittent positive pressure ventilation) or defined precisely (e.g. number of abortions, hypothermia of the newborn, septicaemia, retinopathy of prematurity).

4.3 Eligibility for entry into the study

All infants, liveborn in the Netherlands in 1983, with a gestational age of less than 32 completed weeks (less than 224 days) and/or a birthweight of less than 1500 g, were eligible for entry into the study.

Life at birth was considered to be present in accordance with the WHO-definition:"when the infant breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles" (WHO, 1977). By including all infants born in the Netherlands, the study was geographically defined by place of birth.

In accordance with FIGO-and WHO-recommendations, gestational age was classified in categories of completed weeks, e.g. 30 weeks meaning 30 weeks and 0 days up to and including 30 weeks and 6 days (210 up to and including to 216 days). Birthweight was classified into categories of 100 g, e.g. 1000 to less than 1100 g.

The upper limits of less than 32 completed weeks gestational age and that of less than 1500 g birthweight were chosen in accordance with internationally accepted standards, and because of the reduced mortality rate beyond those limits. In choosing these limits, we followed the most recent recommendations of the WHO (1977) and FIGO (1986).

The importance of adhering strictly to international standards for classification cannot be overemphasized. Clinicians tend to round birthweights (and other measurements) to the next nearest round figure (Verloove et al, 1985a), resulting in artificially increased numbers of infants with these "easy" weights, e.g. 1000 or 1500 g. Thus the choice of the cut off points (e.g. below 1501 g or below 1500 g) influences the distribution of infants over specific categories (Office of Population Censuses and Surveys, 1984). Consequently the reported mortality rates are affected to such an extent (Hermansen & Hasan, 1986) that comparison is of limited value. Reports such as the recently published volume on "The tiny baby" (Vidyasagar, 1986) only add to the confusion.

Contrary to WHO-recommendations (FIGO, 1982) to use a lower limit of 500 g or 22 weeks for national statistics, no lower limits were set. We considered the collection of information on all infants who showed any sign of life of great importance, regardless of gestational age or birthweight. Since our dataset comprises all birthweight and gestational age categories, it is possible to calculate various rates (incidence and mortality) according to different definitions. Especially with regard to future use this is essential, because the criteria for "viability" of today may easily be obsolete in only a relatively short period of time. It is precisely the lack of information from the past on extremely low birthweight infants, that hampers the epidemiologic research of today.

According to Dutch obstetrical definitions, any birth after a gestational age of 16 completed weeks is called "partus" and is entered into the labour ward ledgers; these are easily accessible to the paediatrician of the hospital. Therefore, it was possible to include in the study infants who were never admitted to paediatric or neonatal departments. This group included infants who died shortly after birth in the delivery room after unsuccessful resuscitation by the paediatrician, and infants who at birth were not attended by a paediatrician.

4.4 Data collection

The data to be collected were agreed upon during many discussions with participating paediatricians, obstetricians and statisticians. In a pilot study preceding the survey, the feasibility of data collection and processing was tested.

For the data collection, precoded forms were used: one for the perinatal period (appendix A), and four during the follow-up period at 3 months (appendix B), 6 months (appendix C), 12 months (appendix D) and 24 months (appendix E) of corrected age respectively. Another form (appendix F) was used to record results from post mortem examinations. A translation of the collected items is presented in tables 4.4.1 (perinatal period) and 4.4.2 (follow-up).

The forms were completed during the hospital stay and outpatient visit, or shortly afterwards, and were sent to the study centre. They were then entered into a registration system which enabled us, on the one hand, to be aware of the number of infants entered into the study and of any threatening loss to follow-up and, on the other hand, to keep in touch with the attending paediatricians of all study infants. Before the start of the study, the participating paediatricians received oral and written instructions. During the study period, progress reports were presented at the meetings of the "Sectie Perinatologie van de Nederlandse Vereniging voor Kindergeneeskunde" (Division of Perinatology of the Dutch Paediatric Association). Detailed instructions and, if neces-

Table 4.4.1 Collected data concerning perinatal period (the numbers correspond to those on the registration forms used)

Mother

1. registration number POPS
2. date of birth
3. maiden name (first 3 letters)
4. postal code (place of residence)
5. education and occupation (mother and father)
   health insurance: national health/private
6. ethnic origin: caucasian, mediterranean, asian, negroid or other (of either parent)
7. marital status

Obstetric history

8. first day of last menstrual period
9. number of previous pregnancies
10. number of previous abortions
11. number of previous preterm deliveries
12. number of children alive
13. pre-existing maternal disease: heart disease, epilepsy, diabetes mellitus, renal disease, hypertension
14. diseases during pregnancy: diabetes mellitus of pregnancy, isoimmunization, hypertension
15. toxic agents during pregnancy: smoking, alcohol abuse, soft drugs, hard drugs, methadon
16. hospital admission during and because of the index pregnancy
17. cardiotocographic tracings before labour (Fischer score < 5 or late decelerations)
18. drug treatment: diuretics, antihypertensives, tranquilizers, antiepileptics, antibiotics, progestatives, asthma-therapeutics, others

Delivery/Birth of infant

19. date of birth
20. time of birth
21. gestational age (best obstetrical estimate)
22. degree of reliability of gestational age
23. sex
24. fetal presentation
25. tocolysis (beta-mimetics, prostaglandin synthesis inhibitors, others), together with glucocorticoid administration

26. use of oxytocic drugs during labour
27. induction of labour
28. mode of delivery: vaginal (vertex, vacuum, forceps, spontaneous breech, breech extraction, version and extraction), caesarean section (with or without labour and/or ruptured membranes)
29. cardiotocographic tracings during labour
30. sedatives and/or analgesic drugs
31. anaesthesia during labour and delivery
32. prolonged duration of ruptured membranes
33. chorioamnionitis
34. staining of amniotic fluid (clear, fetid, meconium or bloodstained)

Infant

35. birthweight
36. length at birth
37. head circumference at birth
38. paediatric maturity score (Dubowitz, Ballard, Finnström, other)
39. Apgar scores
40. pH (umbilical artery, umbilical vein, capillary)
    PCO2 (umbilical artery, umbilical vein, capillary)
43. singleton or multiple pregnancy; number of infants; birthing order
44. place of birth (perinatal intensive care centre in university hospital, perinatal unit in general hospital, other obstetrical ward with or without paediatric service, elsewhere)
45. transport (antenatal and neonatal)
46. infant transport service used
47. hypothermia
48. respiratory tract disorders (idiopathic respiratory distress syndrome; wet lung; (congenital) pneumonia; atelectasis; air leaks; interstitial emphysema; meconium aspiration; milk aspiration; bronchopulmonary dysplasia; Mikity Wilson's disease)
49. persistent fetal circulation
50. persistent ductus arteriosus Botalli (treated by fluid restriction and diuretics; indomethacin; surgical closure)
51. apneic spells (treated with caffein/theophylline; continuous positive airway pressure; intermittent positive pressure ventilation)
52. bradycardia
53. continuous positive airway pressure (days)
54. intermittent positive pressure ventilation (days)
55. intrauterine infection (haemolytic streptococcus Group B; hepatitis B; herpes; cytomegalovirus; listeriosis; rubella; toxoplasmosis; syphilis)
56. septicaemia
57. causative bacteria

58. meningitis
59. highest serum bilirubin concentration
60. day of highest value
61. phototherapy
62. exchange transfusions (for hyperbilirubinaemia, septicaemia, metabolic disorder, intoxication)
64. total parenteral nutrition; duration
65. transpyloric nutrition
66. necrotizing enterocolitis
67. intracranial haemorrhage (diagnosed by lumbar puncture; ultrasound; computerized tomography scan; pulsatility index; postmortem)
69. localization (subependymal, parenchymal, subarachnoidal, intraventricular, cerebellar, subdural)
70. convulsions
71. hydrocephaly, (ventricular dilatation, increased headcircumference; treatment)
72. central nervous system disorders
73. peripheral nervous system disorders
74. retinopathy of prematurity
75. drug treatment (antibiotics, diuretics, digoxin, corticosteroids, anticonvulsives, other)
76. congenital malformations (lethal, non-lethal)
77. description of congenital malformation
78. causes of death (congenital malformation; idiopathic respiratory distress syndrome; intracranial haemorrhage; intrauterine infection; septicaemia; necrotizing enterocolitis; other)
79. date of death
80. time of death
81. special features of death (spontaneous; intensive care withheld or withdrawn; error or accident)
82. date of discharge from neonatal intensive care unit in university hospital
83. date of discharge home
84. condition at discharge home
85. weight at discharge home
86. mental and psychomotor development at discharge home.

Table 4.4.2 Collected data concerning follow-up (the numbers correspond to those on the registration forms used)

3. date of visit to outpatient department
4. cause of loss to follow-up (death, family move, other)
5. length
6. weight
7. headcircumference
8. psychomotor development (according to Dutch standards, appendix G)
29. central nervous system disorders
30. peripheral nervous system disorders
31. convulsions
32. physical therapy
33. respiratory tract disorders (bronchopulmonary dysplasia, Mikity Wilson's disease; other chronical disorders; repeated infections of upper respiratory tract; repeated (broncho) pulmonary infections)
34. digestive tract disorders (feeding difficulties; infections)
35. inguinal and umbilical hernias
36. hearing disorder
37. visual disorder (retinopathy of prematurity, squint; other)
38. rehospitalization
39. consultation of other specialists (e.g. ophthalmology, ear-nose-throat surgery, paediatric neurology, orthopedic surgery, physical rehabilitation, paediatric cardiology)
40. psychosocial problems (crying, sleeping disorder, restlessness, eating disorder, battering)
41. mother's height
42. father's height

At age 2 years (additional)

45. further particulars (congenital malformations detected at a later age; disease presumably without relation to preterm /VLBW birth; details of central nervous system disorder if present
46. conclusion of attending paediatrician concerning handicap: none, minor, major

sary, explications were given to minimize differences in interpretation when collecting data. One of the members of the study group visited nearly all hospitals involved, in order to maintain personal contact with the participants to the study. In addition, frequent consultations by telephone took place in both directions.

4.5 Data processing

Upon arrival at the secretarial office, all forms were checked by one of the study team. Any incompleteness, ambiguity or other discrepancy (such as between the last menstrual period and the stated gestational age) was traced and crosschecked with the paediatrician concerned. The data were then entered into the computer (IBM-3083 mainframe). A plausibility-control system, written in PL/I, traced improbable values (e.g. mother's year of birth later than 1970) or impossible combinations (e.g. caesarean section, and no anaesthetics whatsoever) prior to entrance into the database. Any questions resulting from these checks were put to the paediatrician concerned once again, who then provided the correct answers. No data were changed without permission from the participating paediatrician. After this verification and correction of the data, the final version was entered into the data base system. Data management was performed with the Statistical Package for the Social Sciences (SPSS-X 2.1), which was also used for analytical purposes.

During the study, summaries were produced at regular intervals for management of the study and to keep the participating paediatricians informed about their own part in the study, including loss to follow-up.

4.6 Data analysis

For the final analyses, the Statistical Package for the Social Sciences (SPSS-X 2.1) and the Statistical Analysis System (SAS, 1982) were used. SPSS-X was used primarily for all descriptive statistics and reporting to the participants. SAS was used for logistic regression analysis.

4.6.1 Descriptive statistics

From the database system, frequencies and rates were computed pertaining to demographic data and events during pregnancy, delivery and the period of hospital stay. These will be described in detail in chapters 5-8 and 10-12.

As stated in chapter 3.2, the study cohort was designed to comprise

several high risk categories simultaneously, based on gestational age and birthweight criteria. In addition to the usual VLBW population, all infants born before 32 weeks gestation were included even if they weighed more than 1500 g at birth. Thus, at gestational ages under 32 weeks, all possible weights are considered, while at gestational ages over 32 weeks only infants weighing less than 1500 g are included.

To study frequencies and rates more fully, the total study population will be divided into the following subpopulations whenever appropriate:

- less than 32 weeks gestational age versus equal to or over 32 weeks
- less than 1500 g birthweight versus equal to or over 1500 g
- small for gestational age (chapter 7.5) and appropriate or large for gestational age

The position of these subpopulations within the total study cohort is depicted in figure 4.6.1. Similar graphics will be used in forthcoming chapters to facilitate the understanding of the subgroups.

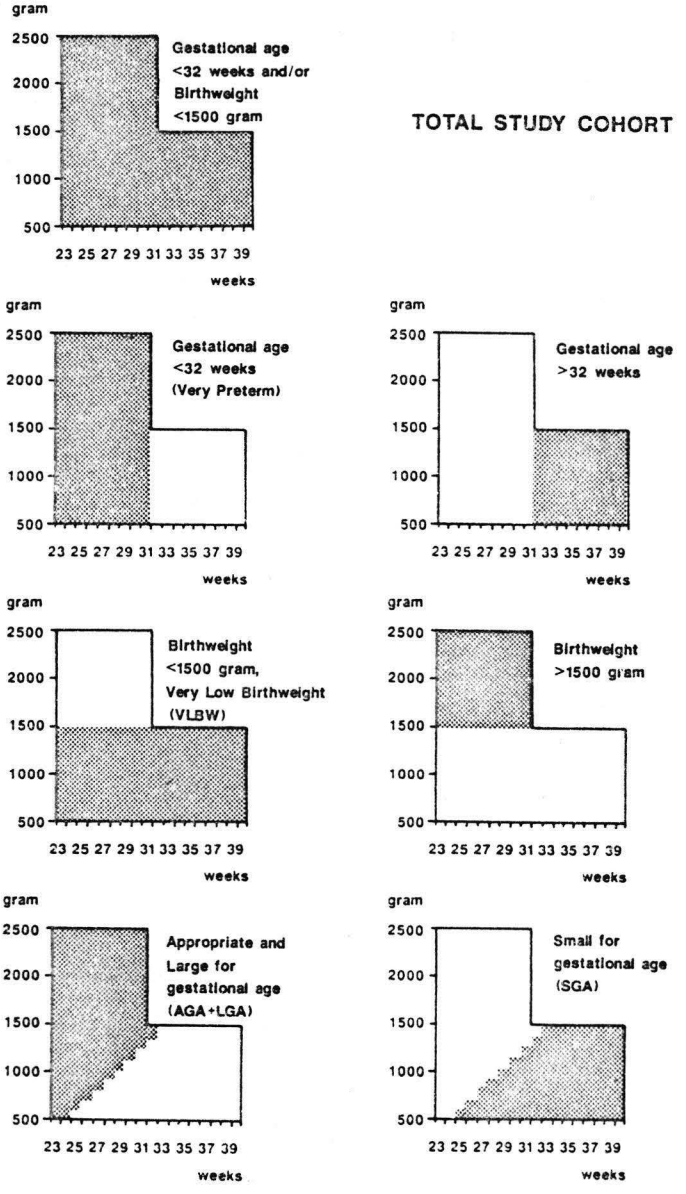
The tables presented in chapters 5-8 and 9-12 are for descriptive purposes only. No statistical tests have been applied. Differences in distribution as expressed by the cross tabulations should be interpreted on the basis of clinical relevance. Application of routine statistics, such as chi squares, would have been inappropriate; the underlying clinical research questions should be addressed in a multivariate way to avoid bias (chapter 4.6.2).

4.6.2. Inferential statistics

Besides describing our study population in terms of mortality and morbidity, and discussing the difference from or similarity to the existing literature on these subjects, we considered it of paramount interest to analyse this large cohort of infants more thoroughly. In the search for associations between a number of perinatal factors on the one hand, and certain measures of outcome on the other hand, the method commonly applied in neonatal literature until recently was to evaluate separately the relationship between each perinatal factor and each outcome. Usually Student t-tests or chi squares test statistics (univariate analyses) were used. These procedures have a distinct disadvantage: in using univariate analyses only, the many interdependencies between the various factors cannot be taken into account. For instance, the relationship between "mode of delivery" and neonatal mortality should not be analysed just by itself; fetal presentation and gestational age, for example, have to be taken into account.

A multivariate analysis is especially suited for the study of the relationship between two (or more) variables while controlling for one

Figure 4.6.1 Position of various subpopulations within the total study cohort, by gestational age and birthweight



or more other variables. The advantages of a multivariate over univariate analysis can be summarized as follows:

1. Controlling for more "confounding" factors at the same time
2. Quantification of the prognostic influence of more than one factor simultaneously
3. Assessment of "interaction" between factors

The choice of which factors to include in a multivariate analysis can be made in several ways. The practice of using only the "significant" factors of a number of univariate procedures in a subsequent multivariate analysis (Bergman et al, 1985; Low et al, 1986; Ounsted et al, 1986) has a distinct disadvantage: factors not significantly associated with the outcome in the univariate analysis, due to positive or negative associations with other factors, may be wrongly omitted from the multivariate analysis, which could lead to highly biased estimates and misleading conclusions. It is far better to select perinatal factors in advance. With the available literature and medical science as a basis, a deliberate choice can be made. We used this procedure in the present study: 31 perinatal factors were selected for inclusion into the multivariate analysis. Each factor was studied in relation to all other factors by scrutinizing crosstabulations. We decided not to include three of the factors as such into the multivariate analysis because of the number of missing data on these variables (chapter 14.1.2).

If the number of factors to be studied simultaneously in relation to the outcome is small, stratification into subgroups can be a good solution. However, in our study population we wanted to study many perinatal factors in relation to several different measures of outcome. We deliberately refrained from univariate statistical testing when estimating associations between factors and outcome, and used multivariate modeling techniques (such as logistic regression) to obtain information on adjusted odds ratios, confounding effects, and interaction effects. These methods can be applied very well to cohorts such as our study population.

The logistic regression technique is well suited to obtain valid and precise estimates of exposure-disease relationships, while controlling (adjusting) for the effects of many other factors.

Chapter 13 presents details of the statistical technique used and serves as an introduction to the later chapters. An excellent description of logistic regression in epidemiological research can be found in Kleinbaum et al (1982).

PART 2 DESCRIPTIVE STATISTICS

Chapter 5 Maternal data

5.1 Introduction

The participating paediatricians prospectively entered data on a cohort of 1338 infants, born alive in 1983 with a gestational age of less than 32 weeks and/or a birthweight of less than 1500 g. The population will be described in the following way: maternal data in chapter 5; pregnancies and deliveries in chapter 6; study infants in chapter 7; place of birth and transport in chapter 8. In chapter 9 the completeness of the study population will be discussed: the study cohort comprises 94% of all such infants born alive in 1983 in the Netherlands.

The participating paediatricians entered each of the 1338 infants into the study as an "individual patient". For each infant all variables on the forms were recorded separately. Three hundred and twelve infants were born after a multiple pregnancy and 1026 infants were born after a singleton pregnancy (table 5.1.1).

Between January 1st and December 31st, 1983, none of the mothers experienced another pregnancy that resulted in the delivery of an infant eligible for inclusion into the study. All data regarding maternal factors and pregnancies in chapter 5, refer to 1214 mothers and their pregnancies.

The 1214 mothers of the study cohort are characterized by the following parameters.

Table 5.1.1 Outline of the cohort

		mothers		infants	
singleton births			1026		1026
twins,	complete sets	107		214	
	first only	26		26	
	second only	37		37	
triplets,	complete sets	7		21	
	incomplete	10		13	
quadruplet		1		1	
			188		312
total			1214		1338

5.2 Maternal age

Maternal age was calculated in days as the difference between the date of delivery and the date of birth, thus representing the exact age at delivery. Maternal age ranged from 13 to 44 years. The distribution of maternal age over the study population and over the general population of mothers who delivered a baby in 1983 is presented in table 5.2.1 and figure 5.2.1.

The population curve has been normalized in such a way that the areas under both curves are proportionally equal (%). The curve of maternal ages in the POPS-cohort is shifted to the left compared to the curve of the total population. The mean age of the POPS-mothers was 27 years. In the general population of mothers who delivered a baby in 1983 in the Netherlands (170,246 births) the mean age at delivery was 27.9 years (Centraal Bureau voor de Statistiek, 1985b).

The teenage mothers are an important group in the POPS-cohort, as is demonstrated in table 5.2.1. Fifty nine (1.3%) of the 4666 infants born to teenage mothers in the general population in 1983 in the Netherlands were very preterm and/or very low birthweight infants. This is twice as frequent as in the 20-34 year old group (table 5.2.2). The same phenomenon is observed in cases with advanced maternal age: 22 out of 1465 infants (1.5%) born in 1983 to a mother aged 40 years or more, met the criteria for inclusion into the POPS-study.

Table 5.2.1 Maternal age at delivery

maternal age (years)	POPS-cohort n	%	general population n	%
≤19	59	4.4	4,666	2.7
20-24	334	25.0	40,304	23.7
25-29	516	38.6	74,862	44.0
30-34	290	21.7	39,263	23.1
35-39	78	5.8	9,686	5.7
≥40	22	1.6	1,465	0.9
unknown	39	2.9	-	-
total	1,338	100.0	170,246	100.0

Figure 5.2.1 Maternal age at delivery

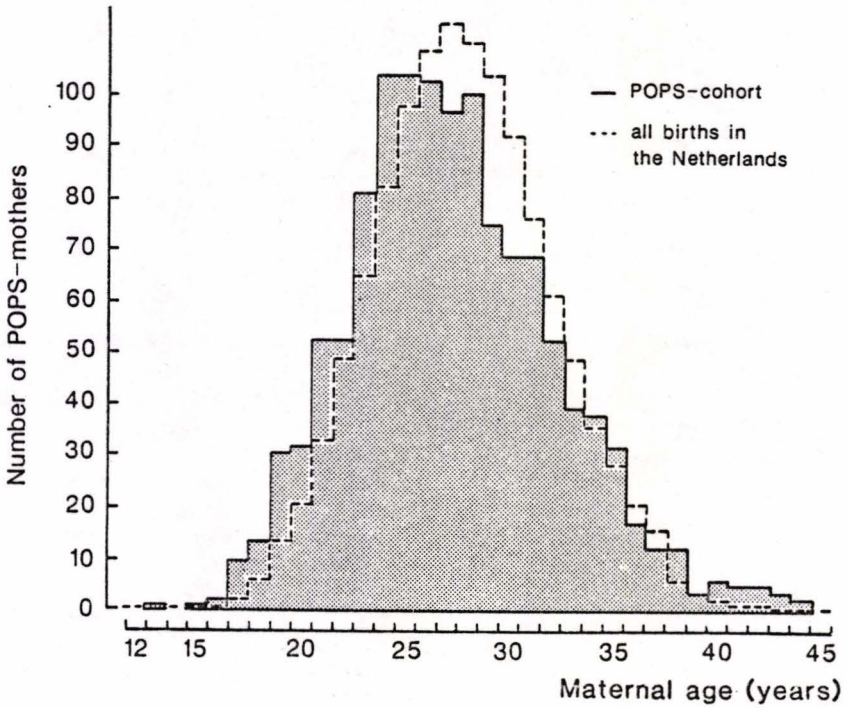


Table 5.2.2 Incidence of very preterm and/or very low birthweight deliveries in various maternal age groups

maternal age (years)	incidence of very preterm and/or very low birthweight deliveries n	%
≤19	59/ 4,666	1.3
20-24	334/40,304	0.8
25-29	516/74,862	0.7
30-34	290/39,263	0.7
35-39	78/ 9,686	0.8
≥40	22/ 1,465	1.5

discussion

These findings agree with the majority of previous studies, e.g. Miller & Handsleigh (1978) and Hall (1985). However, as has been demonstrated in the 1958 British Perinatal Mortality Survey (Butler et al, 1969), pregnancy in young mothers has been associated with several adverse factors, such as illegitimacy, lower socio-economic class and minimum education. Maternal age will be included in the analyses in chapters 14 and 15.

5.3 Ethnic origin

Ethnic origin has been reported as an important factor influencing perinatal outcome. However, the high socio-economic level of the population as a whole, limits the significance of this variable in the cohort. The ethnic origin of the POPS-mothers is presented in table 5.3.1.

discussion

No comparison has been made between the group of POPS-mothers and the general population, because in the Netherlands the certificate of birth only registers nationality. Since the immigration and subsequent naturalization of considerable groups of different ethnic origins, nationality is not equivalent to race in the Netherlands. Roughly estimated, there seem to be no notable differences in distribution of ethnic origin, compared to the general population.

Table 5.3.1 Ethnic origin

ethnic group	n	%
caucasian	1025	84.4
mediterranean	77	6.4
asian	50	4.1
negroid	42	3.5
other/unknown	20	1.6
total	1214	100.0

5.4 Socio-economic class

Socio-economic class cannot be represented by one single characteristic, but is usually described by a variety of indices, such as education, occupation of the father and/or mother, average income, mode of health insurance or other variables. At the same time, it may be closely related to other factors such as the use of antenatal care, hygienic environment, alcohol consumption, and dietary and smoking habits. Various studies point at the (inverse) relationship of social class and preterm birth (Fedrick & Anderson, 1976).

As listed in table 4.4.1, in the POPS registration form questions were asked about mother's and father's education and occupation and about mode of health-insurance. Based on the stated occupation(s), each case was classified in accordance with the "Beroepenklapper" (a standard of classification by profession) from Het Instituut voor toegepaste Sociologie in Nijmegen (van Westerlaak et al, 1975). The classes range from 1 (low) to 6 (high). Whenever parents had occupations with different classifications, the highest class was chosen. In case of doubt, the level of education and the mode of health-insurance were used to decide between classes. Notwithstanding vigorous efforts of the secretarial staff of the study centre, information on socio-economic class was complete in only 841 cases (63%). The distribution of socio-economic class in "known" cases is presented in table 5.4.1. To facilitate comparison with the general population in the Netherlands, we included the distribution of socio-economic class in a random sample of 1046 persons in the Netherlands (Prinssen & Kropman, 1975) in table 5.4.1.

Table 5.4.1 Distribution of socio-economic class

socio-economic class	study population		random sample Dutch population	
	n	%	n	%
1 (low)	83	9.9	116	11.4
2	254	30.2	369	35.3
3	258	30.7	231	22.1
4	68	8.1	179	17.1
5	62	7.4	99	9.5
6 (high)	116	13.7	52	5.0
total	841	100.0	1046	100.0

discussion

Unfortunately, in 37% of the study population no adequate information was submitted on the original forms. It was decided to repeat the questions on the form used for the follow-up investigation (form e.3, appendix E). Supplementary data will be added in future. At present no conclusions are justified regarding associations of socio-economic class and outcome variables such as mortality.

5.5 Marital status

Detailed information on marital status and/or cohabitation of the 1214 mothers was recorded on the POPS registration form (table 5.5.1).

discussion

Marital status of the mother is recorded routinely on the certificate of birth in the Netherlands. Illegitimacy depends upon the marital status of the mother at the moment of delivery. Data on numbers and percentages of illegitimate births have been compiled for a long time. Since the beginning of this century, the percentage of illegitimate births has declined from over 3% to approximately 1.3% during the 1950's. This includes infants born to mothers whose marriage had been dissolved more than 306 days before delivery (Centraal Bureau voor de Statistiek, 1979).

Table 5.5.1 Marital status

relationship	n	%
married	1061	87.4
unmarried, but supported	108	8.9
unsupported	34	2.8
unknown/other	11	0.9
total	1214	100.0

Since the 1950's, the percentage and number of illegitimate births have increased sharply, reflecting a change in public opinion with regard to marriage. In 1983, the percentage of illegitimate births in the Netherlands attained 7% (Centraal Bureau voor de Statistiek, 1985b). However, a considerable proportion of the unmarried mothers was supported by a partner sharing their household. The group of truly "single" mothers in the POPS cohort was small: 34 (2.8%).

5.6 Parity

According to Dutch standards, parity is defined as the number of previous pregnancies terminating in either a live birth or a stillbirth after 16 gestational weeks. The frequency and distribution are presented in table 5.6.1.

Table 5.6.1. Parity

parity	POPS-cohort		general population 1983	
	n	%	n	%
nulliparae	535	44.1	74.602	43.8
multiparae	679	55.9	95.644	56.2

discussion

Older studies (Butler et al, 1969) found increasing parity to be related to an increasing frequency of spontaneous preterm birth. This is in accordance with the tendency of preterm labour to repeat itself (Keirse et al, 1978). In a recent study, Hall found preterm labour to be more common in the first pregnancy (Hall, 1985). However, these studies were based on cross-sectional data. Bakketeig and Hoffman (1981) have shown that such studies are hampered by artifacts. They used data from the Medical Registration of Birth in Norway, covering all births with a gestational age of more than 16 weeks. In a subset of 81,400 mothers who had both their first and second births registered during a seven year study period, the risk of preterm labour proved to be decreasing with successive pregnancies up to the fourth.

5.7 History of preterm birth or abortion

The 679 multiparous mothers had various obstetrical histories. Some mothers had as many as eight previous pregnancies. The proportion of mothers with an obstetrical history that included one or more preterm births, defined as a birth from 16 up to and including 36 completed weeks (112 up to and including 258 days), is shown in table 5.7.1. Of the 679 multiparae, 200 mothers (29.4%) had such an obstetrical history.

Table 5.7.1 Number of previous preterm births in multiparous mothers

previous preterm births n	multiparous mothers n	%
0	479	70.6
1	160	23.6
2	26	3.8
3	11	1.6
≥ 4	3	0.4
total	679	100.0

A history of previous abortion (pregnancy ending before 16 gestational weeks = up to and including 111 days) was present in 248 (36.5%) of the

679 multiparous mothers. The number of previous abortions varied from 1 to 6 and is presented in table 5.7.2.

Table 5.7.2 Number of previous abortions in multiparous mothers

previous abortions n	multiparous mothers n	%
0	431	63.4
1	175	25.8
2	53	7.8
3	12	1.8
4	3	0.4
5	3	0.4
6	2	0.3

discussion

A history of previous live birth with the infant weighing less than 2500 g, increases the likelihood of spontaneous preterm birth (< 37 weeks) in subsequent pregnancies from 2 to 7-fold depending upon the number of previous infants weighing < 2500 g (Fedrick & Anderson, 1976). However, Bakketeig et al (1977; 1979) showed that the incidence of preterm delivery in a second single pregnancy correlates far better with the gestational age than with birthweight of the first single birth. In 76,938 cases for which birthweight and gestational age were known for both the first and second births from 16 weeks of gestation onwards, the over-all risk of preterm delivery in the second pregnancy was 4.9%, but this percentage increased to over 20% if the birthweight of the first birth was less than 2500 g and the gestational age was less than 34 weeks. The relative risk of a subsequent preterm delivery was 4 times higher for mothers who had previously delivered preterm compared to those who had not. This is in agreement with the findings of a retrospective study by Keirse et al (1978) of more than 8000 singleton live births. They showed that the incidence of spontaneous preterm delivery is closely related to a history of two or more pregnancies ending spontaneously in the first trimester (<14 weeks) and one or more in the second trimester (14-27 weeks) or from 28 to less than 37 completed weeks. The risk of spontaneous preterm delivery was highest in patients with previous deliveries between 28 and 37 weeks and lowest in those

with only first trimester abortions. Up to now, there are no national data available on the incidence and recurrence-risk of preterm delivery in the Netherlands. Based on data collected by the "Nederlands Huisartsengenootschap" (Dutch Society of General Practitioners), the incidence of births before the 37th gestational week is estimated around 5-6%, comparable to the neighbouring countries (chapter 1.3.2).

In the past, there has been confusion about the late effects of induced abortions. Whereas some authors (Liu et al, 1972; Wright et al, 1972) found a positive correlation between induced abortion and subsequent spontaneous preterm delivery, others have found no such associations in carefully controlled studies (Daling & Emanuel, 1975). The reasons for these differences are unknown. In the Netherlands, there are at present no indications that abortions, induced in the first trimester of pregnancy, significantly increase the likelihood of spontaneous preterm labour and delivery in subsequent pregnancies (van der Slikke & Treffers, 1978). For practical purposes, in this study a composite index was established to characterize a mother with a history of previous preterm delivery (defined as a delivery from 16 up to and including 36 completed gestational weeks) and/or a history of two or more first trimester abortions. In chapters 14 and 15 we shall focus on the relationship between a history of preterm delivery or abortions and neonatal mortality or morbidity.

Table 5.8.1 Surviving infants from previous pregnancies in multiparous mothers

surviving infants n	multiparous mothers n	%
0	186	27.4
1	313	46.1
2	121	17.8
3	33	4.9
4	17	2.5
5	2	0.3
6	2	0.3
7	1	0.1
8	3	0.4
unknown	1	0.1
total	679	100.0

5.8 Surviving infants from previous pregnancies

In studying neonatal mortality and morbidity, parity by itself is insufficient. In our opinion, the number of surviving infants from previous pregnancies in multiparous mothers should be taken into account as well. This parameter is of particular interest to the mothers, since the result of a pregnancy is all that counts. Vlaanderen (1983) demonstrated the tendency of mothers to repeat pregnancies until the desired results have been achieved. Therefore, in addition to parity, the number of surviving infants from previous pregnancies was recorded. The frequencies are presented in table 5.8.1.

5.9 Pre-existing maternal disease

In table 5.9.1 the frequencies of maternal diseases are presented. All recorded diseases were present before the beginning of the index pregnancy.

Table 5.9.1 Pre-existing maternal disease

disease	n	%
hypertension	50	4.1
renal disease	23	1.9
heart disease	12	1.0
epilepsy	5	0.4
diabetes mellitus	4	0.3
no disease	1120	92.2
total	1214	100.0

discussion

Previous aetiological studies failed to establish a firm relationship between pre-existing maternal disease and spontaneous preterm delivery. Yet, adverse maternal conditions may lead to an increased percentage of elective preterm deliveries, especially if the disease is associated with poor fetal growth. For instance, hypertension has been associated with low birthweight for a long time, but an association with spontane-

ous preterm labour is less certain.

The vast majority of mothers were healthy women. Because of the small number of women with a pre-existing disease, all mothers with (any) pre-existing disease have been brought together into a group with a composite index variable named pre-existing maternal disease. In this group, 82 mothers were delivered of 86 infants.

5.10 Summary

As stated in chapter 4, various subpopulations may be distinguished within the total study population. The distribution of the discussed maternal factors is not equal in the various subpopulations, possibly as a result of the influence of these same factors. In order to facilitate comparison between subpopulations, we present the distribution of the various factors according to subpopulation in table 5.10.1.

As stated in chapter 5.1, each infant in the POPS-study was entered into the study as an "individual patient". For the sake of clarity, in the following chapters all variables will be counted per infant concerned.

Table 5.10.1 Distribution of maternal factors over various subpopulations (numbers adjusted to the infants)

chapter	maternal factors	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
								
		n %	n %	n %	n %	n %	n %	n %
5.2	maternal age <20 yr	68 (5.0)	50 (5.0)	18 (5.5)	54 (4.9)	14 (5.8)	46 (5.4)	21 (4.6)
	≧36 yr	56 (4.2)	40 (4.0)	15 (4.6)	42 (3.8)	14 (5.8)	34 (4.0)	21 (4.6)
5.3	ethnic: caucasian	1135 (84.8)	857 (85.3)	275 (84.9)	928 (84.8)	207 (87.0)	740 (83.7)	395 (87.0)
	non-caucasian	193 (14.4)	146 (14.4)	47 (14.5)	164 (14.9)	29 (12.0)	137 (15.5)	56 (12.3)
5.5	marital status (married)	1169 (87.8)	889 (88.5)	278 (85.5)	943 (86.4)	226 (93.8)	775 (87.7)	394 (86.8)
5.6	parity >0	640 (47.8)	524 (51.9)	116 (35.7)	511 (46.6)	129 (53.5)	445 (50.3)	181 (39.9)
5.7	history of preterm birth or abortion	273 (20.4)	230 (22.8)	43 (13.2)	224 (20.4)	49 (20.3)	185 (21.7)	80 (17.6)
5.9	pre-existing maternal disease	86 (6.4)	50 (5.0)	35 (10.8)	77 (7.0)	9 (3.0)	38 (4.5)	47 (10.4)

Chapter 6 Obstetrical data on pregnancies and deliveries

6.1 Introduction

In this chapter, we present and discuss obstetrical data concerning pregnancies and deliveries in the study population. As in the other chapters of part 2 of this thesis, the data will be presented by means of descriptive statistics only and we shall refrain from univariate statistics however tempting this may be. Application of univariate statistical techniques would preclude controlling for confounding factors and quantification of the prognostic influence of more factors simultaneously (chapter 4.6.2). Most variables discussed in this chapter will be included in the logistic regression analyses presented in chapter 14 and 15.

Generally, the data will be presented for the cohort as a whole. Whenever appropriate, the data on very preterm infants (< 32 weeks) and very low birthweight infants (< 1500 g) will be presented separately.

Since one of the key concepts of the POPS-project is to analyse the survival and development of the study population, each of the 1338 infants is considered as an individual case. Data concerning multiple pregnancies and deliveries are presented in chapter 7.8. In forthcoming chapters, special reference to twin and triplet infants will be made when appropriate.

6.2 Pregnancies complicated by diabetes mellitus

A diagnosis of diabetes mellitus prior to the index pregnancy was present in 4 mothers, who all had a singleton pregnancy. They were treated with insulin throughout their pregnancies.

Gestational diabetes, defined by Coelingh Bennink (1980) as a disturbance in glucose tolerance which occurs during, but disappears after pregnancy, was present in 59 cases (4.4%). Half of this group, 29 cases, was treated solely with a diet. The other half, 30 cases, received insulin therapy which was started at various stages of pregnancy. No one received oral antidiabetic drugs.

discussion

The observed frequency of gestational diabetes mellitus is high in comparison to the general population. According to Coelingh Bennink's (1980) estimate, gestational diabetes mellitus occurs in 1-2% of all pregnant women. Since diagnostic criteria and treatment protocols vary widely between different hospitals, we did not study (possible) associations between gestational diabetes mellitus and outcome variables.

Maternal diabetes mellitus has been associated with increased fetal risk. Consequently, most obstetricians opt for a timely delivery by either an induction of labour or an elective caesarean section. In the Netherlands, this usually takes place at 38-39 gestational weeks and is, therefore, beyond the scope of this study. However, instability of the diabetes or, more frequently, concomitant hypertension, may indicate earlier intervention. Infants born from any such preterm delivery may seem large, but this is a poor indicator of fetal development. Although there is evidence of a delayed initial growth in diabetic pregnancies, which can occur as early as the first trimester (Fog Pedersen & Mølsted-Pedersen, 1979), this may later be either clouded or compensated for by macrosomic influences.

6.3 Bloodgroup incompatibility

Evidence of haemolytic disease caused by Rhesus(D)isoimmunization was found in 4 (0.3%) pregnancies. Three infants were born by elective caesarean section at gestational ages of 27-38 weeks. One infant was born after spontaneous labour at 31 gestational weeks. Three infants survived and were discharged home.

discussion

In previous years, Rhesus disease figured prominently on the list of factors involved in preterm births, because this condition often causes intervention to end pregnancy in the preterm period. However, since the introduction of prophylactic anti Rhesus (D)immunoglobulin in 1969 in the Netherlands (administered within 48 hours of delivery) the number of sensitized women has been greatly reduced: in 1969, 3.5% of Rhesus negative, pregnant women had a positive Coombs-test in the 32nd gestational week. In 1982 this percentage had declined by 85% to under 0.5% (Bennebroek Gravenhorst et al, 1984).

6.4 Maternal hypertensive disorders

In spite of many efforts to establish international definitions and standards, the classification of hypertensive disease in pregnancy is still a matter of debate. The "Committee on terminology of the American College of Obstetricians and Gynaecologists" recommended the following grouping (Hughes, 1972):

1. Normotensive: mothers who have blood pressure readings recorded, but none as high as 90 mm diastolic.
2. Pregnancy induced hypertension: a blood pressure in excess of 140/90 mm Hg, measured at least twice in the second half of pregnancy in a previously normotensive mother.
3. Preeclampsia: acute hypertension arising after the 20th week of gestation, together with abnormal edema or proteinuria, or both.
4. Eclampsia: the occurrence of one or more seizures in a mother with preeclampsia. Epilepsy and other convulsive disorders must be excluded.
5. Pre-existing or chronic hypertension: hypertension diagnosed before the onset of pregnancy (any cause). This condition may be complicated by a superimposed preeclampsia or eclampsia.

The frequencies of the various types of hypertensive disorder in pregnancy in the cohort are presented in table 6.4.1.

Although the various types of hypertension may have different aetiologies, all cases with (any) hypertensive disorder in pregnancy were brought together. The total number of cases was 300 (22.4%), of whom 126 (42%) were treated with antihypertensive drugs during pregnancy.

The difference in distribution of hypertension over the various birthweight and gestational age categories is remarkable. While there is little difference between successive 100 g birthweight categories, the frequency of hypertension increases in advancing gestational age

Table 6.4.1 Frequency of various types of hypertensive disorders in pregnancy

condition	infants n	infants %
normotensive pregnancy	1033	77.2
pregnancy induced hypertension	174	13.0
preeclampsia	73	5.5
eclampsia	6	0.4
pre-existing hypertension + no complication	30	2.2
+ preeclampsia	16	1.2
+ eclampsia	1	0.1
blood pressure not recorded	5	0.4
total	1338	100.0

categories. For instance, the group with a gestational age of less than 32 weeks experienced hypertension in 139 out of 1010 cases (13.7%) versus 161 out of 325 (49.5%) cases in the group with a gestational age of 32 weeks or more. In table 6.4.2, the distribution of hypertension in pregnancy is presented according to gestational age categories, while in table 6.4.3 the data are presented according to birthweight categories.

Table 6.4.2 Hypertension in successive gestational age categories

gestational age (weeks)	number of infants	hypertension n	hypertension %
≤23	8	0	
24-25	67	1	1.5
26-27	180	11	6.1
28-29	307	39	12.7
30-31	448	88	19.6
≥32	325	161	49.5
total	1335	300	22.5

Table 6.4.3 Hypertension in successive birthweight categories

birthweight (g)	number of infants	hypertension	
		n	%
<500	5	0	0.0
500-599	14	4	28.6
600-699	33	9	27.3
700-799	51	9	17.6
800-899	88	23	26.1
900-999	101	24	23.8
1000-1099	124	29	23.4
1100-1199	139	54	38.8
1200-1299	161	43	26.7
1300-1399	179	47	26.3
1400-1499	202	47	23.3
≥1500	241	11	4.6
total	1338	300	22.4

All infants were classified as AGA or SGA by means of the Amsterdam growth charts (Kloosterman, 1969). Infants with a birthweight below the 10th percentile have been classified as SGA (chapter 7.4). As might be expected from the data mentioned above, we observed a large number of SGA infants in the hypertensive group (table 6.4.4).

Table 6.4.4 Distribution of AGA and SGA infants according to hypertension

blood pressure	number of infants	AGA/LGA		SGA	
		n	%	n	%
normotensive	1038	801	77.2	237	22.3
hypertensive	300	83	27.2	217	72.3
total	1338	884	66.1	454	33.9

discussion

Depending on definitions and patient selection, the reported incidences of hypertensive disorders in pregnancy in the medical literature vary from 2.4% to 34% (Chesley, 1978; MacGillivray, 1983). The observed incidence in the study population (22.8%) may be considered high, since our study population represents the total population of very preterm and very low birthweight infants.

The groups of patients with pre-existing hypertension and a superimposed hypertensive disease in pregnancy carry an increased risk for both the fetus and the mother (Chesley, 1978). Fifty-one out of 300 cases (17%) with hypertension during pregnancy had pre-existing hypertensive disease. Other authors found a slightly higher percentage (25%) in their (selected) population (Wellen, 1953).

6.5 Smoking during pregnancy

Active smoking of cigarettes by the mother during pregnancy was recorded in 387 (28.9%) out of all cases. Although explicit questions were asked in the questionnaire, it is remarkable that this very item has a high number of cases with missing information. The recorded frequencies of smoking during pregnancy are presented in table 6.5.1.

Table 6.5.1 Smoking during pregnancy

mother's smoking	infants	
	n	%
no smoking	785	58.7
from 1 up to 10 cigarettes per day	221	16.5
more than 10 cigarettes per day	166	12.4
no information recorded	166	12.4
total	1338	100.0

The distribution of cases with a mother who smoked cigarettes in pregnancy shows some association with other perinatal factors. For instance, the incidence of smoking mothers is highest among very young mothers and decreases with advancing maternal age (table 6.5.2).

Table 6.5.2 Distribution of infants of smoking mothers according to maternal age

maternal age (years)	number of infants	infants of smoking mothers n	%
≤19	53	23	43.4
20-35	1044	350	33.5
≥36	50	13	26.0
age unknown	25	1	4.0
total	1172	387	33.0

As described in chapter 5.4, socio-economic class is recorded in only 910 (68%) out of all cases. Although the number of unknown cases restricts the validity, there is an interesting association between socio-economic class and the incidence of smoking in pregnancy. In the 841 cases with both variables recorded, we observed a higher incidence of maternal smoking in the lower socio-economic classes (table 6.5.3).

Table 6.5.3 Distribution of infants of smoking mothers according to socio-economic class

socio-economic class	number of infants	infants of smoking mothers n	%
1	83	33	39.8
2	254	114	44.9
3	258	96	37.2
4	68	21	30.0
5	62	16	25.8
6	116	22	18.9
total	841	302	35.9

discussion

As in other European countries, the incidence of smoking by women has increased in the Netherlands since the second world war (Russell, 1980). In 1979, de Haas and de Haas-Posthuma (1982) found that 55-60% of the women in the 20-34 year old group smoked. The highest prevalence of smoking occurred in the lower socio-economic classes.

Data on the incidence of smoking in pregnancy in the Netherlands were collected by 317 midwives throughout the country. They found a decrease in the incidence of smoking from 56% at the beginning of pregnancy to 46% during the rest of pregnancy (de Jonge & van der Klaauw, 1982). These figures comply with data from other European countries.

Several authors reported a reduction in the average duration of pregnancy in smokers compared to non-smokers of 1.4 to 1.8 days (Lowe, 1959; Buncher, 1969), whereas other authors did not find a difference in length of gestation (Yerushalmy, 1964). However, the limited reduction in the duration of pregnancy cannot account for the average 200 g reduction in birthweight of infants of smoking mothers (van der Velde, 1985).

Although we do not have information on smoking during pregnancy in 12.4% of the cases, the observed 28.9% of cases with a smoking mother is low in comparison to the general population in the Netherlands. We did not look for further associations between outcome variables and maternal smoking, because we considered the number of cases with missing data on smoking too high for unbiased results.

6.6 Other intoxications during pregnancy

Consumption of alcoholic beverages in such quantities that the consulting physicians classified the mother as an alcoholic, occurred in 7 cases (0.5%). All were singleton pregnancies. Four infants were born with a gestational age of less than 32 weeks and 3 infants were born with a gestational age beyond 32 weeks, all growth retarded.

The use of marijuana or other "soft drugs" was recorded for 6 mothers who all delivered a singleton infant (0.4% of all cases). Only one of these was born in the very preterm period with a gestational age of less than 32 weeks (0.1% in that group). The remaining 5 cases were born with a gestational age of more than 32 weeks, but with a birthweight of less than 1500 g (1.5% in that group).

Addiction to "hard drugs" was recorded for 4 mothers, who all delivered a singleton infant (0.3% of all cases). All 4 mothers used heroin as well as methadon during pregnancy. No attempt was made to quantify the doses that were used. Three infants were born with a gestational age of less than 32 weeks (0.3% in that group) and died. Two

of these died of congenital malformations and one died of respiratory problems after a birth at 24 gestational weeks. The fourth infant was born with a gestational age of 36 weeks. This growth retarded but otherwise normal infant (birthweight 1470 g) survived at least one year. The results of the follow-up study will be presented in future.

discussion

During the last 15 years, many reports have drawn attention to the harmful effects of maternal drinking during pregnancy (Rosett et al, 1983). Fetal growth can be severely reduced in the fetal alcohol syndrome which is characterized by:

1. Prenatal growth retardation: birthweight may be reduced by as much as 1200 g at term when compared with controls, and bodylength by as much as 5 cm (Bierich, 1978).
2. Congenital malformations: mostly skeletal, cardiac and genital
3. Characteristic facial dysmorphology.
4. Disturbance of mental development.

Three of the 7 infants with mothers, addicted to alcohol, were "growth retarded". Two of these SGA infants and one AGA infant had congenital malformations other than those characteristic for the fetal alcohol syndrome. Three of the 7 infants born to an alcoholic mother died in the neonatal period. Results of the follow-up investigations of the surviving infants will be published when completed.

The personal use of marijuana is tolerated by the Dutch authorities. No official registry exists, but this soft drug is not uncommon. There is a strong association with smoking. Although previous reports have cautioned against the potential hazards of marijuana during pregnancy (Marihuana and Health, 1976), those reports do not provide conclusive evidence for severe ill-effects of marijuana itself.

The observed incidence (0.3%) of cases with mothers who are addicted to hard drugs may be considered high for the Netherlands. Soepatmi (personal communication, 1986) estimates the number of babies born to mothers addicted to hard drugs in Amsterdam around 70-80 per year and in the country as a whole 150-200 per year. This results in an incidence of 0.1% of live births. The use of heroin during pregnancy has been associated with shortened gestation as well as with reduced weight for gestational age (Hogerzeil et al, 1982). The small number of observed cases precludes conclusions on the higher incidence in the cohort.

6.7 Use of medication during pregnancy and delivery

The use of drugs prescribed during pregnancy was recorded with the exception of iron and vitamin supplements, because these are considered "routine" drugs during pregnancy. The recorded number of cases exposed to drugs in utero was during pregnancy 796 (59.5%), and during delivery 869 (64.9%). The majority of cases has been exposed to several drugs during pregnancy and delivery that have been used concurrently or one after the other.

Inhibition of preterm uterine contractions was attempted in 591 out of 1338 (44.2%) cases and will be described in more detail in chapter 6.10. One hundred and ninety infants (14.3%) were born after a pregnancy in which the mother received glucocorticoids to accelerate fetal pulmonary maturation. These cases will be described in chapter 6.11.

Apart from the above mentioned tocolytic drugs and glucocorticoids, other drugs were used in 398 (29.7%) cases. The observed pharmacological groups and frequencies are presented in table 6.7.1.

Table 6.7.1 Drugs used during pregnancy

pharmacological group	infants	
	n	%
diuretics	33	2.5
anti-hypertensive drugs	126	9.4
sedatives	103	7.7
anti-epileptic drugs	16	1.2
antibiotics	141	10.5
progestagens	23	1.7
anti-asthma drugs	11	0.8
various other drugs	112	8.4

The drugs used during labour and delivery are presented in table 6.7.2.

discussion

In spite of tragedies such as the "thalidomide-affair", drugs are still frequently prescribed and used during pregnancy. Although Eskes et al (1983) found a decrease in the use of medication from 82.7% to 71.7% during the years 1974-1977, this percentage is still alarmingly

Table 6.7.2 Drugs used during labour and delivery

pharmacological group	infants	
	n	%
oxytocic drugs	35	2.6
prostaglandins	4	0.3
pethidine	40	3.0
diazepam	71	5.3
other sedatives	61	4.6
local analgesics	77	5.7
epidural analgesia	56	4.2
general anaesthesia	525	39.2

high. The observed frequencies of medication in the POPS-cohort are lower than expected for a population with complicated pregnancies. The interpretation of the effects of drugs is hampered, because many cases received more than one drug at a time.

The use of medications, of excess alcohol, heroin, and marijuana as well as maternal smoking all have a potential deleterious influence during pregnancy. Therefore, the exposed cases were brought together in one group with a composite index: "medication and intoxication during pregnancy". The total number of exposed cases is 668 out of 1338 (49.9%). In chapters 14 and 15 we shall analyse possible associations with outcome parameters.

6.8 Premature rupture of membranes

Premature rupture of the membranes is defined as a spontaneous rupture of the fetal membranes which occurs at any moment before the onset of labour. The period of time elapsing from the moment of rupture of membranes to the moment regular uterine contractions start, is designated the "latent period".

A diagnosis of premature rupture of membranes had been established in 517 cases (38.9%). Since clinical management relates particularly to gestational age, it is worth mentioning that there are differences in incidence when one considers infants with a gestational age of less than 32 weeks versus older infants. Of the 1010 cases with a gestational age of less than 32 weeks, 453 (45.5%) had premature rupture of membranes, whereas this diagnosis was made in only 64 (19.6%) of 325 cases with a

gestational age of 32 weeks or more.

In cases with premature rupture of membranes, the latent period has been recorded. For practical purposes, the various latent periods have been stratified into four groups. The observed frequencies of premature rupture of membranes in relation to the latent period are presented in table 6.8.1.

Table 6.8.1 Number of cases with premature rupture of membranes in relation to the latent period

latent period	infants	
	n	%
not ruptured	812	60.7
<12 hours	231	17.3
12-24 hours	46	3.4
1- 7 days	149	11.1
> 7 days	91	6.8
not recorded	9	0.7
total	1338	100.0

In 309 out of 517 cases (59.7%) with premature rupture of membranes, beta-mimetic drugs have been administered to inhibit secondary uterine contractions, with the aim to prolong pregnancy. In 182 cases (58.8%), this tocolytic therapy was successful for a period of at least 24 hours, but in 127 cases (41.1%) the course of this therapy did not last that long. The cases in which more than 24 hours elapsed between the moment of rupture of membranes and the moment of delivery are described in chapter 6.9.

A well-known complication of premature rupture of membranes is chorioamnionitis caused by an ascending infection. On clinical grounds (fever and/or leucocytosis), a diagnosis of chorioamnionitis had been established in 100 cases. The association between chorioamnionitis and the duration of the latent period is illustrated in table 6.8.2.

discussion

Premature rupture of membranes is a fairly common event, occurring in approximately 10% of all pregnancies (Mead, 1980). The incidence

Table 6.8.2 Number of cases with chorioamnionitis according to the duration of the latent period

latent period	number of infants	chorioamnionitis n	chorioamnionitis %
not ruptured	810	10	1.2
<12 hours	230	7	3.0
12-24 hours	46	12	26.1
1- 7 days	149	52	34.9
> 7 days	91	19	20.9
total	1326	100	7.6

shows an inverse relationship with gestational age, and in preterm studies like ours, higher incidences have been reported (Kanhai, 1981; Schutte, 1983). The observed incidence of 45.5% in cases with a gestational age of less than 32 weeks must be considered high.

The aetiology of premature rupture of membranes is unknown and may be different at various gestational ages. In the preterm period the aetiology may include subclinical infection in a number of cases. In this cohort, we observed a sharp rise in the incidence of overt chorioamnionitis when the latent period exceeded only 12 hours. After this initial rise in the incidence of chorioamnionitis, the association with the duration of the latent period is less clear. In 240 out of 517 cases (46.4%) the latent period exceeded 24 hours. Data on these cases are presented in chapter 6.9.

6.9 Prolonged duration of ruptured membranes

Prolonged duration of ruptured membranes designates those cases in which a period of at least 24 hours elapses between the moment of membrane rupture and the onset of labour.

The observed frequency of prolonged duration of ruptured membranes in the POPS-cohort is 17.9% (240 cases). In 149 cases, the time interval between the rupture of membranes and the onset of labour is 1-7 days and in 91 cases the duration exceeds 7 days.

In agreement with current standards in obstetric care in the Netherlands, most cases with prolonged duration of ruptured membranes have been admitted to hospital for observation. Out of 240 cases, 225 (94%)

have been admitted for periods of varying duration. Fifteen cases (6%) were admitted only after labour had begun.

Although the percentage of cases with prolonged duration of ruptured membranes was nearly the same in all 100 g birthweight groups, the incidence of prolonged duration of membrane rupture is higher in the younger gestational age groups (table 6.9.1).

Table 6.9.1 Prolonged duration of ruptured membranes in successive gestational age categories

gestational age (weeks)	number of infants	prolonged duration of ruptured membranes	
		n	%
≤23	8	0	0.0
24-25	67	16	23.9
26-27	180	46	24.2
28-29	307	64	25.5
30-31	448	100	22.3
≥32	325	14	4.3
total	1335	240	18.0

In accordance with this finding are the higher incidences of tocolysis and administration of glucocorticoids in cases with prolonged duration of ruptured membranes. Out of 240 cases with prolonged duration of ruptured membranes, 182 (76%) received tocolytic treatment, versus 409 out of 1098 cases (37%) without. In 47 out of 240 cases (20%) with prolonged duration of ruptured membranes, the mother received glucocorticoids in an attempt to accelerate fetal pulmonary maturation, whereas the incidence in cases without prolonged duration of ruptured membranes was 143 out of 1096 (13%).

The well-known association between prolonged duration of ruptured membranes and chorioamnionitis is confirmed by this study. The incidence of chorioamnionitis is ten times higher in cases with prolonged duration of ruptured membranes as is illustrated in table 6.9.2.

The association between neonatal septicaemia as diagnosed by the paediatrician on clinical grounds after delivery (chapter 12.5), and a history of prolonged duration of ruptured membranes is illustrated in table 6.9.3.

Table 6.9.2 Distribution of cases with chorioamnionitis according to prolonged duration of ruptured membranes

fetal membranes	number of infants	chorioamnionitis n	%
intact or ruptured <24 hours	1094	29	2.6
prolonged rupture	240	71	29.6
total	1334	100	7.5

Table 6.9.3 Distribution of cases with clinical septicaemia according to prolonged duration of ruptured membranes

fetal membranes	number of infants	clinical septicaemia n	%
intact or ruptured <24 hours	1091	346	31.7
prolonged rupture	238	98	41.2
total	1329	444	33.4

discussion

The presented data reflect to some extent the conservative approach Dutch obstetricians take when managing a pregnancy in which the membranes rupture spontaneously in the preterm period. Most cases have been admitted to hospital for close observation (94%).

Whether a cause or a result of preterm, premature rupture of membranes (Thomsen et al, 1987), intrauterine infection is potentially a serious complication. Of the cases with prolonged duration of ruptured membranes 76% received tocolytic treatment with the aim to prolong pregnancy. In spite of the controversy around the administration of glucocorticoids to women with preterm, premature rupture of membranes (Simpson & Harbert,

1985; Morales et al, 1986), 20% of the cases with prolonged duration of ruptured membranes received such treatment.

The observed association between prolonged duration of ruptured membranes and chorioamnionitis is unexpectedly strong (Wilson et al, 1982), but the association between prolonged duration of ruptured membranes and septicaemia is difficult to interpret. All cases with clinical septicaemia have been brought together and so the group includes cases with "early" neonatal septicaemia related to obstetric infection, as well as cases with "late" neonatal septicaemia related to factors in the neonatal period.

6.10 Tocolysis

Tocolysis is defined as the suppression of uterine contractions. Medical drugs used by obstetricians to arrest the course of preterm labour are termed tocolytics.

Use of tocolytic drugs has been recorded when the therapy lasted at least 24 hours. Very short lasting courses of therapy were not recorded, because in such cases a distinct prolongation of the pregnancy had not been achieved.

On pharmacological grounds, three major groups of tocolytic drugs were distinguished: beta-mimetics such as ritodrine and phenoterol, prostaglandin synthesis inhibitors such as indomethacin, and a third group comprising all others. The pharmacological groups and the observed frequencies of their use are presented in table 6.10.1.

Table 6.10.1 Tocolytic drugs used during pregnancy

pharmacological group	n	%
beta-mimetics	582	43.5
prostaglandin synthesis inhibitors	49	3.7
others	12	0.9

Fifty-two cases received tocolytic drugs from more than one pharmacological group, e.g. a beta-mimetic drug and a prostaglandin synthesis inhibitor. Tocolytic drug therapy of at least 24 hours duration has been administered to 591 cases (44.2%). These 591 infants emanate from 515 pregnancies: 410 were singleton infants and 181 cases were part of a

multiple pregnancy.

The difference in the percentage of cases with tocolysis in the various birthweight and gestational age categories is remarkable. Tocolysis occurred more frequently in cases with a gestational age of less than 32 weeks: 533 cases (52.8% in that category), whereas there were only 58 cases with a gestational age of more than 32 weeks (17.8% in that category). It should be noted that this latter category comprises many SGA infants (chapter 7.4). A postponement of delivery was often contra-indicated.

In the birthweight categories, the inverse trend was observed. Tocolysis occurred less frequently in infants with a birthweight of less than 1500 g: 445 cases (40.6% in that category) versus 146 cases (60.6%) with a birthweight of more than 1500 g but a gestational age of less than 32 weeks. In tables 6.10.2 and 6.10.3, the distribution of tocolysis is presented according to gestational age and birthweight categories respectively.

Table 6.10.2 Tocolysis in successive gestational age categories

gestational age (weeks)	number of infants	tocolysis	
		n	%
≤23	8	3	37.5
24-25	67	31	46.3
26-27	180	98	54.4
28-29	307	165	53.7
30-31	448	236	52.7
≥32	325	58	17.8
total	1335	591	44.3

In agreement with the above mentioned difference in the distribution of tocolysis over birthweight and gestational age categories is the observation of a lower incidence of small for gestational age infants in cases treated with tocolytics. This phenomenon is illustrated in table 6.10.4.

Table 6.10.3. Tocolysis in successive birthweight categories

birthweight (g)	number of infants	tocolysis n	tocolysis %
<500	5	1	20.0
500-599	14	5	35.7
600-699	33	6	18.2
700-799	51	22	43.1
800-899	88	41	46.6
900-999	101	47	46.5
1000-1099	124	53	42.7
1100-1199	139	43	30.9
1200-1299	161	67	41.6
1300-1399	179	68	38.0
1400-1499	202	92	45.5
≥1500	241	146	60.6
total	1338	591	44.2

Table 6.10.4 Distribution of tocolysis according to "appropriate" and "small" for gestational age

classification	number of infants	tocolysis n	tocolysis %
AGA/LGA	884	477	53.9
SGA	454	114	25.1
total	1338	591	44.1

discussion

Although various therapeutic measures such as bedrest and diets have been employed in attempts to reduce the incidence of preterm delivery, tocolytic drugs are used increasingly to inhibit untimely uterine

activity. In 1983, prostaglandin synthesis inhibitors were not (yet) generally accepted for the treatment of preterm uterine contractions. Beta-mimetics were obviously the drugs of choice since 582 out of 591 cases (98.4%) with tocolysis have been treated with these drugs for a period of at least 24 hours. The low frequency of tocolysis in cases that are small for gestational age suggests careful selection of cases by the obstetricians. Symptoms of placental insufficiency are sometimes considered a contra-indication for the use of tocolysis.

Obviously, none of the presently used beta-mimetics can qualify as the perfect tocolytic agent to arrest preterm labour, as is demonstrated by the number of preterm deliveries that occurred in these gestational age categories in spite of tocolytic treatment. Nevertheless, Falck Larsen et al (1986) and Leveno et al (1986) showed that beta-mimetics can inhibit preterm labour in the initial stage, resulting in a gain of 24 hours to a few weeks in the duration of gestation. Possibly, such (short) gains are important to increase the chances of survival. In any case, the advantage of a short increase in the duration of pregnancy is the possibility of an antepartum transport of the mother to a more specialized hospital with a neonatal intensive care unit or the administration of glucocorticoids to accelerate fetal pulmonary maturation.

6.11 Administration of glucocorticoids

In 190 cases (14.2%), glucocorticoids have been administered to the pregnant mother for the acceleration of fetal pulmonary maturation. This group comprises 131 infants from singleton pregnancies and 59 infants from multiple pregnancies, with a total of 165 mothers.

In accordance with the accepted treatment protocols in the Netherlands, most cases who received glucocorticoid treatment had a gestational age ranging from 26 weeks up to 32 weeks. We found no association between the administration of glucocorticoids and birthweight. The distribution of cases treated with glucocorticoids according to gestational age and birthweight categories is presented in tables 6.11.1 and 6.11.2.

With the exception of 21 singleton pregnancies, all glucocorticoid therapies have been combined with tocolysis. The observed frequencies of combined glucocorticoid- and tocolytic treatment are presented in table 6.11.3.

Table 6.11.1 Use of glucocorticoids according to successive gestational age categories

gestational age (weeks)	number of infants	glucocorticoids n	glucocorticoids %
≤23	8	0	-
24-25	67	5	7.5
26-27	179	34	19.0
28-29	307	54	17.6
30-31	445	80	18.0
≥32	324	17	5.2
total	1330	190	14.3

Table 6.11.2 Use of glucocorticoids according to successive birthweight categories

birthweight (g)	number of infants	glucocorticoids n	glucocorticoids %
<500	5	0	-
500-599	14	1	7.1
600-699	33	4	12.1
700-799	51	8	15.7
800-899	87	17	19.5
900-999	101	13	12.9
1000-1099	123	14	11.4
1100-1199	139	12	8.6
1200-1299	161	20	12.4
1300-1399	178	17	9.5
1400-1499	201	33	16.4
≥1500	240	51	21.2
total	1333	190	14.2

Table 6.11.3 Use of glucocorticoids according to tocolytic treatment

tocolysis	number of infants	glucocorticoids n	glucocorticoids %
beta-mimetics	542	157	29.0
PG-synthesis inhibitors	9	2	22.2
combination	40	10	25.0
no tocolysis	747	21	2.8
total	1338	190	14.2

Surprisingly, 90 out of 190 cases (47.3%) treated with glucocorticoids had a diagnosis of premature rupture of membranes as well. In 47 cases (24.7% of that subgroup), the membranes had ruptured at least 24 hours before the onset of labour, thus establishing a diagnosis of prolonged duration of ruptured membranes. In table 6.11.4 we present the incidence of cases treated with glucocorticoids according to the duration of ruptured membranes.

Table 6.11.4 Distribution of glucocorticoid treated cases according to the duration of ruptured membranes

latent period	number of infants	glucocorticoids n	glucocorticoids %
not ruptured	812	100	12.3
<12 hours	229	34	14.8
12-24 hours	46	7	15.2
1- 7 days	146	28	19.2
> 7 days	91	19	20.9
total	1324	188	14.2

discussion

In 1983, the administration of glucocorticoids for the acceleration of fetal pulmonary maturation was still a matter of debate in the Netherlands. Betamethasone was the almost exclusively used drug for the acceleration of fetal pulmonary maturation. With only few exceptions, all cases received the glucocorticoid treatment in accordance with the protocol described by Schutte (1981). In 1983, use of this therapy was limited to 41 hospitals. One hundred and two cases (53.6%) were patients of 3 university hospitals, the remaining 88 cases (46.3%) were collected from all over the Netherlands. These findings are in agreement with the results from a questionnaire survey conducted by Keirse (1984b) in the Netherlands: 17% of the responding obstetricians routinely used glucocorticoids, 57% occasionally and 26% would never use glucocorticoids.

Several reports (Kubli, 1977; Elliott et al, 1978) cautioned against combined use of glucocorticoids and beta-mimetics, because of the risk of maternal pulmonary oedema. Nevertheless, we found that the majority of cases were treated with both drugs. Maternal complications have not been recorded in this study. However, in the last decade Dutch obstetricians have not reported maternal deaths associated with the combined use of these drugs (Nederlandse Vereniging voor Obstetrie en Gynaecologie, Committee on maternal deaths; personal communication, 1987).

The administration of glucocorticoids to pregnant mothers with ruptured membranes is even more controversial (Simpson & Harbert, 1985; Morales et al, 1986). The number of cases with ruptured membranes, that have been treated with glucocorticoids, is surprisingly high. In chapter 14, we shall analyse the influence of these factors on perinatal outcome variables.

6.12 Hospital admissions

Admissions to hospital during pregnancy for reasons directly related to the index pregnancy are described in this section. Admissions during delivery are described in chapter 8.

Out of 1214 pregnant mothers, 955 (78.6%) experienced one or more admissions to hospital of varying duration. Multiple pregnancies were evenly distributed over mothers who had been admitted to hospital and those who had not. As a result, 1051 infants (78.6%) were born after a pregnancy during which the mother had been hospitalized and 287 (21.4%) infants were born to mothers without hospitalization during pregnancy.

The duration of the mothers' admission to hospital varied greatly, because different medical reasons were involved. For practical reasons the lengths of the hospital admissions have been classified into three groups, presented in table 6.12.1.

Table 6.12.1 Distribution of cases whose mother had been admitted to hospital, according to length of hospitalization.

admission to hospital	n	%
no admission	285	21.3
from 1 up to and including 6 days	508	38.0
1 week or more	543	40.6
not recorded	2	0.1
total	1338	100.0

Pre-existing maternal disease was recorded in 74 out of 1051 cases (7%) with hospitalization.

The cases with a mother who had been admitted to hospital during pregnancy are evenly distributed over the various gestational age- and birthweight categories. Seven hundred and ninety-one out of 1010 cases (78.3%) with a gestational age of less than 32 weeks have a mother who was hospitalized versus 260 out of 325 cases (80.0%) with a gestational age of 32 weeks or more. Eight hundred and sixty out of 1097 cases (78.3%) with a birthweight of less than 1500 g have a mother who had been admitted to hospital versus 191 out of 241 cases (78.2%) with a birthweight of 1500 g or more, but a gestational age of less than 32 weeks. Nevertheless, we observed an increased incidence of SGA infants in the group whose mother had been hospitalized during pregnancy: 376 out of 1051 cases (35.8%) with a hospital admission were SGA versus 78 out of 287 cases (27.2%) without hospitalization during pregnancy.

discussion

The number of mothers who have been admitted to hospital for a pregnancy related reason is surprisingly high (78.6%). In this study, only general information on the mothers' admissions was recorded, but many different medical reasons were involved. In some cases several reasons occurred concurrently, e.g. maternal hypertension and fetal growth retardation. Although the reasons for admission to hospital vary from case to case, in itself admission to hospital may be considered a beneficial factor, favourably influencing the outcome of a pregnancy.

6.13 Electronic monitoring of fetal heart rate

The use of electronic monitoring (CTG) to determine the fetal condition is widespread in modern obstetric practice; many obstetricians consider it the method of choice for surveillance of a high risk pregnancy or delivery.

A normal fetal heart rate pattern ("reactive nonstress test") is defined as a pattern with accelerations of the fetal heart rate equal to or in excess of 15 beats per minute above the baseline for at least 30 seconds and without decelerations. Such patterns are common in the normal term fetus, although occasionally a flat ("non-reactive") tracing may occur depending on rest-activity cycles (low variability episodes of up to 40 minutes duration).

In the course of a pregnancy, considerable changes occur in fetal heart rate patterns. Before 30 weeks of gestation, there is little baseline variability and accelerations are lower in number and amplitudo than at term. Decelerations of short duration ("spikes") may occur quite frequently without associated fetal impairment. Rest-activity cycles are of shorter duration with low variability episodes of up to 30 minutes. With advancing gestational age, the normal pattern emerges.

In this study, cardiotocographic tracings have generally been interpreted by the obstetrician following Fischer's Score (Fischer et al, 1976). Tracings with either late decelerations or a Fischer score of less than 5 have been classified as "abnormal".

In 1039 out of 1338 cases (77.6%), cardiotocographic tracings have been interpreted. In the remaining cases either no cardiotocographic tracings were made or adequate interpretation of the tracing was impossible because the tracing was of too short a duration or low technical quality. In tables 6.13.1 and 6.13.2 we present the recorded number of tracings during pregnancy and delivery respectively.

Table 6.13.1 Number of cases and cardiotocographic tracings during pregnancy

cardiotocographic tracing	n	%
normal tracing	675	50.4
abnormal tracing	364	27.2
not recorded	299	22.4
total	1338	100.0

Table 6.13.2 Number of cases and cardiotocographic tracings during delivery

cardiotocographic tracing	n	%
normal tracing	446	33.3
abnormal tracing	282	21.2
not recorded	610	45.6
total	1338	100.0

Because of the large number of missing cardiotocographic tracings during delivery (partly due to the high number of caesarean sections) and controversy among obstetricians regarding the interpretation of cardiotocographic tracings made during the second stage of labour, we shall confine ourselves to describing the cardiotocographic tracings that were made during pregnancy.

We observed a consistently increasing incidence of cases with cardiotocographic tracings in relation to advancing gestational age. This observation, as well as the classification of the tracings in the various gestational age categories, is presented in table 6.13.3.

Table 6.13.3 Number of cardiotocographic recordings in successive gestational age categories

gestational age (weeks)	number of infants	abnormal CTG		not recorded	
		n	%	n	%
≤23	8	0	-	7	87.5
24-25	67	0	-	34	50.7
26-27	180	26	14.4	63	35.0
28-29	307	51	16.6	70	22.8
30-31	448	110	24.6	91	20.3
≥32	325	177	54.5	32	9.8
total	1335	364	27.3	297	22.2

The high incidence of abnormal cardiotocographic tracings in cases of more than 32 weeks gestation (but very low birthweight) is the more striking since there are very few missing cases in that gestational age category. All of these infants were growth retarded with birthweights under the 10th percentile for their gestational age. The more even distribution of cases with cardiotocographic tracings over the various birthweight categories is presented in table 6.13.4.

Table 6.13.4 Number of cardiotocographic tracings in successive birthweight categories

birthweight (g)	number of infants	abnormal CTG		not recorded	
		n	%	n	%
<500	5	0	-	2	40.0
500-599	14	6	42.9	5	35.7
600-699	33	16	48.5	9	27.3
700-799	51	14	27.5	17	33.3
800-899	88	27	30.7	26	29.5
900-999	101	34	33.7	27	26.7
1000-1099	124	45	36.3	26	21.0
1100-1199	139	49	35.3	24	17.3
1200-1299	161	52	32.3	32	19.9
1300-1399	179	43	24.0	39	21.8
1400-1499	202	50	24.8	38	18.8
≥1500	241	28	11.6	54	22.4
total	1338	364	27.2	299	22.3

As may be expected from the above mentioned data, the incidence of abnormal cardiotocographic tracings is highest in SGA infants. This phenomenon is illustrated in table 6.13.5.

We observed no difference in distribution of normal or abnormal cardiotocographic tracings in relation to maternal age, pre-existing maternal disease, parity, a history of previous preterm birth or recurrent abortions, fetal sex or the occurrence of a congenital malformation in the infant.

Table 6.13.5 Number of cardiotocographic tracings according to "appropriate" or "small" for gestational age

classification	number of infants	abnormal CTG		not recorded	
		n	%	n	%
AGA/LGA	851	112	13.2	231	27.1
SGA	454	249	54.8	50	11.0
total	1305	361	27.7	281	21.5

discussion

During pregnancy, external electronic monitoring of fetal well-being is generally accomplished by means of ultrasound recording of Doppler effects caused by moving structures in the fetal heart and an abdominal tocodynamometer. With modern equipment the recorded tracings are almost as reliable as direct electrocardiography which is only feasible during labour (Keirse et al, 1981b).

Most monitoring criteria relate to the term fetus. Because considerable changes in fetal heart rate patterns occur in the course of pregnancy (Druzin et al, 1985), it is essential to distinguish the various patterns in order to recognize imminent fetal compromise at early gestational ages. However, as in term pregnancies "late decelerations" are among the first and best identifiable changes in the heart rate pattern when the fetal condition progressively deteriorates (Visser, 1984).

In geographically defined studies concerning preterm births, such as the present one, it will never be possible to attain a 100 per cent "coverage" of cases with cardiotocography. In some cases there may not be a (recognized) indication to perform the examination. Some mothers will deliver unexpectedly at home or during transport, and in the hospital other cases may show such alarming symptoms indicating fetal compromise, that immediate delivery is warranted. In such cases, no formal cardiotocographic tracings will be made. Consequently, the information of whether or not a cardiotocographic tracing has been made is in itself important when studying the relation between abnormal cardiotocographic tracings and outcome variables (chapter 14.1.2).

6.14 Fetal presentation at birth

Fetal presentation designates that fetal element which lies over the inlet of the maternal pelvis when labour begins. Fetal position refers to the relationship of a marking point of the presenting part to one of the four quadrants of the pelvis or to the transverse diameter of the maternal pelvis. This latter parameter has not been recorded in distinct categories. In this study we shall confine ourselves to fetal presentation.

The recorded frequencies of various fetal presentations in the POPS-cohort are presented in table 6.14.1.

Table 6.14.1 Frequency of various fetal presentations at birth

fetal presentation	n	%
vertex	921	68.8
breech	329	24.6
transverse	33	2.5
not recorded	55	4.1
total	1338	100.0

It is noteworthy that all 55 cases in which the fetal presentation has not been recorded, were born by caesarean section. Ten of these cases were twins and triplets and 28 were SGA. The 55 cases with unknown fetal presentation will be omitted from the following frequency tables.

In this cohort, the incidence of breech presentation decreases with advancing gestational age (table 6.14.2). Because the incidence of cases with a transverse lie is virtually equal in the successive gestational age categories, cases with a transverse lie are excluded from this table.

The distribution of breech presentation over the successive birthweight categories is presented in table 6.14.3.

Table 6.14.2 Fetal presentation in successive gestational age categories

gestational age (weeks)	number of infants	breech		vertex	
		n	%	n	%
≤23	8	1	12.5	7	87.5
24-25	67	22	32.8	45	67.2
26-27	171	50	29.2	121	70.8
28-29	280	77	27.5	203	72.5
30-31	424	114	26.9	310	73.1
≥32	297	65	21.9	232	78.1
total	1247	329	26.4	918	73.6

Table 6.14.3 Fetal presentation in successive birthweight categories

birthweight (g)	number of infants	breech		vertex	
		n	%	n	%
<500	5	1	20.0	4	80.0
500-599	14	4	28.6	10	71.4
600-699	28	6	21.4	22	78.6
700-799	48	14	29.2	34	70.8
800-899	84	29	34.5	55	65.5
900-999	96	34	35.4	62	64.6
1000-1099	115	34	29.6	81	70.4
1100-1199	135	33	24.4	102	75.6
1200-1299	147	46	31.3	101	68.7
1300-1399	168	41	24.4	127	75.6
1400-1499	184	48	26.1	136	75.9
≥1500	226	39	17.3	187	82.7
total	1250	329	26.3	921	73.7

The incidence of cases classified as SGA (below the 10th percentile of the Amsterdam growth charts; Kloosterman, 1969) is slightly lower in cases with breech presentation: 101 out of 321 cases (31.4%) with breech presentation were SGA, versus 317 out of 896 cases (35.3%) with vertex presentation. The incidence of SGA was lowest in the cases with transverse lie: 8 out of 33 cases (24%).

The incidence of elective delivery is highest in cases with vertex presentation and lowest in cases with a transverse lie. In 231 out of 921 cases (25.1%) with vertex presentation, obstetricians electively terminated the pregnancy, whereas this happened in 68 out of 329 cases (20.7%) with breech presentation and in 6 out of 33 cases (18%) with transverse lie.

The opposite trend has been observed with regard to the mode of delivery. The incidence of caesarean section was lowest in cases with vertex presentation and highest in cases with transverse lie. The distribution of caesarean section according to fetal presentation is presented in table 6.14.4.

Table 6.14.4 Mode of delivery according to fetal presentation

fetal presentation	number of infants	vaginal delivery		caesarean section	
		n	%	n	%
vertex	921	576	62.5	345	37.5
breech	329	186	56.5	143	43.5
transverse	33	10	30.3	23	69.7
total	1283	772	60.2	511	39.8

In 10 cases with transverse lie, vaginal delivery was made possible by changing the presentation of the infant. By means of external or internal version, the presentation of 6 infants was turned into a vertex presentation and in 4 cases the transverse lie was turned into a breech presentation.

As expected, we found a higher incidence of congenital malformations in cases presenting by the breech, than in other fetal presentations. This phenomenon is illustrated in table 6.14.5.

Table 6.14.5 Distribution of infants with a congenital malformation according to fetal presentation

fetal presentation	number of infants	malformation	
		n	%
vertex	921	89	9.7
breech	329	47	14.3
transverse	33	2	6.1
total	1283	138	10.7

discussion

The observed high incidence of breech presentation is in agreement with results found by others. In a cohort of 400 infants born alive with a gestational age of 26-33 weeks, Lamont (1985) found 23% breech presentation. Scheer and Nubar (1976) found a decrease in the incidence of breech presentation with advancing gestational age: from 23% at 28 weeks gestation to 3% at term.

Fetal presentation is one of the strongest determinants influencing clinical management of labour and delivery, since breech presentation has been associated with adverse fetal outcome for a long time (Goldenberg & Nelson, 1977; Karp et al, 1979). Among obstetricians, considerable controversy exists regarding the optimal mode of delivery for preterm infants presenting by the breech. The recorded caesarean section rate (44%) reflects to some extent the conservative tradition of Dutch obstetrics. A study is needed, in which mothers in preterm labour with breech presentation are randomly allocated to elective caesarean section or vaginal delivery.

The observed higher incidence of congenital malformations in (very preterm) infants presenting by the breech confirms the findings of previous studies (Braun et al, 1975; Cox et al, 1982). No information on neurological sequelae in the infants is available as yet. In the follow-up study, special attention will be given to infants born after breech presentation. Perhaps such information will provide an answer to the fundamental question why some infants fail to assume the vertex position and present by the breech (Hytten, 1982).

6.15 Elective delivery

Elective delivery is defined as any delivery following intentional obstetric termination of pregnancy attempted at a time when no symptoms of spontaneous labour are present: e.g. an elective induction of labour or a primary caesarean section at a moment when fetal membranes are still intact and uterine contractions have not yet started.

In the study population, 333 infants (24.9%) were born after an elective delivery. The frequencies and the various kinds of elective delivery are presented in table 6.15.1.

Table 6.15.1 Mode of delivery in elective births

mode of delivery	n	%
induction of labour, vaginal delivery	27	2.0
induction of labour, caesarean section	8	0.6
primary caesarean section	298	22.3
total	333	24.9

Quite as expected, we observed little difference in the distribution of elective deliveries over the various birthweight categories. However, the frequency of elective delivery increased with advancing gestational age (tables 6.15.2 and 6.15.3).

As may be expected from the data mentioned in the tables, we observed a higher incidence of SGA infants in the group born after an elective delivery: 243 out of 333 cases (73.0%) versus 211 out of 1005 cases (21.0%) in which labour had started spontaneously.

Pre-existing maternal disease has been recorded in 47 out of 333 cases (14.1%) with an elective delivery, whereas only 39 out of 1005 cases (3.9%) without an elective delivery had such a medical history. Hypertensive disorders during pregnancy were present in 196 out of 333 cases (58.9%) with an elective delivery, which contrasts sharply with 104 out of 1005 cases (10.3%) without an elective delivery.

The incidence of tocolysis was lower in cases with an elective delivery: 53 out of 333 cases (15.9%) received tocolytic treatment during pregnancy against 538 out of 1005 cases (53.5%) in which labour had started spontaneously. Surprisingly, glucocorticoids were administered less frequently in cases with an elective delivery than in cases with a

spontaneous onset of labour: 26 out of 333 cases (7.8%) versus 164 out of 1000 cases (16.4%) with a spontaneous onset of labour received this treatment to accelerate fetal pulmonary maturation.

Table 6.15.2 Elective deliveries in successive gestational age categories

gestational age (weeks)	number of infants	elective delivery n	elective delivery %
≤23	8	1	12.5
24-25	67	3	4.4
26-27	180	12	6.6
28-29	307	39	12.7
30-31	448	100	22.3
≥32	325	178	54.8
total	1335	333	24.9

Table 6.15.3 Elective deliveries in successive birthweight categories

birthweight (g)	number of infants	elective delivery n	elective delivery %
<500	5	1	20.0
500-599	14	4	28.6
600-699	33	14	42.4
700-799	51	13	25.5
800-899	88	25	28.4
900-999	101	25	24.8
1000-1099	124	31	25.0
1100-1199	139	51	36.7
1200-1299	161	48	29.8
1300-1399	179	51	28.5
1400-1499	202	43	21.3
≥1500	241	27	11.2
total	1338	333	24.9

discussion

Elective termination of a term pregnancy by induction of labour or caesarean section carries a small risk which has been well documented (Visser, 1978; Vierhout & Out, 1983). This risk must be balanced against possible advantages of an elective termination of pregnancy. In the preterm period, this balancing of risks is more elaborate due to additional risks imposed by insufficient maturation of fetal organs. For instance, iatrogenic neonatal respiratory distress syndrome is a serious and, in principle, preventable source of neonatal morbidity (Goldenberg & Nelson, 1975).

The number of elective deliveries in our study population (24.9%) is high considering the criteria for entry into the study. Surprisingly, in only 7.8% of cases born after an elective delivery, the mother had been treated with glucocorticoids during pregnancy in an attempt to accelerate fetal pulmonary maturation.

Potential hazardous conditions, such as hypertensive disorders in pregnancy and fetal growth retardation, have been recorded very frequently in cases born after an elective delivery. The high number of caesarean sections reflects the current obstetric practice in these high risk cases.

6.16 Mode of delivery

Although sometimes the course of labour leaves the obstetrician no choice, the mode of delivery is considered an important determinant of neonatal mortality and morbidity in very preterm or very low birthweight infants.

The frequencies and the various modes of delivery recorded in the POPS-study are presented in table 6.16.1.

In this section, we examine the mode of delivery with regard to other perinatal factors. For practical purposes, all vaginal deliveries have been grouped together, irrespective of the type of delivery, into one category: vaginal delivery (n=772). Similarly, all cases born by caesarean section have been brought together into one group (n=566). The associations between fetal presentation or elective delivery and mode of delivery have been described in chapters 6.14 and 6.15.

We observed no difference in the incidence of caesarean section in relation to the obstetrical history of the mother, her socio-economic class, or maternal smoking. However, the incidence of caesarean section increased with advancing maternal age(table 6.16.2).

Table 6.16.1 Mode of delivery in the POPS-study

mode of delivery	n	%
vaginal delivery:		
spontaneous delivery in vertex presentation	567	42.4
vacuum extraction	7	0.5
forceps delivery	8	0.6
spontaneous breech delivery (Bracht)	155	11.6
breech extraction	28	2.1
podalic version and extraction	7	0.5
subtotal	772	57.7
caesarean section:		
elective (intact membranes, no contractions)	298	22.3
emergency (ruptured membranes, no contractions)	30	2.2
emergency (intact membranes, contractions)	148	11.1
emergency (ruptured membranes, contractions)	90	6.7
subtotal	566	42.3
total	1338	100.0

Table 6.16.2 Mode of delivery according to maternal age

maternal age (years)	number of infants	caesarean section n	caesarean section %
≤19	68	20	29.4
20-35	1181	501	42.3
≥36	56	28	50.0
unknown	33	17	51.5
total	1338	566	42.3

Multiparous cases had a lower incidence of caesarean section than primiparous cases: 249 out of 640 cases (38.9%) with a multiparous mother were born by caesarean section versus 316 out of 694 cases

(45.5%) with a primiparous mother.

The incidence of caesarean section was higher in cases with a mother with pre-existing maternal disease: 58 out of 86 cases (67.4%) with pre-existing maternal disease were delivered by caesarean section versus 508 out of 1252 cases (40.6%) without such a history.

The distribution of cases with a hypertensive mother is remarkably different in cases born by caesarean section when compared to cases born after a vaginal delivery: 255 out of 565 cases (45.1%) born by caesarean section had a hypertensive mother versus 45 out of 772 cases (5.8%) born after a vaginal delivery.

The incidence of multiple pregnancy was lower in cases born by caesarean section: 89 out of 566 cases (15.7%) born by caesarean section were part of a multiple pregnancy, whereas 223 out of 772 cases (28.9%) born after a vaginal delivery were part of a multiple pregnancy.

Cases with prolonged duration of ruptured membranes were more likely to be delivered vaginally: 192 out of 772 cases (24.9%) born after a vaginal delivery experienced an interval of at least 24 hours between rupture of the membranes and delivery versus 48 out of 566 cases (8.5%) born by caesarean section. Associated with this is the higher incidence of chorioamnionitis in cases born after a vaginal delivery: 80 out of 772 cases (10.4%) born after a vaginal delivery had clinical signs of chorioamnionitis versus 20 out of 566 cases (3.6%) born by caesarean section.

In 1039 cases, antepartum cardiotocographic tracings have been made to obtain information on the fetal condition (chapter 6.13). In the remaining 299 cases, cardiotocographic tracings were either absent or have not been interpreted by the obstetricians. The incidence of caesarean section is lowest in the group with missing data on cardiotocography and highest in cases with abnormal antepartum cardiotocographic tracings (table 6.16.3).

Table 6.16.3 Mode of delivery according to antepartum cardiotocography

cardiotocography	number of infants	caesarean section		vaginal delivery	
		n	%	n	%
abnormal tracing	364	320	87.9	44	12.1
normal tracing	675	191	28.3	484	71.7
no tracings	299	55	18.4	244	81.6
total	1338	566	42.3	772	57.7

Although still controversial among obstetricians, during the last decade there has been a tendency to perform caesarean sections at increasingly lower gestational age. In 1983, in one case a caesarean section was performed at a gestational age of 25 weeks. Whilst the overall incidence of caesarean section in the study population is 42.4%, we observed an increasing incidence of caesarean section with advancing gestational age (table 6.16.4).

Table 6.16.4 Mode of delivery according to successive gestational age categories

gestational age (weeks)	number of infants	caesarean section		vaginal delivery	
		n	%	n	%
≤23	8	0	-	8	100.0
24-25	67	1	1.5	66	98.5
26-27	180	32	17.8	148	82.2
28-29	307	106	34.5	201	65.5
30-31	448	182	40.6	266	59.4
≥32	325	244	75.1	81	24.9
total	1335	565	42.3	770	57.7

Although the incidence of caesarean section is more evenly distributed over the various birthweight categories, we observed a slightly higher incidence of caesarean section in successive birthweight categories between 1000 g and 1399 g (table 6.16.5).

As may be expected from the data presented in the tables, the incidence of caesarean section is higher in cases that have been classified as SGA, than in AGA and LGA infants. This phenomenon is illustrated in table 6.16.6.

The incidence of tocolysis was lower in cases born by caesarean section than in cases that were born after a vaginal delivery: 176 out of 566 cases (31.1%) born by caesarean section had been treated with tocolytic drugs versus 415 out of 772 cases (53.8%) that were born by vaginal delivery. The same trend was observed with regard to the administration of glucocorticoids: 64 out of 566 cases (11.3%) born by caesarean section received this treatment against 126 out of 772 cases (16.3%) born vaginally.

Table 6.16.5 Mode of delivery according to successive birthweight categories

birthweight (g)	number of infants	caesarean section n	%	vaginal delivery n	%
<500	5	0	-	5	100.0
500-599	14	5	35.7	9	64.3
600-699	33	19	57.6	14	42.4
700-799	51	17	33.3	34	66.7
800-899	88	34	38.6	54	61.4
900-999	101	41	40.6	60	59.4
1000-1099	124	60	48.4	64	51.6
1100-1199	139	79	56.8	60	43.2
1200-1299	161	77	47.8	84	52.2
1300-1399	179	86	48.0	93	52.0
1400-1499	202	90	44.6	112	55.4
≥1500	241	58	24.1	183	75.9
total	1338	566	42.3	772	57.7

Table 6.16.6 Mode of delivery according to "appropriate" and "small" for gestational age

classification	number of infants	caesarean section n	%	vaginal delivery n	%
AGA/LGA	851	228	26.8	623	73.2
SGA	454	335	73.8	119	26.2
total	1305	563	43.1	742	56.9

Quite as expected, the incidence of caesarean section is higher in cases born after an antepartum maternal transport to a tertiary care centre (chapter 8.4): 132 out of 240 cases (55.0%) that were born after an antepartum maternal transport were born by caesarean section versus 434 out of 1098 cases (39.5%) without such a maternal transport.

In agreement with this is the higher incidence of caesarean section in tertiary care centres. The incidence of caesarean section according to "level of care" (chapter 8.3) is presented in table 6.16.7.

Table 6.16.7 Mode of delivery according to classification of the hospital of birth

level of care	number of infants	caesarean section		vaginal delivery	
		n	%	n	%
level 1	498	176	35.3	322	64.6
level 2	359	164	45.7	195	54.3
level 3	481	226	47.0	255	53.0
total	1338	566	42.3	772	57.7

discussion

When delivery at an early gestational age is either inevitable or necessary, the obstetrician faces the dilemma whether to opt for a caesarean section or to allow a vaginal delivery. The decision is influenced by many considerations and sometimes controversy exists regarding the optimal mode of delivery for very preterm or very low birthweight infants. Stewart (1977) reported that delivery by caesarean section of infants weighing between 500 and 1500 g carries a significantly lower neonatal mortality risk than vaginal delivery, irrespective of whether the fetal presentation is vertex or breech. Because a controlled prospective study has yet to prove his point, most obstetricians do not share his view (Newton et al, 1986; Barrett & Boehm, 1982; Kitchen et al, 1985). They serve the interests of both fetus and mother and strive for a balanced decision. In our study population, the observed percentage of infants, delivered by caesarean section (42.3%) is substantially higher than the 5.6% caesarean births in the general population of the Netherlands in 1983 (Centraal Bureau voor de Statistiek, 1984).

One of the most important factors, influencing the optimal mode of delivery, is fetal presentation. Some considerations regarding this factor are discussed in chapter 6.14. Other important factors are fetal condition and the progress of labour. In this study, we observed a high incidence of maternal hypertension in cases born by caesarean section

(45%). Maternal hypertension is often associated with impaired placental circulation. Abnormal cardiotocographic tracings were followed by a caesarean section in 320 cases (88%).

With an increasing regionalization of perinatal intensive care services and the tendency to arrange an antepartum maternal transport in high risk cases, the perinatal intensive care centres face increasing rates of caesarean section (Huisman et al, 1983). The proper technique at very early gestational ages is, however, still a matter of debate.

6.17 Analgesia during labour

Analgesics and sedatives are systemic drugs which may be administered to produce both a state of analgesia and mood elevation. These drugs usually pass through the placenta freely.

Analgesia is the loss of perception of pain. It may be local, affecting only a small area (perineum) or regional, affecting a larger area (epidural: lower abdomen).

Anaesthesia is the loss of the ability to perceive touch, pain, and other sensations and is commonly associated with total loss of sensation by the use of "general" anaesthesia. Anaesthesia may be considered to be composed of analgesia plus amnesia, and relaxation.

The use of analgesics and/or sedatives has been recorded in 143 cases (10.6%). In 28 of those, more than one drug has been administered. The analgesics and sedatives used are presented in table 6.17.1.

Table 6.17.1 Analgesics and sedatives used during labour

analgesic drug	n	%
pethidine	40	3.0
diazepam	70	5.3
others	61	4.6

Analgesia, achieved by a local infiltration technique applied during labour, has been recorded in 77 cases (5.8%). These cases have all been delivered vaginally.

The use of epidural analgesia has been recorded in 56 cases (4.2%). This technique was used during labour resulting in vaginal delivery in 9 cases, and in caesarean section in 47 cases.

General anaesthesia has been used in 525 cases (39.2%). In 4 cases, general anaesthesia was used in the course of a vaginal delivery and in 521 cases it was used in cases with caesarean section.

In cases with caesarean section, various analgesic techniques have been used. The distribution of analgesic techniques in all 566 cases with caesarean section is presented in table 6.17.2.

Table 6.17.2 Analgesic techniques during caesarean section

analgesic technique	n	%
general anaesthesia	519	91.7
epidural analgesia	45	7.9
both epidural and general anaesthesia	2	0.4
total	566	100.0

discussion

Anaesthesia and/or analgesia are not routinely administered during labour and delivery in the Netherlands. A longtime tradition of natural childbirth influences obstetric practice.

As a high risk population in obstetrics, the study population experienced a great many interventions and the more frequent use of pain-relieving techniques is accordingly. Although general anaesthesia is known to exert a stronger depressing effect on the neonate, this technique has been used in 92% of the caesarean sections. Unfortunately, not all hospitals have an anaesthesiologist available who is specially trained in obstetric anaesthesia.

The use of the sedative diazepam (70 cases, 5.3%) appeared more widely spread than we expected in view of the well-known side-effects to the newborn. The drug crosses the placenta, and its active metabolite desmethyldiazepam is only slowly metabolized by neonates. The maternal use of diazepam is associated with neonatal respiratory depression, hypotonia, reluctance to feed (Cree et al, 1973), and hyperbilirubinaemia (Rosanelli, 1970).

6.18 Summary

To facilitate an easy review of the obstetrical factors, we present in table 6.18.1 the distribution over the various subpopulations.

Table 6.18.1 Distribution of obstetrical data (pregnancies and deliveries) over various subpopulations (numbers adjusted to the infants)

chapter	obstetrical data	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
								
		n %	n %	n %	n %	n %	n %	n %
6.2	diabetes mellitus	59 (4.4)	47 (4.7)	12 (3.6)	53 (4.8)	6 (2.5)	40 (4.5)	19 (4.2)
6.3	bloodgroup incompatibility	4 (0.3)	3 (0.3)	1 (0.3)	2 (0.2)	2 (0.8)	3 (0.3)	1 (0.2)
6.4	maternal hypertensive disorders	300 (22.4)	139 (13.8)	161 (49.5)	289 (26.3)	11 (4.6)	81 (9.5)	217 (47.8)
6.5	smoking during pregnancy	387 (28.9)	267 (26.4)	119 (36.6)	329 (30.0)	58 (24.1)	227 (26.7)	155 (34.1)
6.6	other intoxications	17 (1.2)	8 (0.8)	9 (2.7)	16 (1.4)	1 (0.4)	9 (1.0)	8 (1.8)
6.7	medication and intoxication during pregnancy	668 (49.9)	474 (46.9)	193 (59.4)	563 (51.3)	105 (43.6)	395 (46.4)	265 (58.4)
6.8	premature rupture of membranes	517 (38.6)	453 (44.8)	64 (19.6)	401 (36.6)	116 (48.1)	429 (48.5)	88 (19.4)
6.9	prolonged duration of ruptured membranes	240 (17.9)	226 (22.4)	14 (4.3)	180 (16.4)	60 (24.9)	207 (24.3)	29 (6.4)
6.9	chorioamnionitis	100 (7.3)	96 (9.5)	4 (1.2)	75 (6.8)	25 (10.4)	89 (10.5)	10 (2.2)

Table 6.18.1 (continued)

chapter	total	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
								
		n %	n %	n %	n %	n %	n %	n %
6.10	tocolysis	591 (44.2)	533 (52.8)	58 (17.8)	445 (40.6)	146 (60.6)	469 (55.1)	114 (25.1)
6.11	glucocorticoid administration	190 (14.2)	173 (17.1)	17 (5.2)	139 (12.7)	51 (21.2)	151 (17.8)	38 (8.4)
6.12	hospital admission	1051 (78.6)	791 (78.3)	260 (80.0)	860 (78.4)	191 (79.3)	651 (76.5)	376 (82.2)
6.13	electronic monitoring:							
	abnormal CTG	365 (27.2)	187 (18.5)	177 (54.5)	336 (30.6)	28 (11.6)	112 (13.2)	249 (54.8)
	none	299 (22.3)	265 (26.2)	32 (9.8)	245 (22.3)	54 (22.4)	231 (27.1)	50 (11.1)
6.14	fetal presentation (breech)	362 (27.1)	293 (29.0)	69 (21.2)	314 (28.6)	48 (19.9)	245 (28.8)	109 (24.1)
6.15	elective delivery	333 (24.9)	155 (15.3)	178 (54.8)	306 (27.8)	27 (11.2)	85 (10.0)	243 (53.5)
6.16	mode of delivery (C.S.)	566 (42.3)	321 (31.8)	244 (75.1)	508 (46.3)	58 (24.1)	228 (25.8)	335 (73.8)
6.17	general anaesthesia during labour	525 (39.4)	306 (30.4)	218 (67.2)	472 (43.1)	53 (22.0)	220 (24.9)	305 (67.2)

Chapter 7 Study infants

7.1. Introduction

In this chapter, we discuss data on the study infants as observed immediately after birth. Data on the mortality, causes of death, and morbidity of the study infants in the neonatal period will be presented in chapters 10, 11, and 12 respectively.

As in chapter 6, the data will pertain to the cohort as a whole. Whenever appropriate, the data will be presented separately for infants from a multiple pregnancy, very preterm infants (less than 32 gestational weeks), and very low birthweight infants (less than 1500 g birthweight).

As in other chapters in Part 2 of this thesis, the data will be presented by means of descriptive statistics only. All variables discussed in this chapter will be included in the logistic regression analyses which are described in chapters 14 and 15.

7.2.1 Gestational age

Gestational age is defined by the World Health Organization (WHO, 1976) and the International Federation of Gynaecology and Obstetrics (FIGO, 1977) as the duration of gestation as measured from the first day of the last normal menstrual period. Gestational age is expressed in completed weeks, e.g. events occurring between 280 and less than 287 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation.

However, inflexible employment of this definition may give rise to obvious nonsense such as the reporting by Hoffman (1974) of birthweights higher than 1000 g at less than 20 gestational weeks, and gestations up to 56 weeks (Guinness book of records, 1975). Evidently, clinical

issues like irregular menstrual cycles, use of oral contraceptives or uncertainty about the date of the last menstrual period may cause considerable differences between the calculated gestational age and the actual time that elapsed between ovulation and delivery increased by two weeks. Employment of one single other parameter like ultrasound examination or Dubowitz scores is illogical since each of these criteria has its own problems (Hall, 1985).

For epidemiological research it is far better to use as much information as possible to determine the gestational age while adhering to the principle that corroborated evidence takes precedence over uncorroborated evidence.

In our study, data were recorded on last menstrual period, best obstetric estimate of gestational age, degree of reliability of this estimate and paediatric maturity score (table 4.4.1). In the Netherlands the Dubowitz score (Dubowitz et al, 1970) is the most widely used scoring system for assessing the gestational age after birth, although the systems of Ballard (Ballard et al, 1979) and Finnström (Finnström, 1977) are used occasionally as well.

In all but 3 cases a "best obstetric estimate of gestational age" was available. This best obstetric estimate was usually based upon irrefutable menstrual dates, but in a substantial minority upon other evidence as well. The certainty of this estimate was classified by the obstetrician as "certain", "questionable" or "unreliable".

In 1037 cases (77.7%) the obstetrician classified the reliability of the estimated gestational age as certain. In 462 of these infants no paediatric score was recorded because there was obvious agreement between the infant's appearance and the estimated gestational age. In the other 575 cases with a certain gestational age, a paediatric maturity score was performed. In 41 cases, the paediatric estimate differed more than two weeks from the obstetric estimate, resulting in a discordance of 3.9% in all cases in which the obstetric estimate of the gestational age was considered certain. This percentage is well within the variability of the paediatric scoring systems (Spinnato et al, 1984).

All cases with a gestational age classified as "questionable" or "unreliable", were grouped together. In these 298 cases, a paediatric maturity score was performed 210 times. In this group we found a discordance of more than two weeks in 37 cases (17.6%). Assuming a similar percentage of discordance in the 88 uncertain cases without a maturity score, we have to consider a maximum number of 52 infants (3.9%) that may have been misclassified. However, in view of the variability of the paediatric scoring systems, it is highly probable that the number of misclassified infants is lower. We therefore decided to use throughout this thesis, the "best clinical estimate of gestational age" as provided by the obstetrician.

The lowest gestational age that was recorded in the study population was 22 weeks + 2 days. The highest gestational age of an infant born in 1983 with a birthweight below 1500 g was 40 weeks + 5 days. The median gestational age of the study population was 30 weeks + 2 days. The number of study infants in successive gestational age categories is presented in table 7.2.1

Table 7.2.1 Number of study infants in successive gestational age categories

gestational age (weeks)	n	%
22 weeks	3	0.2
23 weeks	5	0.4
24 weeks	19	1.4
25 weeks	48	3.6
26 weeks	77	5.8
27 weeks	103	7.7
28 weeks	136	10.2
29 weeks	171	12.8
30 weeks	204	15.2
31 weeks	244	18.2
32 weeks	94	7.0
33 weeks	80	6.0
34 weeks	52	3.9
35 weeks	52	3.9
36 weeks	20	1.5
37 weeks	16	1.2
38 weeks	8	0.6
39 weeks	2	0.1
40 weeks	1	0.1
unknown	3	0.2
total	1338	100.0

The decrease in number of infants with a gestational age of 32 weeks or more is caused by the entry criteria of the study (chapter 3.2). In figure 7.2.1 this phenomenon and the numbers mentioned in table 7.2.1 are illustrated.

discussion

Accurate determination of gestational age is fundamental to modern perinatal care. However, in spite of a high level of education in Europe, as many as 20% of pregnant women lack accurate menstrual data (Hall et al, 1985). In our study population, 14% of cases lacked exact menstrual dates. Ultrasound dating in these situations has greatly improved the accuracy of the "best obstetric estimate of gestational age". This technique and the high frequency of antenatal visits in the Netherlands have rendered the number of pregnancies with unknown gestational age very small. Consequently, in our study population the number of cases in which the gestational age could not be estimated by the obstetrician was very low (3 cases). The number of cases with a disputable duration of gestation amounted to less than 52 cases.

Figure 7.2.1 Distribution of study infants over various gestational age categories

7.2.2 Incidence of very preterm birth

In 1983 in the Netherlands the Centraal Bureau voor de Statistiek registered a total of 170,246 liveborn infants (CBS, 1985b). As described in table 7.2.1, in the study population 1010 infants were born alive after a gestational age of less than 32 weeks. In 1983 another 58 of such infants were born alive in non participating hospitals in the Netherlands (chapter 9.2). Consequently, the total number of liveborn very preterm infants in 1983 in the Netherlands was: 1068.

The observed incidence of very preterm liveborn infants in the Netherlands in 1983 is 1068 / 170,246 = 0.63%.

discussion

The observed incidence of 0.63% liveborn, very preterm infants in 1983 in the Netherlands is in agreement with reports from Norway: 0.63% (Bjerkedal et al, 1973) and the United Kingdom: 0.8% (Alberman, 1977). However, in the United States of America in 1983 64,593 out of 3,611,316 infants were born alive with a gestational age of less than 32 weeks, resulting in an incidence of very preterm birth in the USA of 1,78% (National Center for Health Statistics, 1983). Further study is needed to investigate such discrepancies.

7.3.1 Birthweight

Birthweight is the first weight of the infant obtained after birth and is expressed in grams. In most cases this weight was measured directly after the birth of the infant. However, in some cases the infant's condition warranted such expeditious treatment that weighing had to be postponed to a later hour. Nevertheless, these delays were too short for postnatal weight loss to occur.

In all 1338 cases, birthweight has been recorded. The lowest recorded birthweight of a liveborn infant in 1983 was 420 g. In the study population, the highest recorded birthweight of an infant born after less than 32 gestational weeks is 2780 g (fetal hydrops). The median birthweight of the study population is 1250 g.

To facilitate analysis of the cohort, birthweight has been stratified in 100 g categories. In accordance with the recommendations of the World Health Organisation (WHO, 1977) the limits of singular strata were chosen in the following way:

from 400 up to and including 499 g,
from 500 up to and including 599 g,
from 600 up to and including 699 g, etc.

The number of study infants in successive 100 g birthweight categories is presented in table 7.3.1 and figure 7.3.1. The decrease in the number of infants weighing 1500 g or more is caused by the entry criteria of the study (chapter 3.2).

Table 7.3.1 Number of infants in successive birthweight categories

birthweight (g)	n	%
400-499	5	0.4
500-599	14	1.0
600-699	33	2.5
700-799	51	3.8
800-899	88	6.6
900-999	101	7.5
1000-1099	124	9.3
1100-1199	139	10.4
1200-1299	161	12.0
1300-1399	179	13.4
1400-1499	202	15.1
1500-1599	74	5.5
1600-1699	57	4.3
1700-1799	52	3.9
1800-1899	27	2.0
1900-1999	16	1.1
2000-2099	4	0.3
2100-2199	3	0.2
2200-2299	3	0.2
2300-2399	1	0.1
2400-2499	2	0.1
2500-2599	1	0.1
2600-2699	-	-
2700-2799	1	0.1
total	1338	100.0

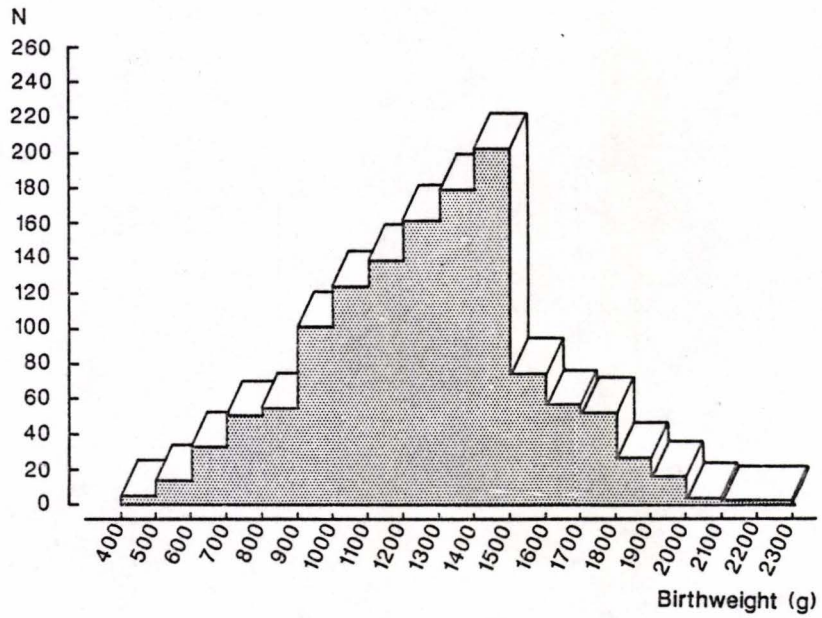
7.3.2 Incidence of very low birthweight

As depicted in table 7.3.1, 1097 infants of the study population had a birthweight of up to and including 1499 g. In 1983, another 67 infants

with a birthweight of less than 1500 g were born alive in non-participating hospitals in the Netherlands (chapter 9.2). The addition of these two numbers results in the total number of liveborn very low birthweight infants in 1983 in the Netherlands: 1164.

The observed incidence of very low birthweight, liveborn infants in the Netherlands in 1983 is 1164/170,246= 0.68%.

Figure 7.3.1 Distribution of infants over successive birthweight categories (5 infants with a birthweight >2300 g omitted)



discussion

This is the first time that national data on the incidence of very low birthweight have become available (chapter 1.5). Until now, only an estimate was available (Gezondheidsraad, 1983). To monitor changes over time in the incidence of very low birthweight, it is necessary to have a permanent national registration of birthweight (and gestational age) of liveborn infants in the Netherlands.

The observed incidence of 0.68% very low birthweight infants in 1983 in the Netherlands compares well with the reports from England: 0.7% (Mutch et al, 1981) and Sweden: 0.6% (Wallace & Goldstein, 1975).

7.4 Small for gestational age

Following the Amsterdam growth charts (Kloosterman, 1969), all study infants have been classified either as appropriate/large for gestational age (AGA/LGA) or as small for gestational age (SGA). SGA was defined as a birthweight below the 10th percentile for gestational age.

As mentioned in chapter 1.4, the Amsterdam growth charts start at 25 gestational weeks and therefore 27 infants could not be classified. Another 8 infants have not been classified because of missing information about sex (n=5) or gestational age (n=3). The classification of weight for gestational age is shown in table 7.4.1.

Table 7.4.1 Classification of weight for gestational age according to the Amsterdam growth charts

classification	infants	
	n	%
AGA/LGA	851	63.6
SGA	454	33.9
not classified	33	2.5
total	1338	100.0

Because of the entry criteria of the study, SGA cases were unevenly distributed over various subpopulations. This phenomenon is illustrated in table 7.4.2 for gestational age categories and in table 7.4.3 for birthweight categories.

discussion

The (large) number of SGA infants in the study population was an unexpected finding. In the subpopulation of infants with a birthweight below 1500 g, the percentage of SGA attained 41.3%. Yu et al (1982) found 11% SGA in a birthweight defined population of infants weighing 501-1500 g. To some extent this difference might be attributed to the entry criteria of the POPS-study.

However, in the subpopulation of infants with a gestational age of less than 32 weeks, the observed percentage SGA: 16.9%, is well in excess of the expected 10% (defined by the Amsterdam growth charts).

Table 7.4.2 SGA in successive gestational age categories

gestational age (weeks)	number of infants	SGA n	SGA %
≤23	8	0	-
24-25	67	0	-
26-27	180	25	13.9
28-29	307	51	16.6
30-31	448	95	21.2
≥32	325	282	86.8
total	1335	454	33.9

There are several possible explanations for the high percentage of SGA infants in the POPS-population.

Firstly, intensive perinatal surveillance techniques nowadays enable

Table 7.4.3 SGA in successive birthweight categories

birthweight (g)	number of infants	SGA n	SGA %
<500	5	0	-
500-599	14	7	50.0
600-699	33	23	69.7
700-799	51	21	41.2
800-899	88	47	53.4
900-999	101	49	48.5
1000-1099	124	46	37.1
1100-1199	139	65	46.8
1200-1299	161	60	37.3
1300-1399	179	62	34.6
1400-1499	202	74	36.6
≥1500	241	0	-
total	1338	454	33.9

the obstetrician to detect a jeopardized fetus accurately. This has led to an increased number of obstetrical interventions during the last decades. Consequently, the study population may indeed comprise more liveborn growth retarded infants than would have been possible at the time of the Amsterdam growth charts. If this holds true, the standards are still a useful measure, indicating a pathological condition occurring at a specific gestational age.

Secondly, because the Amsterdam growth charts have been constructed with only small numbers of infants in the lower gestational age categories, extrapolation of the curves at the lower end may have caused artifacts. In that case, the charts should be revised according to the present data.

Thirdly, in the course of time the median birthweight for gestational age may have changed. However, in the general population no changes in birthweight distribution have occurred between 1965 and 1980 (Roede & van Wieringen, 1985).

At present, there is insufficient evidence to consider the latter explanations as plausible ones. Therefore, we used the Amsterdam growth charts for the classification of all infants. However, further study of the present data is warranted, preferably using different methods of classification of weight for gestational age (FIGO, 1986).

7.5 Infants' sex

Sex was established by examination of the infant's external genital organs. Sex could be determined unequivocally in all but 5 infants. Four of these 5 infants were born after a very short gestation and died immediately after birth. In one infant additional examinations were necessary to establish its sex.

Of the 1333 cases with unequivocally determined sex, 698 infants (52.4%) were male and 635 infants (47.6%) were female. The sex ratio, i.e. the number of males per 100 females, was 109.9.

In cases with a gestational age of less than 32 weeks, the overall sex ratio was 119.1, whereas in cases with a longer gestation (but with a birthweight below 1500 g), the overall sex ratio was 86.1.

In table 7.5.1 we present the distribution of sex ratios over successive gestational age categories.

The distribution of male and female infants and the calculated sex ratios in successive birthweight categories are presented in table 7.5.2. The sex ratio in cases with a birthweight of 1500 g or more is remarkably higher (167.7) than in other birthweight categories.

As described in chapter 7.4, the infants were classified either as "appropriate/large" or as "small" for gestational age following the Amsterdam growth charts (Kloosterman, 1969). Two hundred and forty-five

Table 7.5.1 Sex ratio in successive gestational age categories

gestational age (weeks)	infants n	male n	female n	sex ratio
≤ 23	8	4	4	100.0
24 - 25	66	36	30	120.0
26 - 27	179	98	81	120.9
28 - 29	307	172	135	127.4
30 - 31	448	239	209	114.3
≥ 32	322	149	173	86.1
total	1330	698	632	109.9

Table 7.5.2 Sex ratio in successive birthweight categories

birthweight (g)	infants n	male n	female n	sex ratio
<500	4	1	3	33.3
500-599	14	5	9	55.5
600-699	33	16	17	94.1
700-799	50	25	25	100.0
800-899	88	41	47	87.2
900-999	100	54	46	117.3
1000-1099	124	52	72	72.2
1100-1199	139	71	68	104.4
1200-1299	160	84	76	110.5
1300-1399	179	88	91	96.7
1400-1499	201	110	91	120.9
≥1500	241	151	90	167.7
total	1333	698	635	109.9

out of 698 boys (35.1%) appeared small for gestational age, whereas 209 out of 635 girls (32.9%) had a birthweight below the 10th percentile. In small for gestational age infants the sex ratio was 117.2 (245 boys versus 209 girls).

discussion

Hytten and Leitch (1971) showed that the sex ratio changes throughout pregnancy. They demonstrated that approximately equal numbers of females and males are conceived. But after a marked excess of females among early, spontaneous abortions, there are about 120 male fetuses for every 100 females by the end of the first trimester. Excess male representation in second trimester deliveries and stillbirths reduces the sex ratio in infants born at term to 105-107 in most European populations.

The data from the POPS-study support Hytten's view. In the younger gestational age categories, we observed a high sex ratio of 120. The overall sex ratio in the POPS-cohort (109.9) proved to be slightly higher than in the total population in 1983 (104.6). In the Netherlands a total of 83,209 girls and 87,037 boys were registered as born alive in 1983 (Centraal Bureau voor de Statistiek, 1985b).

We have no data on stillbirths and consequently we cannot provide a sex ratio for stillborn, very preterm infants in the Netherlands. Only after the implementation of a national registry into which obstetrical data relating to all pregnancies and deliveries are entered, relevant information will be available.

In the Aberdeen City district, Hall and Carr-Hill (1982) found a higher sex ratio in very preterm infants. In 165 liveborn infants with a gestational age of 32 weeks or less, born between 1961 and 1979, the sex ratio was 146.3. Such higher sex ratios in very preterm infants have also been recorded in the National Medical Birth Registry of Norway. In 1967-1968, 411 boys and 273 girls were born alive after a gestation of 28.0 to 31.9 weeks, resulting in a sex ratio of 150.5 (Bjerkedal et al, 1973).

7.6 Apgar score

The study protocol (appendix A, item 39), offered the possibility to record the Apgar score (Apgar, 1953) at 1 minute, 3 minutes, 5 minutes and 10 minutes after birth. In most cases, the paediatrician recorded the Apgar scores at 1 and 5 minutes, or at 3 and 5 minutes. The score at 10 minutes was chiefly used if prior values of the Apgar score were low or missing.

The Apgar score at 5 minutes after birth is generally considered a measure of intrapartum asfyxia and (or) neonatal depression (Silverman

et al, 1985). In the POPS-study, the Apgar score at 5 minutes was recorded for 1157 cases. Of these, 919 (79.4%) had a value of 7 or more ("high" Apgar score), and the other 238 (20.6%) had a value of less than 7 ("low" Apgar score). The 181 cases for which no Apgar score at 5 minutes after birth was recorded, have been assigned a value based on the available information. Thus, cases with an Apgar score of 7 or more at 1 or 3 minutes after birth as well as at 10 minutes after birth, were classified as "high" Apgar score (52 cases). Cases with an Apgar score at 1 or 3 minutes after birth of 4 or less, and with all other values missing or less than 6, were classified as "low" Apgar score (9 cases). Infants with an Apgar score of 6 or less at 10 minutes after birth without previous "high" values, were also classified as "low" Apgar score (4 cases). Thus, a total of 1222 infants could be classified (table 7.6.1).

Table 7.6.1 Apgar score

Apgar score	n	%
high ($\geq$7)	971	72.6
low (<7)	251	18.8
unknown	116	8.7

We observed a consistently decreasing percentage of low Apgar scores in relation to advancing gestational age (table 7.6.2).

discussion

In addition to the Apgar score, the study protocol permitted the recording of other measures of intrapartum asphyxia representing the neonatal acid-base status: pH and PCO_2 in arterial or venous umbilical cord blood samples, or in a capillary sample taken within 30 minutes after birth (appendix A, items 40-42). Unfortunately, these values were missing in the majority of cases, rendering these data useless.

Although the relationship between the Apgar score and ultimate outcome (mortality and neurological morbidity) is much questioned (Silverman et al, 1985), the Apgar score is still the best recorded measure of the infant's well-being immediately after birth. Measures, such as the acid-base status are not (yet) feasible in a national study involving all levels of care.

Table 7.6.2 Apgar score in successive gestational age categories

gestational age (weeks)	number of infants	low Apgar score		not recorded	
		n	%	n	%
≤23	8	5	62.5	2	25.0
24-25	67	36	53.7	13	19.4
26-27	180	59	32.8	24	13.3
28-29	307	60	19.5	32	10.4
30-31	448	64	14.3	26	5.8
≥32	325	29	8.9	17	5.2
total	1335	251	18.8	114	8.5

The more even distribution of cases with low Apgar scores over various birthweight categories is presented in table 7.6.3.

Table 7.6.3 Apgar score in successive birthweight categories

birthweight (g)	number of infants	low Apgar score		not recorded	
		n	%	n	%
<500	5	1	20.0	4	80.0
500-599	14	4	28.6	4	28.6
600-699	33	13	39.4	2	6.1
700-799	51	17	33.3	8	15.7
800-899	88	33	37.5	8	9.1
900-999	101	27	26.7	6	5.9
1000-1099	124	22	17.7	16	12.9
1100-1199	139	16	11.5	13	9.4
1200-1299	161	31	19.5	17	10.6
1300-1399	179	23	12.8	15	8.4
1400-1499	202	26	12.9	12	5.9
≥1500	241	38	15.8	11	4.6
total	1338	251	18.8	116	8.7

There are several possible explanations as to why the Apgar score has not been recorded in all cases. For infants who appear to be in prime condition after birth, meticulous recording of the Apgar score is sometimes omitted. Some infants require such expeditious intensive treatment immediately after birth, that the paediatrician postpones establishing the Apgar score. Thirdly, infants that are born extremely asphyxiated, may die within minutes after birth without being resuscitated or scored.

The percentage of cases with a low Apgar score decreased with advancing gestational age. Partly, this reflects the advancing maturity of the nervous system, accompanied by increasing muscle tone and reflex irritability. However, neurological immaturity of the infant may influence the Apgar score only to some degree. In most cases a low Apgar score indeed reflects the infant's clinical condition immediately after birth. As such, it will be included in the analyses in chapters 14 and 15.

7.7 Congenital malformations

Congenital malformations were recorded in 146 cases, according to a classification by organ system(s) involved (appendix A). All malformations, diagnosed during the hospital admission, were recorded.

The incidence of congenital malformations appeared to be similar in successive gestational age categories (table 7.7.1) and in successive birthweight categories (table 7.7.2).

Table 7.7.1 Congenital malformations in successive gestational age categories

gestational age (weeks)	number of infants	congenital malformations n	%
≤23	8	1	12.5
24-25	67	4	6.0
26-27	180	15	8.3
28-29	307	31	10.1
30-31	448	45	10.0
≥32	325	49	15.1
total	1335	145	10.9

Table 7.7.2 Congenital malformations in successive birthweight categories

birthweight (g)	number of infants	congenital malformations n	%
<500	5	1	20.0
500-599	14	0	-
600-699	33	5	15.2
700-799	51	10	19.6
800-899	88	10	11.4
900-999	101	10	9.9
1000-1099	124	15	12.1
1100-1199	139	15	10.8
1200-1299	161	21	13.0
1300-1399	179	20	11.2
1400-1499	202	19	9.4
≥1500	241	20	8.3
total	1338	146	10.9

discussion

Due to the criteria for inclusion into the study, the subpopulation of infants with a gestational age of 32 weeks or more but a birthweight of less than 1500 g, shows a higher incidence of congenital malformations (15.1%). This finding is in agreement with other reports associating congenital malformations and low birthweight (Perkins, 1981).

A relatively high percentage of infants with congenital malformations were cases with breech or transverse presentation (49 out of 146, 33.6%) compared to non-malformed infants (313 out of 1192, 26.3%) (chapter 6.14).

Congenital malformations are one of the main causes of mortality and morbidity in the neonatal period. Therefore, these disorders will be discussed in more detail in chapters 11 and 12.

7.8 Infants of multiple pregnancy

In the study population, 312 infants were born as part of a multiple pregnancy, as specified in table 7.8.1.

Table 7.8.1 Infants of multiple pregnancy

multiple pregnancy		infants n	infants %
twins,	complete sets	214	68.6
	first only	26	8.3
	second only	37	11.9
triplets,	complete sets	21	6.7
	incomplete	13	4.2
quadruplet		1	0.3
total		312	100.0

Gestational age was calculated in days for each infant. The median gestational age of infants of multiple pregnancy was 29 weeks and one day (range: 22-39 weeks). This is 8 days less than that of singleton pregnancies: 30 weeks and 2 days. The distribution of infants born as part of a multiple pregnancy, over successive gestational age categories is presented in table 7.8.2. The median birthweight of infants of multiple pregnancies was the same as in singleton pregnancies: 1250 g. The distribution of infants, born as part of a multiple pregnancy, over successive birthweight categories is presented in table 7.8.3.

Table 7.8.2 Multiple births in successive gestational age categories

gestational age (weeks)	number of infants	multiple births n	multiple births %
≤23	8	4	50.0
24-25	67	17	25.4
26-27	180	46	25.5
28-29	307	83	27.0
30-31	448	113	25.2
≥32	325	48	14.8
total	1335	311	23.3

Table 7.8.3 Multiple births in successive birthweight categories

birthweight (g)	number of infants	multiple births n	%
< 500	5	1	20.0
500- 599	14	5	35.7
600- 699	33	5	15.2
700- 799	51	12	23.2
800- 899	88	22	25.0
900- 999	101	22	21.8
1000-1099	124	26	21.0
1100-1199	139	29	20.9
1200-1299	161	48	29.8
1300-1399	179	39	21.8
1400-1499	202	45	22.3
≥1500	241	58	24.1
total	1338	312	23.3

As may be expected from the data presented in the tables above, the percentage of SGA was lower in infants born as part of a multiple pregnancy: 22.8% (71 out of 312) than in singleton infants: 37.3% (383 out of 1026).

We observed an uneven distribution of fetal presentation over cases born as part of a multiple pregnancy as compared to singletons. Of the infants born out of a multiple pregnancy, 117 (37.5%) presented by the breech versus 245 out of 1026 singleton infants (23.9%). Curiously, the caesarean section rate was much lower: 89 out of 312 (28.5%) in multiple births as opposed to 477 out 1026 (46.5%) in singletons.

discussion

Because of the entry criteria of the POPS study, a number of multiple births have not been included into the study as a complete set. Either one of the infants was stillborn or was not entered into the study because of a birthweight over 1500 g.

An unexpected finding is the lower median gestational age of the subpopulation of multiple births, while the median birthweights were equal. This observation and the uneven distribution of other perinatal factors adversely affecting the pregnancy, (e.g. maternal hypertensive

disorders 26.2% in singletons and 9.9% in multiple births) suggests that the subpopulation of multiple births differs substantially from the singleton infants. Therefore, we include the factor multiple pregnancy in the logistic regression analyses in chapters 14 and 15.

7.9 Summary

In the previous sections of this chapter, data on the study infants have been discussed as observed immediately after birth. To facilitate an easy review, we present the distribution of these factors over various subpopulations in table 7.9.1.

Table 7.9.1 Distribution of data on study infants over various subpopulations

chapter	data on infants	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
								
		n %	n %	n %	n %	n %	n %	n %
7.2	sex (male)	698 (52.2)	549 (54.4)	149 (45.8)	547 (49.9)	151 (62.7)	442 (51.9)	245 (54.0)
7.5	SGA (<10th percentile)	454 (33.9)	171 (16.9)	282 (86.8)	454 (41.3)	0	0	454 (100)
7.6	Apgar score 5 min (<7)	251 (18.8)	222 (22.0)	29 (8.9)	213 (19.4)	38 (15.8)	175 (20.6)	59 (13.0)
7.7	congenital malformation	146 (10.9)	96 (9.5)	49 (15.1)	126 (11.5)	20 (8.3)	77 (9.0)	63 (13.9)
7.8	multiple pregnancy	312 (23.3)	263 (26.0)	48 (14.8)	254 (23.2)	58 (24.1)	232 (27.3)	71 (15.6)

Chapter 8 Place of birth and transport

8.1 Introduction

Although we originally intended to limit our study to the 8 neonatal intensive care units of the 8 university hospitals (tertiary care) and a representative sample of general hospitals, many paediatricians were willing to participate in the study so that a truly nationwide survey could be accomplished.

8.2 Hospitals

On January 1st, 1983 the "Nationaal Ziekenhuis Instituut" (National Hospital Institute) recognized 224 hospitals in the Netherlands as approved "institutions for intramural health care". The list comprises the following categories:

- university hospitals	8
- specialized hospitals[1]	48
- general hospitals	168
- total	224

All of the 8 university hospitals have a department of obstetrics, paediatrics and a neonatal intensive care unit. In 1983 10,132 women

[1] A specialized hospital provides only one kind of health care: e.g. maternity clinic; children's hospital; physical rehabilitation clinic; psychiatric hospital

were delivered in this group of hospitals (9.2% of all hospital deliveries in the Netherlands). All university hospitals cooperated in the POPS-study.

Only 3 specialized hospitals practised obstetrics in 1983. In this category 3194 deliveries took place (2.9% of all hospital deliveries in the Netherlands). Another 3 specialized hospitals are paediatric hospitals providing care for newborn infants born elsewhere. All six specialized hospitals cooperated in the POPS-study.

In 4 general hospitals there is no department of obstetrics nor labour ward. In those hospitals no babies were born in 1983. The remaining 164 general hospitals took care of 96,314 deliveries (87.8% of all hospital deliveries in the Netherlands). Because of existing obstetric referral arrangements, or accidentally, in 26 (smaller) general hospitals in 1983 no infants were born alive with a gestational age of less than 32 weeks and /or a birthweight of less than 1500 g. These hospitals were excluded from the study.

Only 14 general hospitals were unable to cooperate in the POPS-study. In these 14 hospitals, 85 infants were born in 1983 who met the criteria for inclusion in POPS.

The remaining 124 general hospitals cooperated wholeheartedly throughout the study period. Thus, a total of 138 hospitals participated in the study (appendix H). The distribution of these hospitals is shown in figure 8.2.1.

8.3 Levels of care

The level of care provided in these 138 hospitals varied from very sophisticated perinatal intensive care to basic obstetric care without special facilities for very preterm or very low birthweight infants. To allow adequate evaluation of results of perinatal care we felt the need to classify the participating hospitals according to level of care. The existing systems of hospital classification (Nationaal Ziekenhuis Instituut classification; teaching versus non-teaching hospitals) could not be applied because they are based on criteria, irrelevant to our study. The item in question in our protocol (appendix A, nr. 44) appeared to be useless due to the definitions being not strict enough: the same hospital was classified into different categories by paediatricians within the same team in the hospital.

Therefore, a scoring system was devised based on the scoring system used by Paneth et al (1982b), and similar to the "Categorization of Perinatal Services" (American Academy of Pediatrics, American College of Obstetricians and Gynecologists, 1983). The scoring enquiry was completed by one of the members of our study team, mostly during a visit to the hospital or, occasionally, by telephone. The items scored included

Figure 8.2.1 POPS 1983: participating hospitals

staffing, specialization of medical and nursing staff, teaching qualification (obstetrics/gynaecology and paediatrics) and round-the-clock availability of medical staff of both the obstetric and the neonatal department, as well as the measure of cooperation between these departments (e.g. regular staff meetings about high risk cases, perinatal conferences, formal and informal consultations). Moreover, the equipment of the neonatal unit and the standard policies and procedures regarding delivery and management immediately after birth of high risk infants were included in the scoring system. Thus, the score for each hospital ranged from 0-30 penalty points (appendix I). The final ranking procedure was carried out without knowledge of the identity of the individual hospital.

Based on this score, the participating hospitals could be classified into 3 levels of care:

level 3 - hospitals with perinatal intensive care centres (score 0-1)
level 2 - hospitals with many facilities for obstetric as well as neonatal special care, but only short term intensive care (score 2-8)
level 1 - hospitals with limited or no facilities for very preterm and very low birthweight infants (score $\geq$9)

Three paediatric hospitals and 2 obstetric hospitals were classified together with their obstetric respectively paediatric counterpart, resulting in a classification for all 138 hospitals involved in the study. Only the 8 university hospitals were classified as level 3. Nineteen hospitals were assigned level 2. The other 75 hospitals fell into level 1, as well as 31 non-participating hospitals referring all high risk infants to participating neonatal units (table 8.3.1).

Table 8.3.1 Levels of perinatal care of hospitals and study infants

level of care	number of hospitals	number of infants born in each level	
		n	%
level 1	106	498	37
level 2	19	359	27
level 3	8	481	36
total	133	1338	100

The number of infants born in the different levels is shown in table 8.3.1. The study infants who were born at home or on the way to the hospital (n=19) were classified as born in level 1.

8.4 Transports

Although no official program for regionalization or centralization of intensive care for newborn infants was instituted in the Netherlands, the recommendations of the "Nederlandse Vereniging voor Kindergeneeskunde" (Dutch Paediatric Association), the "Nederlandse Vereniging voor Obstetrie en Gynaecologie" (Dutch Association for Obstetrics and Gynaecology) and the "Gezondheidsraad" (Health Council of the Netherlands) stressed the importance of the availability of intensive care for very preterm and very low birthweight infants as soon as possible after birth. A tendency to centralization occurred, based on geographical areas surrounding the university hospitals.

8.4.1 Antenatal transport

Antenatal transport was considered to be present if the mother was transferred either prior to or during labour from one hospital to another (chapter 8.3). In most cases this would be a hospital offering a higher level of care. The initial transport from home to hospital was not considered antenatal transport.

Antenatal transport happened to 265 infants (table 8.4.1.1), of which 240 to level 3 hospitals.

Table 8.4.1.1 Antenatal transfer (number of infants)

	prior to labour	in labour	total
transferred within level 1	6	5	11
transferred to level 2	6	8	14
transferred to level 3	139	101	240
total	151	114	265

8.4.2 Neonatal transport

Neonatal transport was considered to be present if the infant was transferred during the first days of life to a hospital in a higher level (chapter 8.2) or between hospitals within the same level. This occurred in 427 cases (32% of this study population). Of these, 43 transports were carried out by car, taxi or standard ambulance without special facilities; 50 were effectuated by standard ambulance with a paediatrician or neonatologist present. The other 334 transports were accomplished by one of the 8 specialized neonatal transport teams of the neonatal intensive care units in the university hospitals (neonatologist or paediatrician training for neonatology, often accompanied by neonatal nurse), using a special ambulance ("babylance") provided with facilities for neonatal intensive care (e.g. transport-incubator with CPAP, IPPV, cardio-respiratory monitoring, continuous measuring of temperature and bloodpressure, i.v. pumps, suction).

The standard procedure for neonatal transfer by one of the 8 babylance-teams was, that each team went out to the hospitals in the region surrounding the university hospital, and provided transport to the own NICU. If no intensive care accommodation was available in the NICU in question due to overcrowding, the infant was transferred to the next nearest NICU where a place was available. The availability of intensive care facilities was monitored continuously by Viditel, a database-system to which all NICUs were linked.

In our study population, such "interregional" long distance transports were effectuated in 58 of the 427 cases, all due to lack of available intensive care accommodation. Apart from these "upgrading" interregional transferrals, 20 infants were referred within level 3 from one NICU to another because of overcrowding; 6 of these infants had been transferred antenatally as well.

Neonatal referrals were grouped according to the period of time that elapsed between birth and the start of intensive treatment by the transport team (table 8.4.2.1).

The 6 infants, that had been transferred antenatally as well, belonged to the first category. The second category was subdivided in "primary" (transferral arranged during or shortly after birth, delay due to travelling distance), "secondary" (transferral arranged after the development of unfavourable clinical symptoms, e.g. respiratory distress) and "after near-death" (no primary transfer arranged because of expected death). For the sake of clearness, no such distinctions will be used in forthcoming chapters in this study.

Of 427 cases of neonatal transfer, 282 were born in a level 1 hospital, 125 in a level 2 hospital and 20 in a level 3 hospital (table 8.4.2.2). The relative number of transfers was highest in level 1 hospitals (57%) compared to level 2 (35%) and level 3 hospitals (4%).

Table 8.4.2.1 Neonatal transport by age at transfer

age at transfer	number of infants	
< 1 h after birth	133	
≥ 1 h after birth	294	
"primary"		132
"secondary"		157
after near-death		5
total	427	

Table 8.4.2.2 Neonatal transport by level (number of infants)

place of birth	number of infants	transport <1h n	transport ≥1h n	total n	%
level 1	498	55	227	282	57
level 2	359	61	64	125	35
level 3	481	17*	3	20	4
total	1338	133	294	427	32

* including 6 infants with antenatal transport as well

Of the total of 427 neonatal transferrals, 79 infants were transported to a level 2 hospital and 334 infants were transferred to a level 3 hospital (274 from level 1, 60 from level 2; including 6 with antenatal transport as well).

8.4.3 Gestational age, birthweight and transport

In table 8.4.3.1 we present the median gestational age and weight at birth according to type of transport.

Table 8.4.3.1 Gestational age and birthweight in referred infants

transport	median gestational age (weeks)	median birthweight (g)
antenatal transport	29.7	1160
neonatal transport	30.0	1240
both	29.8	1250
none	31.0	1315

8.4.4 Backtransfer

Many infants were transferred back from a level 3 hospital to a hospital in a lower level after the initial need for intensive care had passed. If any antenatal or neonatal transport had occurred, the infant was usually transferred back to the referring hospital. If no previous transfer had taken place, the infant was transferred back to a hospital near the home of the parents.

Backtransfer occurred in a total of 397 infants: 126 after initial antenatal transfer, 192 after initial neonatal transfer, 6 after both, and 73 where no previous transfer had taken place (table 8.4.4.1). Moreover, 6 infants were transferred back to the level 3 hospital near the home of the parents, after previous interregional antenatal transfer due to overcrowding of the NICU.

Table 8.4.4.1 Backtransfer from level 3 to level 1 or 2, by previous transfer (number of infants)

previous transfer	number of infants	died	backtransfer	stayed in level 3
antenatal	234	71	126	37
neonatal	328	103	192	33
both	6	-	6	-
none	247	52	73	122
total	815	226	397	192

8.4.5 Recapitulation of transfer

In the total study population, 759 infants were transferred 1089 times. In figure 8.4.5.1, the "routing" of infants is depicted according to level of hospital, as it has occurred in the perinatal period. For the sake of clarity all transferrals between NICUs (neonatal: 20; back: 6) have been omitted. Each time-level is represented by a bar, depicting the total of 1338 study infants. From left to right, the population has been split according to the level of care at that time-level.

From this figure, it is evident that the majority of the study infants (62%, white part of the bar) have been admitted to a level 3 hospital for some time during the neonatal period. Most of the surviving infants have been transferred back to a hospital in a lower level. Consequently, 81% of the surviving infants were discharged home from a level 1 or 2 hospital (hatched part of the bar).

8.5 Discussion

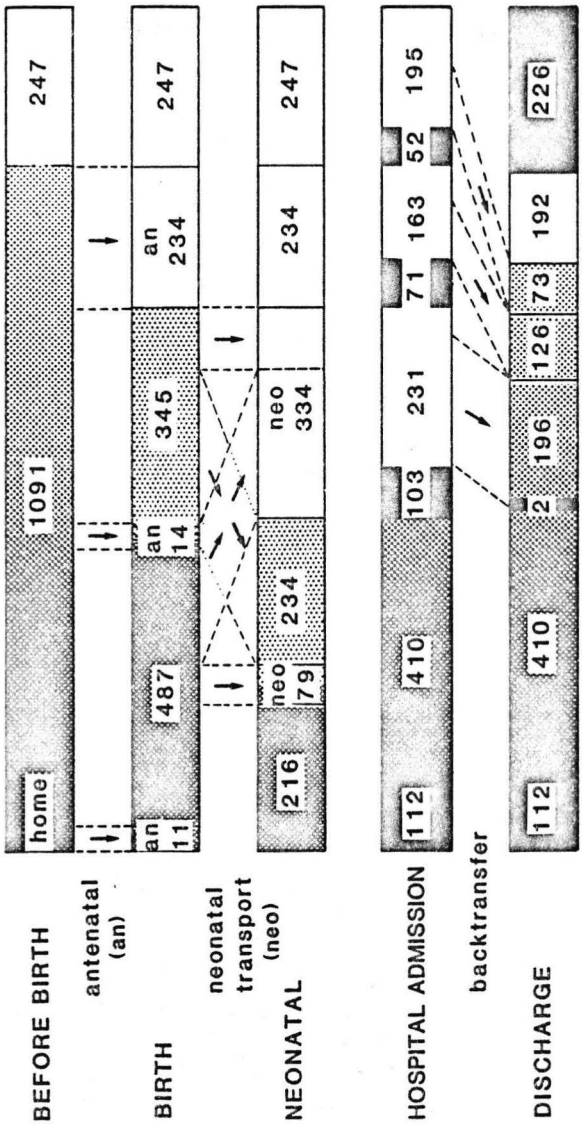
The willingness of nearly all paediatricians in the Netherlands to participate directly or indirectly by agreeing to participation of a member of their team in this study shows, that the collecting of data concerning this group of high risk infants was felt to be a priority. The paediatricians who did not participate in the study were prevented from doing so mainly by lack of manpower at that time.

The ranking of all participating hospitals, based on our own enquiry and finally carried out without knowledge of the identity of the individual hospital, resulted in a classification in 3 levels of care comparable to classifications used in the literature (Bowes, 1981; Peddle et al, 1983; Paneth et al, 1982b; Paneth et al, 1984).

The percentage of infants born in level 3 hospitals is far greater than the percentage in the general population. Of all 109,640 hospital deliveries in the Netherlands in 1983, only 9.2% took place in university hospitals. This tendency to centralization in our study population is partly due to maternal referral before or early in pregnancy because of maternal disease or previous obstetric complications and partly to antenatal transport. Of the very preterm infants (less than 32 weeks gestation) a relatively larger number (40%) was born in level 3 hospitals than of the more mature VLBW infants (24%), due to more antenatal transport.

As shown in figure 8.4.5.1, the greater part (62%) of all infants was treated in a level 3 hospital for some time. The number of interregional "long distance" transports due to overcrowding of NICUs is striking: 78 such cases (17% of all neonatal transports) were recorded in our study. This is probably an underestimation, because interregional transports

Figure 8.4.5.1 POPS 1983: recapitulation of transfer according to hospital level



which were carried out by the transport team belonging to the referral unit (instead of the regional team) or by a standard ambulance could not be recorded as such. Although "long distance" in the Netherlands means a maximum of some 300 kilometers, and in most cases less than 100 kilometers, such transports should be abolished. Besides being harmful for the infant (Shenai et al, 1981; Clark et al, 1981; Fetter et al, 1986) and an additional burden for the transport team (Marshall & Kasman, 1980), the transport is an expensive procedure for health care providers[2] as well as for the parents (Smith & Baum, 1983) for whom costs of visiting the baby may be double or more. Since the overcrowding, and hence the need for interregional transport occurs in all NICUs, the total capacity for neonatal intensive care needs to be expanded.

Of those who survived, 65% was transported back to a hospital in a lower level, even if no previous "upgrading" transport had occurred. Backtransport occurred in all NICUs. The fear that NICUs "cling" to patients seems unwarranted.

Goldenberg et al (1985d) proposed a measurement of regionalization[3]. In Alabama as a whole, this measurement of regionalization increased from 10% in 1970 to 66% in 1980. In the present study, 481 of 1338 births (36%) and 127 of 340 in-hospital deaths (37%) occurred in level 3 hospitals (perinatal centres in university hospitals), an average of 37% regionalization. Further regionalization and centralization of care for these high risk infants may lead to a further decrease of neonatal mortality, as was described in regional studies in Sweden (Eksmyr et al, 1986), Finland (Tenovuo et al, 1986), and Iowa (Hein & Lathrop, 1986).

[2] For each neonatal transport, the "Ziekenfonds" (National Health Insurance) only refunds the costs of babylance maintenance. Neonatal nurses assist in transports only as far as possible within their shift. However, neonatologists and neonatal fellows on call do not receive any extra payment for service rendered during that time, nor can fees be charged for neonatal transports. Only quite recently, a few of the private insurance companies have agreed to fund part of these costs. This implies that most of the burden of these transport services is carried by neonatal staff without any compensation in money or free time.

[3] The average of the rate of VLBW-births and the rate of VLBW-deaths in the perinatal centres, taking as denominator the total number of VLBW-births respectively deaths in the geographical region concerned:

$$\left[\frac{\text{VLBW births centre}}{\text{VLBW births region}} \times 100 + \frac{\text{VLBW deaths centre}}{\text{VLBW deaths region}} \times 100 \right] : 2$$

For the analyses in chapter 14 and 15, all infants have been classified by level of hospital of birth (level 1,2,3), by antenatal transport to a level 3 hospital, and by neonatal transport to a level 2 or 3 hospital ("upgrading" transport).

8.6 Summary

As stated in chapters 4 and 7, various subpopulations may be discerned within the study population. In order to demonstrate variations in the distribution of the factors discussed in this chapter, the frequencies concerned are summarized in table 8.6.1.

Table 8.6.1 Distribution of transport and level of perinatal care (hospital of birth) over various subpopulations

chapter	factor	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
								
		n %	n %	n %	n %	n %	n %	n %
8.4	antenatal transport to level 3	240 (18.0)	205 (20.4)	35 (10.8)	204 (18.6)	37 (15.4)	159 (18.7)	80 (17.6)
8.3	level 1	498 (37.2)	352 (34.9)	143 (44.0)	406 (37.0)	92 (38.2)	341 (36.9)	163 (35.9)
	level 2	359 (26.8)	254 (25.1)	104 (32.0)	291 (26.5)	68 (28.2)	216 (25.4)	137 (30.2)
	level 3	481 (35.9)	404 (40.0)	78 (24.0)	400 (36.4)	81 (33.6)	321 (37.7)	154 (33.9)
8.4	neonatal transport (upgrading)	407 (30.4)	330 (32.7)	75 (23.1)	340 (30.9)	67 (27.8)	294 (34.5)	110 (24.1)

Chapter 9 Completeness of the study cohort

9.1 Introduction

In chapters 7 and 8, the study cohort of 1338 infants has been characterized in terms of the composition and origins of the study population. Since the survey was conducted on a voluntary basis, it was impossible to obtain a 100% coverage; i.e., there will have been infants, liveborn in the Netherlands in 1983, and fulfilling the selection criteria for inclusion in the study, who were nevertheless not included.

To assess the degree of completeness of the survey, as well as a potential bias arising from infants missing from the survey, all non-participating hospitals with paediatric departments were sent a questionnaire in 1984. If any infants suitable for inclusion into the study had been born in 1983 in these hospitals (and had not already been included in the survey, e.g. after transfer to a participating hospital), a few essential details about each infant were recorded on the questionnaire.

As stated in chapter 1.5, no data on the gestational age or birthweight of liveborn infants are routinely available in the Netherlands. As one of the very few West-European countries, and contrary to the recommendations of the WHO (1977) and the FIGO Standing Committee on perinatal mortality and morbidity (Dunn, 1985), the Netherlands have no mandatory registration or notification of such vital information, neither by parents nor by attending physicians or midwives (table 9.1.1).

However, a voluntary registration system of all births exists in the Netherlands: the "Landelijke Verloskunde Registratie, LVR" (National Obstetric Registration). In 1983, 118 hospitals (departments of obstetrics) participated in the LVR, i.e. 67% of all hospitals with obstetric departments (van Hemel, 1986). Details on the 59,770 infants born in these hospitals were recorded in the "Stichting Informatiecentrum voor de Gezondheidszorg" (SIG)[1]. With permission of the supervi-

[1] Stichting Informatiecentrum voor de Gezondheidszorg
Maliebaan 50, 3508 SC Utrecht

Table 9.9.1

Vital Statistics

Tabulations - Most recent Year Available

Country	Natality: Birth Rates by Maternal Age	Births by Maternal Age and Marital Duration	Births by Maternal Age and Birth Order	Births by Birthweight	Births by Crown-Heel Length	Births by Length of Gestation	Births by Marital Status	Death Rates by Cause, Age and Sex	Death by Age, Sex and Marital Status	Life Expectancy by Age and Sex	Legally Induced Abortions by Age of Woman	Late Fetal Deaths	Perinatal Deaths by Cause	Infant Deaths by Age, Cause and Sex	Infant Deaths by Birthweight	Crude Marriage Rates	Marriages by Age of Bride and Groom	Crude Divorce Rate
Australia	83	83	83			83	78	83	83		83	83	81			84	84	84
Austria	84	84	84	84	84	84	84	84	84		84	84	84	84	84	84	84	
Belgium	81	81	81				79					79	79				81	
Canada	83		83	83		83	83	83	83	80-82	83	83	83	83	79	83	83	83
Czechoslovakia	83	83	83	83	83		83	83	83	83	83	83		83	83	83	83	83
Denmark	83	83	83	83	83	81	83	83	83	82-83	83	83	83	83	81	83	83	83
Finland	83	83	83	83			83	83	83	83	83	83	83	83	83	83	83	83
France	83	83	83			83[1]	83	83	83	83	82	83		83		84	83	83
Germany, Federal Republic of	83	83	83	83	83		83	83	83	81-83	84	83		83	83	84	83	83
Great Britian: England and Wales	84	84	84	83		81	84	83	83	81-83	83	83	83	83	83	83	83	83
Scotland	84	84	84	84		84	84	84	84	84	84	84	84	84		84	84	84
Greece	83	83	83	83		83	83	83	83	83	83	83	83	83		83	83	83
Hungary	83	83	83	83		83	83	83		83	83	83	83	83	83	83	83	83
Israel	84	76	84	84			84	84	84	84	84	84	84	84	84	84	84	84
Italy	83[4]	80	83[4]	80		80		83[4]	83[4]	80	81	84[4]			80	84[4]	83[4]	84[4]
Japan	83	83[3]	83	83		83	83	83	83	83	83	83	83	83		83	83	83
Netherlands	84	84	84				84	83[5] 84[5]	84	83-84	83	84	83	82		84	84	84
New Zealand	84	84	84	84		84	84	83	84	84	84	84	84	83	83	84	84	84
Norway	83	83	83	81		81	83	83	88	82-83	84	83	83	83	83	83	83	83
Portugal	83	84	84	84		84	84	83	84	82		84	84	84		83	84	83
Spain	80	80	80	80		80	80	80	80	81		83	80	80		83	80	
Sweden	84	84	84	83	83	83	83	83	84	84	84	84	83	83	83	84	84	84
Switzerland	84	84	84	84	84		84	84	84	83-84		84	84	84	79-81	84	84	84
United States	83		83	83		83	83	83	83	83	83	83		83		84	82	84
Yugoslavia	82	82	82				82	82	82	81-82		82	82	82		82	82	82

[1] Stillbirths only
[2] Age and Sex only
[3] Induced abortions reported by law
[4] Provisional data
[5] Legitimate live birth only
[6] Cause
[7] Demographic indicators not available for 1984 until Population Estimate is concluded

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • National Center for Health Statistics

sing committee, those records were used for comparison to our study population.

Two provinces in the Netherlands (Groningen and Drenthe) participate as a region in Eurocat (Cornel et al, 1986), a registration of congenital malformations in countries in the European Community (Wals et al, 1985). The data collected for Eurocat in 1983 were compared to our study population as well.

Finally, data from the "Centraal Bureau voor de Statistiek" (Central Bureau of Statistics)[2], concerning first week deaths of liveborn infants by gestational age and birthweight, were used to assess the completeness of our survey as far as early neonatal mortality was concerned. This last subject will be discussed in chapter 10.9.1.

9.2 Infants in non-participating hospitals

Nearly all 40 non-participating hospitals with a paediatric department responded to our questionnaire. Fourteen hospitals sent details on 85 infants, who fulfilled the criteria for inclusion into the study, but were not included. These 85 infants are listed in table 9.2.1 by gestational age and in table 9.2.2 by birthweight.

In the remaining 26 hospitals, no such infants have been born in 1983 (chapter 8.2).

No difference in the distribution of gestational age and birthweight was found when comparing mean ranks in the two groups (Mann Whitney test). Mortality was similar (25.8%) to that found in the study cohort (chapter 10).

Therefore, we conclude that the study cohort included 94% of all such infants born in the Netherlands in 1983, and that it is representative of the total population at risk.

[2] Centraal Bureau voor de Statistiek
Prinses Beatrixlaan 428, 2273 XZ Voorburg

Table 9.2.1 Eligible infants not included in the study cohort, in successive gestational age categories

gestational age (weeks)	number of infants	in-hospital deaths n
24	1	1
25	4	4
26	8	7
27	4	2
28	7	-
29	4	2
30	17	4
31	13	1
32	6	-
33	8	-
34	6	-
35	3	1
36	2	-
37	1	-
40	1	-
total	85	22

Table 9.2.2 Eligible infants not included in the study cohort, in successive birthweight categories

birthweight (g)	number of infants	in-hospital deaths
500-599	2	2
600-699	3	3
700-799	1	1
800-899	2	1
900-999	6	3
1000-1099	4	1
1100-1199	7	3
1200-1299	10	1
1300-1399	19	1
1400-1499	13	1
≥1500	12	2
unknown	6	3
total	85	22

9.3 "Landelijke Verloskunde Registratie" (LVR)

Unfortunately, the hospitals of which the paediatricians participated in POPS were not (always) the same as the hospitals in which the obstetricians participated in the LVR. This implies that the records cannot be compared as such. Therefore, we compared only the data from 87 hospitals participating in both surveys. Because of the confidentiality of both data-bases, direct "linking" of cases was impossible.

In the LVR-cohort, 1044 infants met the criteria for inclusion in POPS: liveborn in 1983, with a gestational age of less than 32 weeks and/or a birthweight of less than 1500 g. Within the POPS-cohort, 1096 infants have been entered into the study by the hospitals that participated in the LVR. To study this small difference further, the LVR-data were stratified by week of gestational age and by 100 g birthweight categories. The distribution appeared to be similar (tables 9.3.1, 9.3.2). In the extremely low gestational age groups (≤ 24 weeks), the LVR has a surplus of 24 infants. These have probably been considered "not viable" by the attending obstetrician and the paediatrician has not been involved.

Table 9.3.1 Number of infants included in LVR and POPS, according to gestational age categories (87 hospitals)

gestational age (weeks)	LVR	POPS
23	17	7
24	26	12
25	30	43
26	58	63
27	72	83
28	91	112
29	122	140
30	143	164
31	227	198
≥ 32	258	274
total	1044	1096

Table 9.3.2 Number of infants included in LVR and POPS according to birthweight categories (87 hospitals)

birthweight (g)	LVR	POPS
<500	9	4
500-599	20	11
600-699	25	27
700-799	40	38
800-899	57	69
900-999	75	93
1000-1099	92	109
1100-1199	89	116
1200-1299	107	120
1300-1399	119	153
1400-1499	141	163
≥1500	270	193
total	1044	1096

The POPS-study cohort showed a surplus of infants with a gestational age of 25-31 weeks (n=76), due to a number of infants that were transported from home (n=19) or from a non-participating hospital to one of the 87 hospitals. Because they have not been born there, these infants were not included in the LVR.

9.4 Eurocat-registration in the Netherlands

In the Eurocat registration, information on 3 infants, liveborn in 1983 with a gestational age under 32 weeks and/or a birthweight under 1500 g was recorded (Cornel, personal communication, 1986). Two of them could be identified in our study population. The third case was anencephalic, born at 22 weeks gestation, and died shortly after birth.

9.5 Conclusions

From the investigations described in this chapter and chapter 10.9.1, it is evident that the study cohort comprises a remarkably complete and representative population. The cohort originates from a geographically defined area (the Netherlands), and includes all levels of care. Although theoretically, there still may be some eligible infants who have not been accounted for, it is highly unlikely that inclusion would affect our results in any significant way. Therefore, we conclude that the results from this survey are valid for the total population under study.

The main source of inaccuracy are infants in the extremely short gestational age groups. If such infants are considered "not viable", and die very shortly after birth, they may be omitted from all registrations for a variety of practical reasons (Keirse, 1984a). Only a mandatory registration system for all births (stillborn and liveborn) from 16 weeks gestation onward, without practical or financial consequences for parents or physicians, will allow assessment of birth and death rates at extremely low gestations. Only then, the true incidence of preterm birth can be investigated and changes in time will become apparent.

Chapter 10 Mortality

10.1 Introduction

For a long time, death or survival has been the yardstick of success of neonatal intensive care. Although nowadays much attention is paid to later morbidity as well, mortality still is the leading parameter, because it is unequivocal, and known after a relatively short time.

The mortality rates used most widely for national and international comparison are:

- perinatal mortality rate (stillbirths after 28 weeks gestation plus deaths of liveborn infants occurring within 7 x 24 hours after birth)
- neonatal mortality rate (deaths within 28 days of birth)
- infant mortality rate (deaths within the first 365 days of life)

In the present study, stillborn infants were not included; therefore, perinatal mortality rates cannot be calculated. Neonatal mortality rates have been calculated whenever appropriate. However, we felt that often the neonatal mortality insufficiently described the situation: a substantial number of deaths originating in the perinatal period occurred after 28 days of life, due to the perinatal intensive care administered to the infant. Recently, the same problem has been described by others (Beckwitt Turkel et al, 1986). Therefore, these postneonatal deaths during hospital admission have been included in the so-called "in-hospital mortality". Postneonatal deaths after discharge home are often related to perinatal problems as well. However, these deaths will not be discussed in detail in this thesis, but after completion of the follow-up study.

10.2 Mortality by age at death

In the first year of life, 364 of the 1338 study infants died. This means an infant mortality rate in the study population of 272 per thousand live births.

Of these deaths, 40% occurred during the first day, and 73% during the first week of life (table 10.2.1).

Table 10.2.1 Deaths in the first year of life, by age at death

age at death	deaths		
	n	%	% of live born infants
<2 hours	56	15	
2-24 hours	91	25	
24-48 hours	48	13	
48 hours-7 days	71	19	
early neonatal mortality	266		19.9
8-28 days	46	13	
neonatal mortality	312		23.3
>28 days, during hospital stay	28	8	
in-hospital mortality	340		25.4
discharge-1 year	24	7	
infant mortality	364	100	27.2

Early neonatal mortality rate (day 1-7) was 199 per thousand live births, and total neonatal mortality rate (day 1-28) 233 per thousand live births. Postneonatal mortality rate (day 29-365) was 39 per thousand; half of these deaths occurred during hospital stay, the other half after discharge home. As this last category (24 infants) belongs to the follow-up study, it will be omitted in the remainder of this chapter.

10.3 Mortality by gestational age and birthweight

Tables 10.3.1 - 10.3.3 show early neonatal, neonatal and in-hospital mortality rate (%) by gestational age and birthweight. The actual number of infants that died in each gestational age-birthweight category is mentioned in parentheses, as well as the number of liveborn infants in that category.

For the sake of comparability to the existing literature on the subject, neonatal and in-hospital mortality were also calculated by gestational age alone (table 10.3.4) and by birthweight alone (table 10.3.5), in groupings such as used frequently in the literature.

Table 10.3.4 Mortality rate by gestational age

gestational age (weeks)	number of infants	neonatal deaths		in-hospital deaths	
		n	%	n	%
≤23	8	8	-	8	-
24-25	67	58	86.6	60	89.5
26-27	180	90	50.0	95	52.8
28-29	307	72	23.5	83	27.0
30-31	448	57	12.7	64	14.3
total <32	1010	285	28.2	310	30.7

To demonstrate differences in mortality in subpopulations within the study cohort, the separate mortality rates are stated in table 10.3.6.

10.4 Mortality by infants' sex

Of the 698 boys in the study group, 183 (26.2%) died during hospital admission; of the 635 girls, 153 (24.1%) died. Although these observed mortality rates do not differ substantially, the distribution of other perinatal factors (like gestational age) has to be taken into account before any conclusion may be drawn (chapter 14).

Table 10.3.1 EARLY NEONATAL mortality rate (%) by gestational age in completed weeks and birthweight in 100 g categories. Actual number of infants in parentheses (dead/liveborn)

GA (wks)	22	23	24	25	26	27	28	29	30	31
BW (g)										
2700-2799										(1/ 1)
2600-2699										
2500-2599										(0/ 1)
2400-2499									(1/ 1)	(0/ 1)
2300-2399										(0/ 1)
2200-2299								(0/ 1)		(0/ 2)
2100-2199									(0/ 1)	(1/ 2)
2000-2099									(1/ 1)	(0/ 3)
1900-1999								(1/ 1)	(0/ 1)	7 (1/14)
1800-1899								(0/ 2)	(1/ 6)	11 (2/19)
1700-1799								(1/ 5)	13 (2/15)	3 (1/32)
1600-1699						(0/ 1)	(1/ 2)	(1/ 4)	17 (4/23)	11 (3/27)
1500-1599					(0/ 1)		(0/ 4)	7 (1/15)	4 (1/25)	10 (3/29)
1400-1499							16 (3/19)	10 (2/20)	7 (3/43)	0 (0/25)
1300-1399					(0/ 1)	(2/ 8)	13 (3/23)	11 (3/27)	0 (0/25)	6 (1/18)
1200-1299					(2/ 3)	64 (9/14)	27 (6/22)	22 (7/32)	24 (4/17)	12 (2/16)
1100-1199				(0/ 1)	(2/ 8)	27 (3/11)	15 (3/20)	15 (3/20)		20 (4/20)
1000-1099				(3/ 4)	57 (12/21)	26 (6/23)	26 (5/19)	11 (2/19)	(2/ 8)	17 (2/12)
900- 999				78 (7/ 9)	37 (7/19)	26 (6/23)	30 (3/10)	(1/ 8)	(1/ 8)	9 (1/11)
800- 899		(1/1)	(2/2)	81 (13/16)	50 (7/14)	50 (5/10)	33 (4/12)	(3/ 7)	(1/ 8)	(0/ 6)
700- 799		(1/1)	(4/4)	69 (11/16)	(6/ 7)	(1/ 4)	(0/ 1)	(2/ 6)	(1/ 3)	(0/ 2)
600- 699			(7/7)	(2/ 2)	(2/ 2)	(3/ 5)	(2/ 4)	(1/ 3)	(1/ 6)	(1/ 2)
500- 599	(3/3)	(1/1)	(3/3)		(1/ 1)	(2/ 4)		(0/ 1)	(0/ 1)	
400- 499		(2/2)	(3/3)							
Total	(3/3)	(5/5)	100 (19/19)	75 (36/48)	51 (39/77)	36 (37/103)	22 (30/136)	16 (28/171)	13 (27/240)	9 (23/244)

Rates are based on at least 10 infants.

32	33	34	35	36	37	38	39	40	unknown	total
										(1/ 1)
										(0/ 1)
										(1/ 2)
										(0/ 1)
										(0/ 3)
										(1/ 3)
										(1/ 4)
										12 (2/ 6)
										11 (3/27)
										8 (4/52)
										16 (9/57)
										7 (5/74)
18 (3/17)	5 (1/22)	0 (0/10)	0 (0/19)	(0/9)	(0/9)	(0/6)	(0/2)		(0/1)	6 (12/202)
5 (1/21)	(0/16)	0 (0/17)	14 (2/14)	(0/6)	(0/2)			(0/1)		7 (12/179)
8 (1/12)	7 (1/14)	7 (1/14)	(0/ 8)	(0/3)	(0/4)	(0/1)			(0/1)	20 (33/161)
12 (2/17)	0 (0/11)	(0/ 9)	(0/ 8)	(0/1)		(0/1)				15 (21/139)
(0/ 8)	(1/ 7)	(0/ 1)	(0/ 2)							27 (33/124)
(1/ 8)	(0/ 5)									27 (27/101)
(3/ 7)	(0/ 1)	(1/ 1)	(0/ 1)	(0/1)	(0/1)					45 (40/38)
(0/ 2)	(1/ 4)								(0/1)	53 (27/51)
(0/ 2)										58 (19/33)
										71 (10/14)
										(5/ 5)
12 (11/94)	5 (4/80)	4 (2/52)	4 (2/52)	0 (0/20)	0 (0/16)	(0/8)	(0/2)	(0/1)	(0/3)	20 (266/1338)

Table 10.3.2 NEONATAL mortality rate (%) by gestational age in completed weeks and birthweight in 100 categories. Actual number of infants in parentheses (dead/liveborn)

GA (wks)	22	23	24	25	26	27	28	29	30	31
BW (g)										
2700-2799										(1/ 1)
2600-2699										
2500-2599										(0/ 1)
2400-2499									(1/ 1)	(0/ 1)
2300-2399										(0/ 1)
2200-2299								(0/ 1)		(0/ 2)
2100-2199									(0/ 1)	(1/ 2)
2000-2099									(1/ 1)	(0/ 3)
1900-1999								(1/ 1)	(0/ 1)	7 (1/14)
1800-1899								(0/ 2)	(1/ 6)	11 (2/19)
1700-1799								(1/ 5)	13 (2/15)	3 (1/32)
1600-1699						(0/ 1)	(1/ 2)	(1/ 4)	22 (5/23)	11 (3/27)
1500-1599					(0/ 1)		(0/ 4)	13 (2/15)	12 (3/25)	10 (3/29)
1400-1499							26 (5/19)	10 (2/20)	12 (5/43)	0 (0/25)
1300-1399					(1/ 1)	(2/ 8)	17 (4/23)	11 (3/27)	0 (0/25)	6 (1/18)
1200-1299					(2/ 3)	71 (10/14)	32 (7/22)	31 (10/32)	24 (4/17)	12 (2/16)
1100-1199				(0/ 1)	(4/ 8)	36 (4/11)	30 (6/20)	15 (3/20)	33 (4/12)	20 (4/20)
1000-1099				(3/ 4)	67 (14/21)	26 (6/23)	26 (5/19)	16 (3/19)	(2/ 8)	17 (2/12)
900- 999				(8/ 9)	42 (8/19)	30 (7/23)	40 (4/10)	(2/ 8)	(1/ 8)	9 (1/11)
800- 899		(1/1)	(2/2)	87 (14/16)	57 (8/14)	70 (7/10)	33 (4/12)	(3/ 7)	(1/ 8)	(0/ 6)
700- 799		(1/1)	(4/4)	75 (12/16)	(6/ 7)	(2/ 4)	(0/ 1)	(2/ 6)	(1/ 3)	(0/ 2)
600- 699			(7/7)	(2/ 2)	(2/ 2)	(3/ 5)	(2/ 4)	(1/ 3)	(2/ 6)	(1/ 2)
500- 599	(3/3)	(1/1)	(3/3)		(1/ 1)	(3/ 4)		(0/ 1)	(1/ 1)	
400- 499		(2/2)	(3/3)							
Total	(3/3)	(5/5)	100 (19/19)	81 (39/48)	60 (46/77)	43 (44/103)	28 (38/136)	20 (34/171)	17 (34/204)	9 (23/244

Rates are based on at least 10 infants.

32	33	34	35	36	37	38	39	40	unknown	total
										(1/ 1)
										(0/ 1)
										(1/ 2)
										(0/ 1)
										(0/ 3)
										(1/ 3)
										(1/ 4)
										12 (2/16)
										11 (3/27)
										8 (4/52)
										18 (10/57)
										11 (8/74)
18 (3/17)	5 (1/22)	0 (0/10)	0 (0/19)	(0/ 9)	(0/ 9)	(1/6)	(0/2)		(0/1)	8 (17/202)
5 (1/21)	0 (0/16)	0 (0/17)	14 (2/14)	(0/ 6)	(0/ 2)			(0/1)		8 (14/179)
17 (2/12)	7 (1/14)	7 (1/14)	(0/ 8)	(0/ 3)	(0/ 4)	(0/1)			(0/1)	24 (39/161)
12 (2/17)	0 (0/11)	(1/ 9)	(1/ 8)	(0/ 1)		(0/1)				21 (29/139)
(1/ 8)	(2/ 7)	(0/ 1)	(1/ 2)							31 (39/124)
(1/ 8)	(0/ 5)									32 (32/101)
(3/ 7)	(0/ 1)	(1/ 1)	(0/ 1)	(0/ 1)	(0/ 1)					50 (44/88)
(0/ 2)	(2/ 4)								(0/1)	59 (30/51)
(0/ 2)										61 (20/33)
										86 (12/14)
										(5/ 5)
14 (13/94)	7 (6/80)	6 (3/52)	8 (4/52)	0 (0/20)	0 (0/16)	(1/8)	(0/2)	(0/1)	(0/3)	23 (312/1338)

Table 10.3.3 IN-HOSPITAL mortality rate (%) by gestational age in completed weeks and birthweight in 100 g categories. Actual number of infants in parentheses (dead/liveborn)

GA (wks)	22	23	24	25	26	27	28	29	30	31
BW (g)										
2700-2799										(1/ 1)
2600-2699										
2500-2599										(0/ 1)
2400-2499									(1/ 1)	(0/ 1)
2300-2399										(0/ 1)
2200-2299								(0/ 1)		(0/ 2)
2100-2199									(0/ 1)	(1/ 2)
2000-2099									(1/ 1)	(0/ 3)
1900-1999								(1/ 1)	(0/ 1)	7 (1/14)
1800-1899								(0/ 2)	(1/ 6)	11 (2/19)
1700-1799								(1/ 5)	13 (2/15)	3 (1/32)
1600-1699							(0/ 1)	(1/ 2)	(1/ 4)	26 (6/23)	11 (3/27)
1500-1599					(0/ 1)		(1/ 4)	13 (2/15)	16 (4/25)	10 (3/29)
1400-1499							26 (5/19)	10 (2/20)	12 (5/43)	4 (1/25)
1300-1399					(1/ 1)	(2/ 8)	22 (5/23)	15 (4/27)	0 (0/25)	6 (1/18)
1200-1299					(2/ 3)	71 (10/14)	32 (7/22)	31 (10/32)	24 (4/17)	19 (3/16)
1100-1199				(0/ 1)	(4/ 8)	36 (4/11)	40 (8/20)	15 (3/20)	33 (4/12)	20 (4/20)
1000-1099				(3/ 4)	67 (14/21)	26 (6/23)	37 (7/19)	21 (4/19)	(2/ 8)	17 (2/12)
900- 999				(8/ 9)	47 (9/19)	35 (8/23)	50 (5/10)	(2/ 8)	(1/ 8)	9 (1/11)
800- 899		(1/1)	(2/2)	94 (15/16)	64 (9/14)	80 (8/10)	42 (5/12)	(3/ 7)	(2/ 8)	(1/ 6)
700- 799		(1/1)	(4/4)	81 (13/15)	(6/ 7)	(2/ 4)	(0/ 1)	(2/ 6)	(2/ 3)	(0/ 2)
600- 699			(7/7)	(2/ 2)	(2/ 2)	(4/ 5)	(2/ 4)	(1/ 3)	(2/ 6)	(1/ 2)
500- 599	(3/3)	(1/1)	(3/3)		(1/ 1)	(3/ 4)		(1/ 1)	(1/ 1)	
400- 499		(2/2)	(3/3)							
Total	(3/3)	(5/5)	100 (19/19)	85 (41/48)	62 (48/77)	46 (47/103)	34 (46/136)	22 (37/171)	19 (38/204)	11 (26/244)

Rates are based on at least 10 infants.

32	33	34	35	36	37	38	39	40	unknown	total
										(1/ 1)
										(0/ 1)
										(1/ 2)
										(0/ 1)
										(0/ 3)
										(1/ 3)
										(1/ 4)
										12 (2/16)
										11 (3/27)
										8 (4/52)
										19 (11/57)
										14 (10/74)
18 (3/17)	5 (1/22)	0 (0/10)	0 (0/19)	(0/ 9)	(0/ 9)	(1/6)	(0/2)		(0/1)	9 (18/202)
5 (1/21)	0 (0/16)	0 (0/17)	14 (2/14)	(0/ 6)	(0/ 2)			(0/1)		9 (16/179)
17 (2/12)	17 (2/12)	7 (1/14)	(0/ 8)	(0/ 3)	(0/ 4)	(0/1)			(0/1)	25 (40/161)
12 (2/17)	0 (0/11)	(1/ 9)	(2/ 8)	(0/ 1)		(0/1)				23 (32/139)
(2/ 8)	(2/ 7)	(0/ 1)	(1/ 2)							35 (43/124)
(1/ 8)	(0/ 5)									35 (35/101)
(3/ 7)	(0/ 1)	(1/ 1)	(0/ 1)	(0/ 1)	(0/ 1)					57 (50/88)
(0/ 2)	(3/ 4)								(0/1)	65 (33/51)
(0/ 2)										64 (21/33)
										93 (13/14)
										(5/ 5)
15 (14/94)	9 (7/80)	6 (3/52)	10 (5/52)	0 (0/20)	0 (0/16)	(1/8)	(0/2)	(0/1)	(0/3)	25 (340/1338)

Table 10.3.6 Mortality in various subpopulations

chapter	mortality	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
								
		n %	n %	n %	n %	n %	n %	n %
10.4	neonatal mortality	312 (23.3)	285 (28.2)	27 (8.3)	281 (25.6)	31 (12.9)	209 (24.6)	72 (15.9)
	in-hospital mortality	340 (25.4)	310 (30.7)	30 (9.2)	306 (27.8)	34 (14.1)	227 (26.7)	82 (18.1)

Table 10.3.5 Mortality rate by birthweight

birthweight (g)	number of infants	neonatal deaths n	%	in-hospital deaths n	%
<500	5	5	-	5	-
500-749	66	43	65.1	46	69.7
750-999	221	95	43.0	106	48.0
subtotal	292	143	49.0	157	53.8
1000-1249	359	87	24.2	95	26.5
1250-1499	446	50	11.2	54	12.1
subtotal	805	138	17.1	149	18.5
total<1500	1097	281	25.6	306	27.9

10.5 Mortality by hospital level of care

Neonatal and in-hospital mortality rates were calculated for each of the three levels of care, with all births and deaths assigned to the hospital of birth, regardless of antenatal or neonatal transport (table 10.5.1). Again, these crude mortality rates do not take into account the existing differences in perinatal factors such as gestational age and birthweight (table 10.5.2) The importance of such differences will be discussed in chapter 14.

Table 10.5.1 Mortality rates by hospital level of care

level of care	number of infants	early neonatal deaths n	%	neonatal deaths n	%	in-hospital deaths n	%
level 1	498	104	21	119	24	129	26
level 2	359	68	19	76	21	84	23
level 3	481	94	19	117	24	127	26

Table 10.5.2 Mean gestational age and birthweight by hospital level

level	mean gestational age (weeks)	mean birth-weight (g)
1	30.6	1272
2	30.8	1274
3	29.7*	1206*

* $p < 0.001$ (one-sided analysis of variance, Kruskall Wallis)

10.6 Mortality by multiple pregnancy

In the POPS-cohort, 312 study infants were part of a multiple pregnancy (chapter 7.8). Neonatal mortality appeared to be higher in these infants (95 out of 312, 30%) than in singleton infants (217 out of 1026, 21%). The distribution of infants of multiple pregnancy and their neonatal mortality is shown in table 10.6.1, and singleton births and their neonatal mortality in table 10.6.2.

In-hospital mortality in multiple births was higher as well (103 out of 312, 33% versus 237 out of 1026 singletons, 23%).

10.7 Mortality by presentation and mode of delivery

The observed frequencies of neonatal and in-hospital mortality in vertex and non-vertex presentation of the infant before delivery is stated in table 10.7.1.

Table 10.7.1 Mortality by fetal presentation

fetal presentation	number of infants	neonatal deaths		in-hospital deaths	
		n	%	n	%
vertex and unknown	976	205	21.0	228	23.4
non-vertex	362	107	29.5	112	30.9

Although mortality seems higher in the non-vertex presentation infants, interpretation of these observed rates is impossible without taking into account many other perinatal variables, as will be done in chapter 14. The same applies to mortality in infants, delivered vaginally versus caesarean section (table 10.7.2).

Table 10.7.2 Mortality by mode of delivery

mode of delivery	number of infants	neonatal deaths		in-hospital deaths	
		n	%	n	%
vaginal	772	228	29.5	243	31.5
caesarean section	566	84	14.8	97	17.1

10.8 Mortality in small for gestational age infants

Of the 454 infants in the total study population who were considered SGA by Dutch standards (chapter 7.4), 72 (16%) died during the neonatal period (table 10.8.1).

Table 10.8.1 Mortality in small for gestational age infants

classification	number of infants	neonatal deaths		in-hospital deaths	
		n	%	n	%
SGA	454	72	15.8	82	18.1
AGA/LGA	851	209	24.6	227	26.7
not classified	33	31	93.9	31	93.9

Because of the relatively large number of SGA infants with gestational age over 32 weeks in our study population, this observed mortality rate does not necessarily lead to the conclusion that a relatively low weight is a favourable condition at all gestational ages or in all circumstan-

Table 10.6.1 NEONATAL mortality rate (%) in twins by gestational age in completed weeks and birthweight 100 g categories. Actual number of infants in parentheses (dead/liveborn)

GA (wks)	22	23	24	25	26	27	28	29	30	31
BW (g)										
2700-2799										
2600-2699										
2500-2599										
2400-2499										
2300-2399										(0/ 1)
2200-2299										
2100-2199										
2000-2099									(1/ 1)	
1900-1999									(0/ 1)	(0/ 1)
1800-1899									(0/ 1)	(0/ 3)
1700-1799								(1/ 1)	(0/ 4)	8 (1/12)
1600-1699									(2/ 4)	(0/ 6)
1500-1599								(1/ 4)	20 (2/10)	(1/ 9)
1400-1499							(2/ 4)	(0/ 3)	25 (3/12)	(0/ 8)
1300-1399						(1/ 1)	(1/ 3)	(0/ 7)	(0/ 8)	(1/ 5)
1200-1299					(1/2)	(3/4)	(3/ 6)	21 (4/19)	(2/ 8)	(0/ 2)
1100-1199					(3/4)	(1/1)	(2/ 5)	(2/ 5)	(0/ 5)	(1/ 2)
1000-1099					(4/4)	(1/2)	40 (3/10)	(3/ 7)	(1/ 1)	(0/ 1)
900- 999				(1/1)	(4/8)	(1/6)	(1/ 1)	(1/ 2)	(1/ 2)	(0/ 2)
800- 899		(1/1)		(8/8)	(3/5)	(0/2)	(0/ 2)	(2/ 3)	(0/ 1)	
700- 799		(1/1)	(1/1)	(2/3)	(2/2)	(2/2)		(1/ 1)	(0/ 1)	
600- 699			(1/1)	(1/1)		(1/1)			(0/ 1)	(1/ 1)
500- 599	(2/2)		(1/1)		(1/1)	(1/1)				
400- 499			(1/1)							
Total	(2/2)	(2/2)	(4/4)	92 (12/13)	69 (18/26)	55 (11/20)	39 (12/31)	29 (15/52)	20 (12/60)	9 (5/53)

Rates are based on at least 10 infants.

32	33	34	35	36	37	38	39	40	unknown	total
										(0/ 1)
										(1/ 1)
										(0/ 2)
										(0/ 4)
										12 (2/17)
										20 (2/10)
										18 (4/23)
(0/5)	(0/7)		(0/2)		(0/2)		(0/2)			11 (5/45)
(0/5)	(0/1)	(0/5)	(0/3)	(0/1)						8 (3/39)
	(0/2)	(0/2)	(0/2)						(0/1)	27 (3/48)
(1/4)	(0/1)		(1/1)			(0/1)				38 (11/29)
(0/1)										46 (12/26)
										41 (9/22)
										64 (14/22)
(0/1)										75 (9/12)
										(4/ 5)
										(5/ 5)
										(1/ 1)
8 (1/16)	0 (0/11)	(0/7)	(1/8)	(0/1)	(0/2)	(0/1)	(0/2)		(0/1)	30 (95/312)

Table 10.6.2 NEONATAL mortality rate (%) in singleton infants by gestational age in completed weeks a birthweight in 100 g categories. Actual number of infants in parentheses (dead/liveborn)

GA (wks)	22	23	24	25	26	27	28	29	30	31
BW (g)										
2700-2799										(1/ 1)
2600-2699										
2500-2599										(0/ 1)
2400-2499									(1/ 1)	(0/ 1)
2300-2399										
2200-2299								(0/ 1)		(0/ 2)
2100-2199									(0/ 1)	(1/ 2)
2000-2099										(0/ 3)
1900-1999								(1/ 1)		8 (1/13)
1800-1899								(0/ 2)	(1/ 5)	12 (2/16)
1700-1799								(0/ 4)	18 (2/11)	0 (0/20)
1600-1699						(0/ 1)	(1/ 2)	(1/ 4)	16 (3/19)	14 (3/21)
1500-1599					(0/ 1)		(0/ 4)	9 (1/11)	7 (1/15)	10 (2/20)
1400-1499							20 (3/15)	12 (2/17)	6 (2/31)	0 (0/17)
1300-1399					(1/ 1)	(1/ 7)	15 (3/20)	15 (3/20)	0 (0/17)	0 (0/13)
1200-1299					(1/ 1)	70 (7/10)	25 (4/16)	46 (6/13)	(2/ 9)	14 (2/14)
1100-1199				(0/ 1)	(1/ 4)	30 (3/10)	27 (4/15)	7 (1/15)	(4/ 7)	17 (3/18)
1000-1099				(3/ 4)	59 (10/17)	24 (5/21)	(2/ 9)	0 (0/12)	(1/ 7)	18 (2/11)
900- 999				(7/ 8)	36 (4/11)	35 (6/17)	(3/ 9)	(1/ 6)	(0/ 6)	(1/ 9)
800- 899			(2/2)	(6/ 8)	(5/ 9)	(7/ 8)	40 (4/10)	(1/ 4)	(1/ 7)	(0/ 6)
700- 799			(3/3)	77 (10/13)	(4/ 5)	(0/ 2)	(0/ 1)	(1/ 5)	(1/ 2)	(0/ 2)
600- 699			(8/8)	(1/ 1)	(2/ 2)	(2/ 4)	(2/ 4)	(1/ 3)	(2/ 5)	(0/ 1)
500- 599	(1/1)	(1/1)	(2/2)			(2/ 3)		(0/ 1)	(1/ 1)	
400- 499		(1/1)	(2/2)							
Total	(1/1)	(3/3)	100 (15/15)	77 (27/35)	55 (28/51)	40 (33/83)	25 (26/105)	16 (19/119)	15 (22/144)	9 (18/191

Rates are based on at least 10 infants.

32	33	34	35	36	37	38	39	40	unknown	total
										(1/ 1)
										(0/ 1)
										(1/ 2)
										(0/ 3)
										(1/ 3)
										(0/ 3)
										14 (2/ 14)
										13 (3/ 23)
										6 (2/ 35)
										17 (8/ 47)
										8 (4/ 51)
25 (3/12)	7 (1/15)	0 (0/10)	0 (0/17)	(0/9)	(0/7)	(1/6)			(0/1)	8 (12/157)
6 (1/16)	0 (0/15)	0 (0/12)	18 (2/11)	(0/5)	(0/2)			(0/1)		8 (11/140)
17 (2/12)	8 (1/12)	8 (1/12)	(0/ 6)	(0/3)	(0/4)	(0/1)				32 (36/113)
8 (1/13)	0 (0/10)	(1/ 9)	(0/7)	(0/1)						16 (18/110)
(1/ 7)	(2/ 7)	(0/ 1)	(1/2)							27 (27/ 98)
(1/ 8)	(0/ 5)									29 (23/ 79)
(3/ 7)	(0/ 1)	(1/ 1)	(0/1)	(0/1)	(0/1)					45 (30/ 66)
(0/ 1)	(2/ 4)								(0/1)	54 (21/ 39)
(0/ 2)										57 (16/ 28)
										(7/ 9)
										(4/ 4)
15 (12/78)	9 (6/69)	7 (3/45)	7 (3/44)	0 (0/19)	0 (0/14)	(1/7)		(0/1)	(0/2)	21 (217/1026)

ces. Again, many other perinatal factors have to be taken into account. Therefore, SGA will be investigated further in chapter 14.

10.9 Discussion

10.9.1 Official registration

In 1983, the infant mortality rate in the Netherlands was 8.4 per thousand live births. A total of 1432 infants died in the first year of life (Centraal Bureau voor de Statistiek, 1985b). Therefore, the 364 study infants that died during the first year of life, constitute 25% of the total infant mortality in the Netherlands. In the first week of life, this percentage is even higher: 266 study infants of 729 total first week deaths (37%). The same applies to the neonatal mortality: 312 study infants out of 904 total neonatal deaths in the Netherlands (34%).

Total first week mortality is recorded by gestational age and by birthweight (Centraal Bureau voor de Statistiek, 1985b, tables 10.9.1.1 and 10.9.1.2).

Table 10.9.1.1 First week deaths by gestational age

gestational age (weeks)	CBS	POPS		non-POPS	
<24	154	8	139	0	14
24		19		1	
25		36		4	
26		39		7	
27		37		2	
28	35	30		-	
29	29	28		2	
30	31	27		4	
31	28	23		1	
total <32	277	247		22	

Comparison to our data shows only minor or no differences in the numbers of infants. These differences are caused mainly by the 22 deaths among the 85 infants that are not included in the study population

Table 10.9.1.2 First week deaths by birthweight

birthweight (g)	CBS	POPS	non-POPS
<500	140	5	128	10
500-749		40		
750-999		83		
1000-1249	126	73	112	7
1250-1499		39		
total <1500	266	240		17

(chapter 9.2), and partly by infants, who were born alive at home and died before arrival in the hospital (Damstra, 1986). This confirms again the completeness of the study cohort.

10.9.2 Comparison to the literature

In the beginning of this century, the survival rate of very low birthweight infants in the school for midwifery in Rotterdam was 0% (<1000 g) to 11.2% (1000-1500g) (Duyzings, 1935). Intensive care raised the survival rate to 33 and 68% respectively in 4 neonatal intensive care units in the Netherlands in 1972-1975 (Versluys, 1977). Since then, survival has evidently increased further, resulting in survival rates of 46% (<1000 g) to 82% (1000-1499 g) (table 10.3.3) in this study.

These results compare favourably to the mortality rates in two other geographically defined studies that have been published recently (table 10.9.2.1).

The same applies to NICU-based studies (chapter 2.4). In England and Wales, where birthweight is routinely recorded at birth and in cases of infant death, the neonatal mortality in infants with birthweight less than 1500 g was 295 per thousand (Office of Population Censuses and Surveys, 1985). However, comparison of birthweight categories, without knowledge of the gestational age distribution within such categories, is only of limited value, since we demonstrated the importance of gestational age for mortality (Verloove et al, 1986a).

In our study, no clear difference between boys and girls could be detected for mortality. This is in contrast with the generally accepted idea of an excess risk for boys, especially during the first week of life. This difference is believed to be caused by excess spontaneous

Table 10.9.2.1 In-hospital mortality rate in birthweight categories

birthweight (g)	Hamilton-Wentworth 1973-1977 (Saigal et al, 1982)		Turku* 1978-1982 (Tenovuo et al,1986)		the Netherlands 1983 (this study)	
	%	n	%	n	%	n
500-999	77	(76/ 98)	44	(26/ 59)	53	(152/ 287)
1000-1499	22	(38/167)	19	(22/115)	18	(149/ 805)
500-1499	43	(114/265)	28	(48/174)	28	(301/1092)

* neonatal mortality

preterm rupture of membranes (MacGillivray & Davey, 1985) or slower lung maturation (Papageorgiou et al, 1981; Khoury et al, 1985). In the Netherlands, the overall neonatal mortality rate in 1983 was 5.9 per thousand boys as opposed to 4.7 per thousand girls (Centraal Bureau voor de Statistiek, 1985b).

In a regional study, concerning the same kind of infants, Kollée et al (1984) described a much higher mortality in boys than in girls (49 out of 137 (36%) versus 16 out of 104 (15%). The factor "infants' sex" will be discussed more fully in chapter 14 and 15.

The crude mortality rates for the three hospital levels were comparable, despite significant differences in gestational age and birthweight. The relationship between hospital level and mortality will be further investigated in chapter 14. In multiple births, a consistently higher mortality rate was present in nearly all gestational age and birthweight categories. This will be discussed in chapter 14, as well as fetal presentation, mode of delivery, and SGA.

Unfortunately, the number of publications in which gestational age is included is very limited. Recently, Yu et al (1986c) reported on infants, born at 23-28 weeks' gestation. The outstanding results regarding survival, of the "aggressive " policy of Milligan et al (1984) have not yet been achieved elsewhere (table 10.9.2.2).

Papers in which mortality rates are described by gestational age as well as by birthweight, are scarce (Koops et al, 1982; Goldenberg et al, 1984). Table 10.9.2.3 shows a comparison between neonatal mortality rates in these papers and those in our study. The similarity in the variation of mortality in the birthweight/gestational age categories is striking.

Table 10.9.2.3 Neonatal mortality rate (%) by gestational age and birthweight in three studies
University of Alabama/University of Colorado/the Netherlands (POPS)

GA (wks)	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
BW (g)															
2250-2499									0/20/—						
2000-2249								0/20/—	0/20/14						
1750-1999							0/20/40	0/20/23	5/ 6/ 8						
1500-1749					0/20/—	0/20/17	0/20/14	5/ 6/14	9/ 6/ 8						
1250-1499					0/20/46	12/20/22	8/20/18	3/20/ 9	9/20/ 4	3/ 6/14	7/ 6/ 2	25/ 6/ 3	100/ 6/ 5	0/ 6/ 0	0/ 1/ 0
1000-1249			—/—/60	33/20/61	29/20/37	35/20/30	17/20/17	19/20/25	10/ 6/17	0/ 6/10	0/ 6/11	0/ 6/ 0	—/ 6/15	—/ 6/—	
750- 999	—/90/—	50/90/—	33/90/83	43/39/51	43/39/43	43/39/35	19/39/37	9/39/17	0/39/ 5	—/39/25	0/39/14	0/—/—	0/—/—		
500- 749	87/90/—	82/90/100	92/90/85	64/63/100	75/63/67	75/63/—	50/63/17	—/—/37							

University of Alabama, U.S.A., 1979-1981 (Goldenberg et al, 1984)
University of Colorado, U.S.A., 1974-1980 (Koops et al, 1982)
Present study (POPS), the Netherlands, 1983

Table 10.9.2.2 In-hospital mortality rate in gestational age categories

gestational age (weeks)	Ontario 1979-1982 (Milligan et al, 1984) % n	Melbourne 1977-1984 (Yu et al, 1986c) % n	the Netherlands 1983 (this study) % n
23	86 (6/ 7)	93 (26/28)	100 (5/ 5)
24	61 (14/ 23)	67 (27/40)	100 (19/ 19)
25	36 (16/ 44)	75 (33/44)	85 (41/ 48)
26	24 (11/ 45)	43 (27/62)	62 (48/ 77)
27	25 (15/ 60)	27 (24/87)	46 (47/103)
28	19 (17/ 88)	28 (27/95)	34 (46/136)
29	10 (10/ 99)		22 (37/171)
30	11 (10/ 91)		19 (38/204)
31	6 (7/112)		11 (26/244)

10.9.3 Conclusions

Total in-hospital mortality rate in very preterm and very low birthweight infants in the Netherlands compares favourably to earlier Dutch studies, to other geographically defined areas, and to studies based on birthweight categories.

In the analyses in chapter 14, neonatal death and in-hospital death will be used as outcome measures (dependent variables).

Chapter 11 Causes of death

11.1 Introduction

In our study population, a simple classification of causes of death, such as the one proposed by Wigglesworth (1980), could not be used. Nearly all infants would have been classified in one of only two categories: congenital malformation or immaturity.

Therefore, we decided to use a more detailed classification. We grouped the neonatal and postneonatal deaths by the disorder, likely to be the most important cause of death.

The data on cause of death were collected in such a way (table 4.1), that more than one cause of death could be recorded. In the 340 infants who died during the hospital stay, 505 causes of death were stated (table 11.1.1).

In several of the subpopulations within the study cohort, the frequencies of some of the causes of death (as stated by the paediatrician involved) differed considerably (table 11.1.1). For instance, congenital malformations were recorded as a cause of death more often in SGA-infants, while idiopathic respiratory distress syndrome (IRDS) and intracranial haemorrhage (ICH) were more frequently recorded as the cause of death in very preterm infants.

As in perinatal deaths, individual causes of death seldom operated in isolation (Wigglesworth, 1980). In each case a decision had to be made as to which cause of death should be regarded as the most important one. In cases, where more than one disease was recorded as a cause of death, we therefore chose the order stated in table 11.2.1.

Any infant counted in the first group (cause of death: congenital malformation) would not again appear below, even if any of the other disorders were also recorded as cause of death (in many of the infants for example, who died from IRDS, septicaemia or another infectious disease was mentioned as cause of death as well). If the cause(s) of death had changed after a post mortem examination, these changes were included in our classification. The data presented in chapter 11.2-11.4 concern all deaths in the cohort. We did not analyse the main causes of death separately in any of the subpopulations.

Table 11.1.1 Recorded causes of death in all 340 cases of in-hospital death, and over various subpopulations

chapter	cause of death	total n = 340	< 32 weeks n = 310	≧ 32 weeks n = 30	< 1500 g n = 306	≧ 1500 g n = 34	AGA/LGA n = 227	SGA n = 82
								
		n %	n %	n %	n %	n %	n %	n %
11.1	congenital malformation	36 (10.6)	21 (6.8)	15 (41.6)	28 (9.2)	8 (23.5)	20 (8.8)	16 (19.5)
11.1	IRDS	132 (38.8)	127 (41.8)	5 (16.6)	119 (38.9)	13 (39.4)	104 (45.8)	28 (34.1)
11.1	ICH	110 (32.4)	105 (33.9)	5 (16.6)	99 (32.4)	11 (32.4)	88 (38.8)	22 (26.8)
11.1	congenital infection	18 (5.3)	18 (5.8)	0 (0.0)	13 (4.2)	5 (15.2)	17 (7.5)	1 (1.2)
11.1	septicaemia	53 (15.6)	50 (16.1)	3 (10.0)	45 (14.7)	8 (23.5)	42 (18.5)	11 (13.4)
11.1	NEC	12 (3.5)	9 (2.9)	3 (10.0)	11 (3.6)	1 (2.9)	9 (4.0)	3 (3.6)
11.1	other	144 (42.3)	134 (43.2)	10 (33.3)	133 (43.5)	11 (32.4)	111 (48.9)	33 (40.2)

Table 11.2.1 Primary causes of neonatal deaths

primary cause	n	%
congenital malformations	32	10.3
IRDS	63	20.2
IRDS + ICH	56	17.9
ICH	54	17.3
infectious diseases	24	7.7
NEC	6	1.9
asphyxia	6	1.9
miscellaneous	16	5.1
"immaturity"	55	17.6
total	312	100.0

11.2 Neonatal deaths

The primary causes of neonatal death are stated in table 11.2.1. Idiopathic respiratory distress syndrome (IRDS) and intracranial haemorrhage (ICH) are the most important disorders, accounting for 55% of all deaths. Infectious diseases (septicaemia, meningitis, pneumonia) and necrotizing enterocolitis (NEC) caused only relatively few deaths, as did asphyxia.

"Miscellaneous" consisted of lung haemorrhages, hydrops, persistent fetal circulation, meconium ileus, chronic renal insufficiency, bronchopulmonary dysplasia (BPD), disseminated intravascular coagulation, mechanical birth injury, pneumothorax (without IRDS) and aspiration pneumonia.

The congenital malformations are specified in table 11.2.2. In 26 cases, the malformations were considered to have been incompatible with life even in a more mature infant, and therefore were labeled "lethal".

11.3 Postneonatal deaths during hospital stay

The causes of postneonatal deaths are stated in table 11.3.1. Of the congenital malformations, 2 were considered "lethal" (table 11.3.2). "Miscellaneous" was one case of chronic malabsorption and one case of cardio-respiratory insufficiency.

Table 11.2.2 Congenital malformation as primary cause of neonatal death

lethal congenital malformations		
chromosomal defects		
triploïdy	3	
trisomy 18	4	
syndromes		
Potter	5	
Saldino Noonan	1	
Penha Shokeir II	1	
unspecified syndrome	9	
other		
anencephaly	1	
multicystic encephalomalacia	1	
hepatoblastoma	1	
total		26
non-lethal congenital malformations		
chromosomal defects		
trisomy 21 (Down)	1	
cardiac malformation	3	
other		
diaphragmatic hernia	1	
ileal atresia	1	
total		6

11.4 Post mortem examinations

Of the 340 study infants that died during the period of hospital admission following birth, a post mortem examination was performed in 216 cases (63%). For infants, born in level 1 hospitals, a post mortem examination was done in 57% of the cases, for level 2 this was 60%, for level 3 72% .

In 18 cases, the post mortem examination led to a different classification of the cause of death (table 11.4.1). In a further 14 cases, additional information of clinical importance was obtained, but this did not change the primary diagnosis (table 11.4.2). In another 37 infants, the necropsy confirmed or elaborated the original clinical diagnosis (e.g. brainstem haemorrhage in ICH).

Table 11.3.1 Primary causes of postneonatal death

primary cause	n	%
congenital malformations	4	14.3
IRDS	1	3.6
IRDS + ICH	2	7.1
ICH	4	14.3
BPD	11	39.3
infectious diseases	4	14.3
miscellaneous	2	7.1
total	28	100.0

Table 11.3.2 Congenital malformation as primary cause of postneonatal death

lethal congenital malformations		
aquaduct stenosis with hydrocephaly and encephalocele	1	
holoprosencephaly	1	
total		2
non-lethal congenital malformations		
trisomy 21 (Down)	1	
cardiac malformation	1	
total		2

11.5 Discussion

In our study, the causes of death have been classified by the disorder, that was thought to be the most important factor contributing to death. However, in 18% of cases "immaturity" was stated as the cause of death in spite of a post mortem examination in half of those. Although "immaturity" is essentially correct (for in most cases one or more organ systems did not function properly), we regret that no more precise cause of death was mentioned. Ylppö (1919), Capper (1928a) and Duyzings (1935) already condemned the term "debilitas vitae". Immaturity is a

Table 11.4.1 Primary cause of death changed after post mortem examination

clinical cause of death	post mortem cause of death	n
ICH	IRDS + ICH	2
IRDS	IRDS + ICH	5
congenital infection	IRDS + infection	3
congenital infection	IRDS + ICH	1
ICH	tentorium tear	1
PFC	congenital malformation (cardiac)	1
lunghaemorrhage	triploïdy	1
congenital malformation	tentorium tear	1
immaturity	IRDS	1
unknown	ICH	1
hydrocephaly	congenital malformation (CNS)	1
total		18

statement and not a diagnosis. More specific knowledge about causes of death and their aetiology and pathophysiology is needed to develop causal treatment protocols for disorders of very preterm or very low birthweight infants.

A post mortem examination was performed in 63% of all deaths. This percentage was significantly higher in level 3 hospitals (72%) than in level 2 (60%) and level 1 (57%) hospitals (chi square = 6.0; $p < 0.05$). Compared to the 32% of post mortem examinations in all deaths in general hospitals (Anonymous, 1986), the 46% in a university hospital (de Vries et al, 1986), and the overall US autopsy rate in paediatrics of 14% (Dahms, 1986), the percentage of necropsies in neonatal deaths in the present survey is encouraging. However, 15% of the post mortem examinations resulted in a change of diagnosis or added clinically important information. This is in accordance with the reported frequency of 15% in general post mortem studies (Erhardt et al, 1959; Bonte et al, 1985), 12 to 25% in perinatal deaths (Gau, 1977), and 5-25% in paediatric cases (Dahms, 1986). Therefore, the number of post mortem examinations is still too low. We speculate that post mortem examination might have changed the cause of death in 15% of the 127 non-examined cases as well. In that case, we have to consider 19 cases as insufficiently documented. Ideally, extensive post mortem examination should be performed on all neonatal deaths, preferably by an experienced (team of) perinatal

Table 11.4.2 Cause of death unchanged; additional information of clinical importance obtained by post mortem examination

clinical cause of death	additional post mortem diagnosis	n
ICH	hydrocephaly	1
ICH	haemothorax, emphysema	1
ICH	lung haemorrhage, aortic thrombosis	1
ICH	umbilical phlebitis	1
IRDS	septicaemia	1
IRDS + infection	pneumothorax	1
IRDS	lunghaemorrhage	1
IRDS	emphysema	1
IRDS + ICH + infection	emphysema	1
BPD	bronchopneumonia	1
aspiration	lung infection	1
diaphragmatic hernia	microcephaly	1
chromosomal defect	cardiac malformation	1
ileal atresia	perforation and peritonitis	1
total		14

pathologist(s) (Anonymous, 1984), and according to protocol (Laurini, 1986).

The causes of neonatal and postneonatal deaths (tables 11.2.1 and 11.3.1) show a few peculiarities. Firstly IRDS, often in combination with ICH, is the main cause of death; of the 18% diagnosed as "immaturity", a large part probably also belonged to this category, so that in approximately half of all neonatal deaths in our study population, IRDS is the responsible disorder. However, only 122 infants out of a total of 621 cases of IRDS (chapter 12.3), died of the disease (20%). This is in contrast with 60-80% before the introduction of neonatal intensive care (Vapaavuori & Räihä, 1970), and 59% reported in a neonatal intensive care unit in the Netherlands in 1974-1978, when intensive care was being introduced (Keirse & Kanhai, 1981a).

Secondly ICH, with or without IRDS, contributes substantially to neonatal mortality. Whether any change has occurred in the proportion of the infants with ICH that die from this specific disease cannot be evaluated, since the diagnostic procedures and criteria have changed considerably.

Septicaemia was recorded as a cause of death in 53 infants (table 11.1.1), 16% of all deaths. However, in only 28 cases (8%), infectious disease was the only or most important stated cause of death.

The contribution of congenital malformations as a cause of neonatal death in our study population (10%) is comparable to that (5%) in a recent VLBW-population study (Goldenberg et al, 1983c) and to the 9.8% in the under 1500 g birthweight category in England and Wales (Office of Population Censuses and Surveys, 1985). In surveys of neonatal mortality in total populations, 18% (Brans et al, 1984) to 25% (Buckell & Wood, 1985) of deaths is due to congenital anomalies; in England and Wales more than 31% of all neonatal deaths in live born infants were caused by congenital anomalies, as was the case in Iowa-U.S.A. (Hein & Lathrop, 1986). In the Netherlands, 35% of all first week deaths were due to congenital malformations (Centraal Bureau voor de Statistiek, 1985a). In very preterm and very low birthweight infants there is clearly a preponderance of other causes of death.

The congenital malformations that we judged to be incompatible with life were stated separately, to enable re-evaluation. In the future, some of these disorders may no longer be considered lethal, or may be prevented by genetic counseling. The incidence we found in our study population (2.1% of liveborn very preterm or very low birthweight infants) is higher then the 1.0%, 0.4% and 1.6% found in preterm infants in Oxford, Cape Town and Leiden respectively (Keirse & Kanhai, 1981a). This may be due to a different gestational age criterion (Keirse: less than 37 weeks), or to a selection bias.

The list of causes of postneonatal death (table 11.3.1) shows the preponderance of bronchopulmonary dysplasia at this stage, as was found by others (Hack et al, 1980; Yu et al, 1984b; Beckwitt Turkel et al, 1986). Most of the other postneonatal deaths are also cases of "delayded neonatal death" (Verloove & Ruys, 1986b), and will therefore be included in the analyses of in-hospital mortality in our study population (chapter 14).

Chapter 12 Morbidity in the neonatal period

12.1 Introduction

The most noticeable disorders in the neonatal period in very preterm and very low birthweight infants are congenital malformations, idiopathic respiratory distress syndrome (IRDS), intracranial haemorrhage (ICH) and septicaemia. Together these disorders cause the major part of the mortality during hospital stay, and of morbidity later in life (e.g. handicaps, bronchopulmonary dysplasia).

12.2 Congenital malformations

In addition to 28 cases of lethal malformations (2.1% of the study population; chapter 11, tables 11.2.2 and 11.3.2), congenital malformations were diagnosed in 118 infants (8.8%). In 8 of those, the malformation was the cause of death. It could not be treated properly due to the preterm condition of the infant (tables 11.2.1 and 11.3.1). Another 16 infants died as a result from disorders related to the preterm condition; in those, the malformation was not the cause of death.

Details of the recorded non-lethal malformations are given in table 12.2.1. "Major" malformations (threat to life, necessity of surgery, cosmetic significance; Kuliev et al, 1985) were present in 97 cases. Together with 28 cases of lethal malformations, the incidence in the study population of major malformations is therefore 9.3% . In 21 cases, the malformation could be considered to be "minor" (absent umbilical artery, hypospadia, syndactyly, malformations of skin and ears).

The distribution of infants with lethal and non lethal congenital malformations by birthweight and gestational age is shown in table 12.2.2 and 12.2.3. In infants with a birthweight under 1500 g, 126 (11.5%) had congenital malformations, of which 23 lethal. In infants with gestational age under 32 weeks, 96 (9.5%) had malformations, of which 13 lethal.

Table 12.2.1 Infants with non-lethal congenital malformations

congenital malformation	n	%
chromosomal defects		
trisomy 21 (Down's Syndrome)	6	
other chromosomal defect	4	
	10	0.7
central nervous system		
hydrocephalus	3	
meningomyelocele	1	
other CNS malformation	6	
other CNS malformation, hydrocephaly	1	
hydrocephaly, dig. tract malf., umbilical artery absent	1	
hydrocephaly, umbil. art. absent,other malf. not specified	1	
hydrocephaly, cardiac malf., hypospadia, mult. other malf.	1	
	14	1.0
circulatory tract		
cardiac malf. (patent ductus arteriosus excluded)	16	
cardiac malf., absent umbilical artery	1	
cardiac malf., absent umbil. artery, other malf. not spec.	1	
cardiac malf., polydactyly	1	
cardiac malf., cavernous haemangioma	1	
cardiac malf., dig.tract malf. not specified, phocomelia/amelia	1	
absent umbilical artery	3	
cardiac malf., imperforate anus, other malf. genito-urinary tract, other malformation eyes	1	
	25	1.9
alimentary tract		
cleft palate	1	
cleft palate, cleft lip	1	
cleft palate, cleft lip, diaphragmatic hernia	1	
cleft palate, talipes, other malf.of limbs, other malf. of locomotor tract	1	
esophageal atresia, esophageal-tracheal fistula	1	
duodenal/ileal atresia	1	
duodenal/ileal atresia, syndactyly	1	
diaphragmatic hernia	1	
other malformation of digestive tract	7	
other malformation of digestive tract, bloodvessels	1	
other malformation of digestive tract, limbs	1	
	17	1.3

Table 12.2.1 (continued)

congenital malformation	n		%
genito/urinary tract			
hypo- or epispadia	7		
hypo- or epispadia, malf. of limbs	1		
hypo- or epispadia, syndactyly	1		
hypo- or epispadia, inborn error of metabolism	1		
other malformation of genito-urinary tract	1		
other malf. of genito-urinary tract, hypo- or epispadia	1		
other malf. of genito-urinary tract, ears, other malf. of locomotor tract, absent umbilical artery	1		
other malf. of genito-urinary tract; other malf. of eyes; multiple other malformations	1		
		14	1.0
respiratory tract			
lung hypoplasia	1		
other malformation of respiratory tract	2		
		3	0.2
locomotor tract			
polydactyly	2		
polydactyly, cavernous haemangioma	1		
syndactyly	1		
congenital dislocation of hip	2		
talipes	2		
other malformations of limbs	4		
other malf. of limbs, ears; microphthalmia, cav. haemang.	1		
skeletal malformation	1		
other malformation of locomotor tract	1		
		15	1.1
skin			
cavernous haemangioma	9		
other malformation of skin	3		
		12	0.9
miscellaneous			
malformation of ears	2		
inborn errors of metabolism	4		
other defects not specified	2		
		8	0.6
total	118		8.8

Table 12.2.2 Lethal congenital malformations

GA (wks)	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	unknown	total
BW (g)																				
2700-2799									1											1
2600-2699																				
2500-2599																				
2400-2499																				
2300-2399																				
2200-2299																				
2100-2199																				
2000-2099																				
1900-1999									1											1
1800-1899								1	1											2
1700-1799																				
1600-1699								1												1
1500-1599																				
1400-1499								1		2	1					1				5
1300-1399													1							1
1200-1299									1		1	1								3
1100-1199									1	1			1							3
1000-1099					1						1									2
900- 999					2					1										3
800- 899										1		1								2
700- 799							1				2									3
600- 699																				
500- 599																				
400- 499	1																			1
Total	1				3		1	3	5	5	5	2	2			1				28

Table 12.2.3 Non-lethal congenital malformations: total number (number that died in parentheses)

GA (wks)	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	unknown	total
B'W (g)																				
2700-2799																				
2600-2699																				
2500-2599																				
2400-2499																				
2300-2399																				
2200-2299																				
2100-2199																				
2000-2099																				
1900-1999									1											1 (0)
1800-1899									2 (1)											2 (1)
1700-1799								1	2											3 (0)
1600-1699							1	1 (1)	1											3 (1)
1500-1599						1 (1)	2	2 (1)	1											6 (2)
1400-1499						3	1 (1)	3	1		1		3	1		1				14 (1)
1300-1399						1	4	1	3	5	4			1						19 (0)
1200-1299				1 (1)	1	1	5 (3)	3 (1)	1	1		1	2		1	1				18 (5)
1100-1199						2 (1)	2	1 (1)	2	1	1	3 (1)								12 (3)
1000-1099			1 (1)	2 (1)		2	2	1 (1)	3 (1)	1	1									13 (4)
900- 999				3	1			1 (1)		1	1									7 (1)
800- 899				2 (1)		1	1	1	2 (1)					1						8 (2)
700- 799			2 (1)	1 (1)	1 (1)			1 (1)		1									1	7 (4)
600- 699		1 (1)				1		2		1										5 (1)
500- 599																				
400- 499																				
Total		1 (1)	3 (2)	9 (4)	3 (1)	12 (2)	18 (4)	18 (7)	19 (3)	11 (0)	8 (0)	4 (1)	5 (0)	3 (0)	1 (0)	2 (0)			1 (0)	118 (25)

12.3 Idiopathic respiratory distress syndrome

The clinical diagnosis "idiopathic respiratory distress syndrome" (IRDS) was defined by the need of extra oxygen for more than 24 hours, expiratory grunting, tachypnea, sternal and intercostal retractions, nasal flaring (621 infants, 46%). This diagnosis was confirmed by typical x-ray findings (reticulogranular aspect of lungs, air bronchogram, for more than 24 hours) or by findings at the post mortem examination (hyaline membranes) in 447 infants (33% ; table 12.3.1).

Table 12.3.1 Morbidity in the total study population

	clinical diagnosis		confirmed diagnosis	
	n	%	n	%
congenital malformations	146	11		
IRDS	621	46	447	33
ICH	333	25	272	20
septicaemia	469	35	165	12

12.4 Intracranial haemorrhage

In 333 cases (25%), a clinical diagnosis of intracranial haemorrhage (ICH) was made by the attending paediatrician. This diagnosis was confirmed by ultrasound, computerized tomography (CT) scan or post mortem examination in 272 cases (20%; table 12.3.1).

Although in many of these infants data were available allowing classification of intracranial haemorrhage according to Papile et al (1978), this information was not complete for all study infants. We therefore restricted such classification to infants, admitted to 6 NICUs where ultrasound examination of the brain was routinely performed (chapter 12.10 and table 12.10.1).

Of the 272 cases with confirmed ICH, 49 (18%) had convulsions. Of the remaining 1066 only 23 (2%) had convulsions.

12.5 Septicaemia

In this study, septicaemia was defined by means of three items: clinical condition of the infant; haematological findings (white blood

Table 12.5.1 Septicaemia

diagnosis		n		%
positive bloodculture				
clinical condition + haematology + culture	113			
clinical condition + culture	15			
haematological findings + culture	4			
culture only	8			
		140		
post mortem diagnosis only		25		
total confirmed diagnosis			165	12.3
without positive bloodculture				
clinical condition + haematology	232			
clinical condition only	72			
			304	22.7
total clinical diagnosis			469	35.0

count indicating severe infection), and positive bloodculture. In table 12.5.1 the relation between the three is described: in 165 infants (12%), septicaemia was diagnosed unequivocally; in 9 of these cases meningitis was present as well (bacterial culture of cerebrospinal fluid). In another 304 cases (23%), on clinical grounds septicaemia was considered to be present but could not be confirmed by bloodculture or post mortem examination.

Treatment with antibiotics was given in 160 of 165 infants with confirmed septicaemia, and in 781 other cases; this means, that 70% of the study population underwent antibiotic treatment.

12.6 Concurrence of disorders

The disorders described above (congenital malformations, IRDS, ICH, septicaemia) often occurred in the same infant. Thus, a total of 713 infants (53%) was affected by one or more of the confirmed conditions. About 40% of the infants with lethal or non-lethal congenital malformations also suffered from one or more of the other disorder (table 12.6.1). Of the normally formed infants, nearly half had one or more of the other diseases described in this chapter.

Table 12.6.1 Concurrent neonatal disorders (confirmed diagnoses)

disorders	n	
lethal congenital malformation		
congenital malformation only	18	
congenital malformation + IRDS	5	
congenital malformation + IRDS + ICH	1	
congenital malformation + ICH	3	
congenital malformation + IRDS + septicaemia	1	
		28
non-lethal congenital malformation		
congenital malformation only	64	
congenital malformation + IRDS	18	
congenital malformation + IRDS + ICH	14	
congenital malformation + IRDS + septicaemia	2	
congenital malformation + IRDS + ICH + septicaemia	1	
congenital malformation + ICH	8	
congenital malformation + septicaemia	11	
		118
normally formed infants		
IRDS only	220	
IRDS + ICH	125	
IRDS + septicaemia	31	
IRDS + ICH + septicaemia	29	
ICH only	72	
ICH + septicaemia	19	
septicaemia only	71	
		567
total		713

12.7 Morbidity in various subpopulations

Within the study population, we observed differences in the distribution of these disorders over various subpopulations (tables 12.7.1 and 12.7.2). The very low birthweight group and especially the SGA-subpopulation contained relatively more infants with congenital malformations, while short gestational age was associated with a relatively high incidence of IRDS. This was true when the disorder was defined rather widely (clinical diagnosis, table 12.7.1) as well as using the more rigid definition (confirmed diagnosis, table 12.7.2).

Table 12.7.1 Morbidity (clinical diagnoses) in various subpopulations

chapter	clinical morbidity	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
		n %	n %	n %	n %	n %	n %	n %
12.2	congenital malformations	146 (10.9)	96 (9.5)	49 (15.1)	126 (11.5)	20 (8.3)	77 (9.0)	63 (13.9)
12.3	IRDS	621 (46.4)	574 (56.8)	46 (14.2)	498 (45.3)	123 (51.0)	485 (57.0)	126 (27.8)
12.4	ICH	333 (24.9)	306 (30.3)	26 (8.0)	292 (26.6)	41 (17.0)	260 (30.6)	69 (15.2)
12.4	convulsions	72 (5.4)	66 (6.5)	6 (1.8)	63 (5.7)	9 (3.7)	57 (6.7)	15 (3.3)
12.5	septicaemia	469 (33.2)	379 (37.5)	89 (27.4)	391 (35.6)	78 (32.4)	330 (37.3)	137 (30.2)

Table 12.7.2 Morbidity (confirmed diagnoses) in various subpopulations

chapter	confirmed morbidity	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
		n %	n %	n %	n %	n %	n %	n %
12.3	IRDS	447 (33.4)	417 (41.2)	30 (9.2)	372 (33.9)	75 (31.1)	357 (40.3)	84 (18.5)
12.4	ICH	272 (20.3)	251 (24.8)	20 (6.1)	240 (21.8)	32 (13.3)	214 (24.2)	54 (11.9)
12.5	septicaemia	165 (12.3)	133 (13.2)	31 (9.5)	136 (12.4)	29 (12.0)	112 (12.7)	53 (11.7)

12.8 Length of hospital stay

Infants who died during the initial hospital stay did so after 0-295 days, mean 8.6 days, median 1.0 day. The 998 surviving infants were discharged home after an initial hospital stay (often in more than one hospital, due to referrals and backtransports) of 6-380 days, with a mean length of 68 days, median 63 days. The distribution of the length of hospital stay is shown in figure 12.8.1. About 81% of surviving infants was hospitalized for 5-12 weeks.

12.9 Short term outcome of survivors

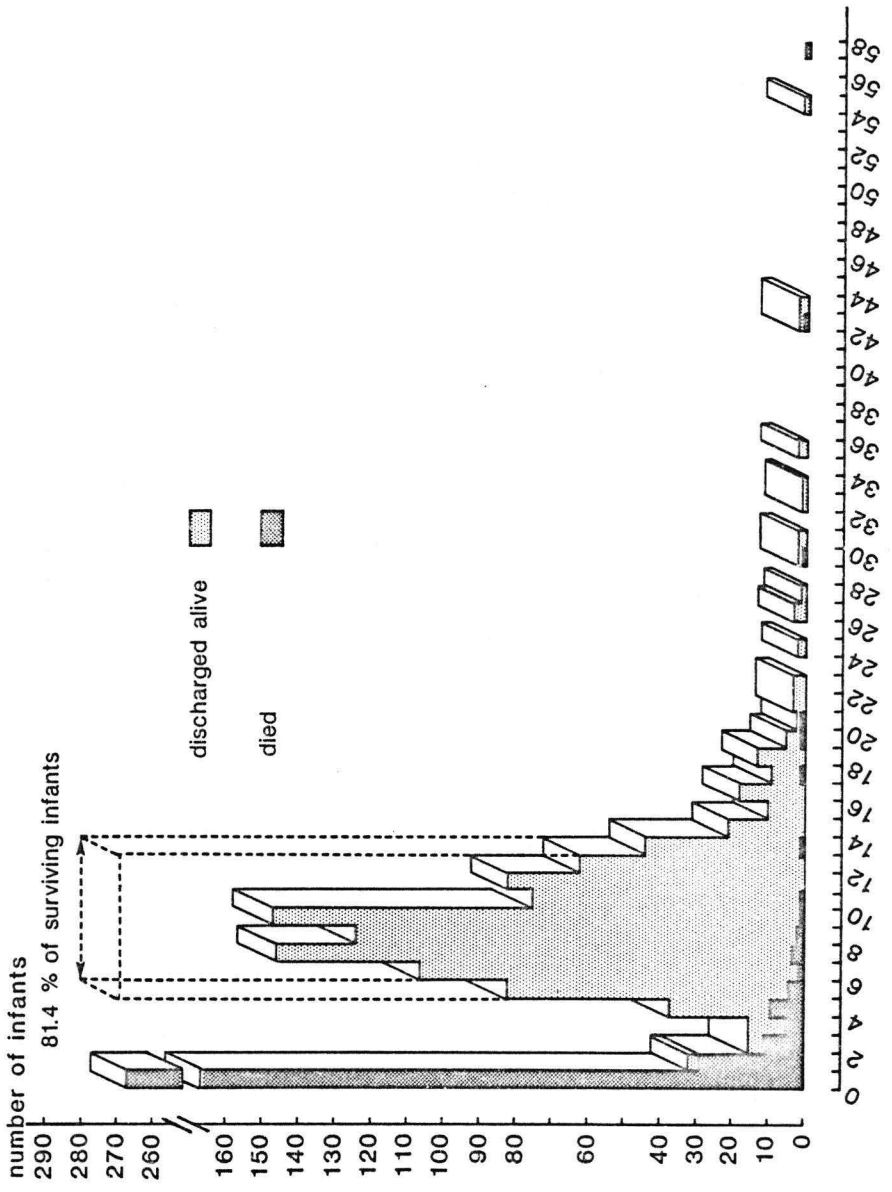
Weight at discharge home ranged from 1750 g to 7000 g, mean 2620 g. Over 80% of infants weighed 2250-3000 g at discharge home (figure 12.9.1 of which one infant of 7000 g has been omitted).

The attending paediatrician was asked to give an opinion on the condition of the infant at the time of discharge home. In 43 cases (3.2% of liveborn infants, 4.3% of surviving infants), the infant was thought to show signs of abnormality: 19 physical, 9 developmental and 15 both (table 12.9.1).

Table 12.9.1 Short term outcome

outcome	n	%
died	340	25.4
alive, discharged home		
physical abnormality	19	
developmental abnormality	9	
combination	15	
	43	3.2
normal	955	71.4
total	1338	100.0

Figure 12.8.1 POPS 1983: length of hospital stay (weeks)



12.10 Discussion

In the study population, the incidence of congenital malformations amounts to 10.9%: 2.1% lethal, and 8.8% non-lethal anomalies. In the subgroup of VLBW infants the incidence attained 11.5% . This is higher than mentioned in a recent report from Belgium (Gérard et al, 1985). In that study, 7% of very low birthweight infants had congenital defects. The difference is probably caused by the fact, that the Belgian study concerns intensive care unit populations, including referred infants, so less lethal congenital malformations may have been included.

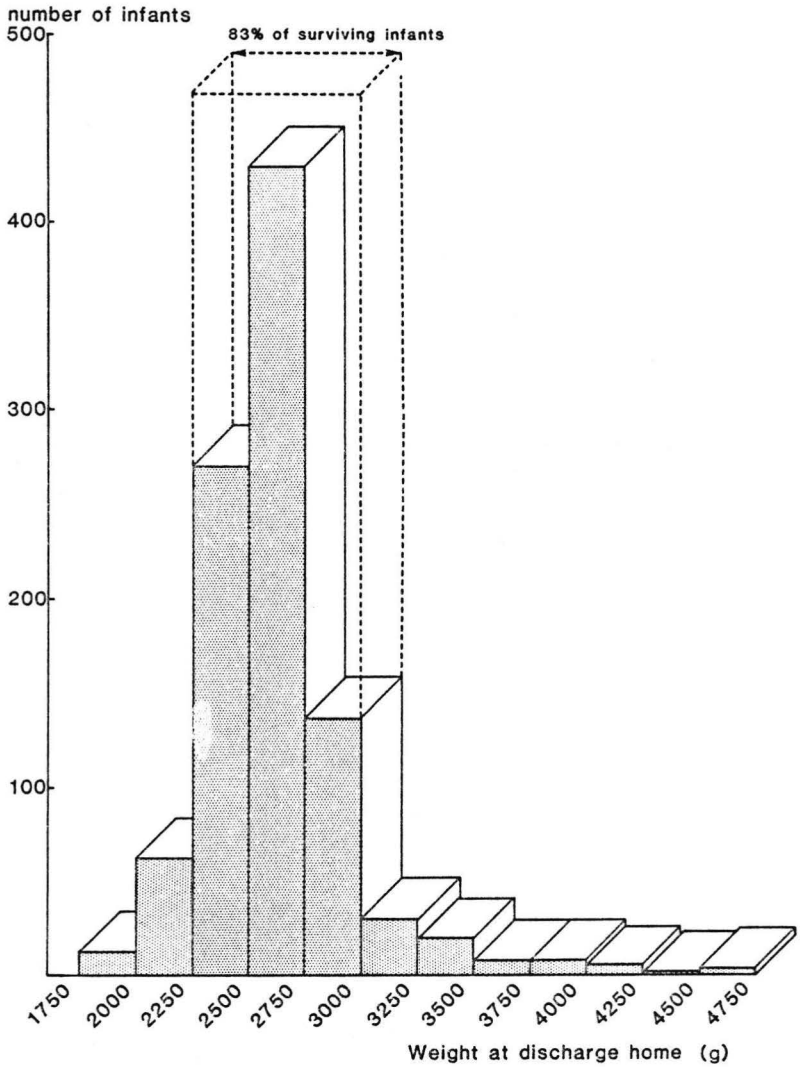
The reported incidence of congenital disorders in term infants varies: Cornel et al (1986) 2%; Kuliev et al (1985) 4-6%; Myrianthopoulos (1985) 15.6% . Presumably, the longer the follow-up period, and the broader the definition of malformation that is used, the higher the rate of malformations will be. The incidence of major malformations in our study (9.3%) is comparable to the 8.3% found in the Collaborative Perinatal Project (Myrianthopoulos, 1985).

Of the 146 infants with congenital defects, 53 died (36%). This percentage is higher than in the total study population. After exclusion of infants with lethal defects, the mortality during hospital stay is 25 out of 118 (21%), approximately the same as in the total group.

IRDS is still the most common disorder in very low birthweight and very preterm infants, as it has always been (Ylppö, 1919). The incidence of IRDS is higher in infants with a gestational age < 32 weeks than in infants with birthweight < 1500 g, when these groups are considered separately. However, as discussed in chapter 11.5, mortality from IRDS has fallen from 60-80% to 20% in our study population, due to the advanced techniques of symptomatic treatment. In our study, 85% of infants with IRDS got ventilatory support (IPPV or CPAP) and over 60% were parenterally fed.

The incidence of confirmed ICH in our study group (20%) is lower than would be expected according to others (Shinnar et al, 1982: 51%; Hawgood et al, 1984: 46%). Firstly, this may be due to the fact that it is an unselected population, in which the incidence should be lower than in intensive care units. Secondly, many reports on ICH concern very preterm infants only, and the relation between short gestation and ICH has well been established. The incidence in very low birthweight infants of relatively longer gestational age is much lower. In our study, only 20 out of 325 infants with gestational age of 32 weeks or more (6%) had confirmed ICH (table 12.7.2). Thirdly, the possibility must be taken into account that haemorrhages have gone unnoticed clinically in hospitals, where routine examination of the brain by CT-scan or ultrasound has not been used. Therefore, we separately analysed the infants,

Figure 12.9.1 POPS 1983: weight (g) at discharge home



admitted to level 3 hospitals where ultrasound examination of the brain was regularly performed. Of 484 infants with gestational age under 32 weeks, 140 (29%) had confirmed ICH (van de Bor et al, accepted for publication). Intracranial haemorrhages were classified according to Papile's grading system (1978):

- grade I subependymal haemorrhage
- grade II intraventricular haemorrhage
- grade III intraventricular haemorrhage with ventricular dilatation
- grade IV intraventricular haemorrhage with parenchymal haemorrhage

Occurrence as well as severity of ICH decreased with increasing gestational age, especially from 30 weeks onwards (table 12.10.1).

Table 12.10.1 Incidence and classification (Papile, 1978) of intracranial haemorrhage in gestational age categories

gestational age (weeks)	number of infants in study group	ICH		classification of ICH (%)			
		n	%	grade I	grade II	grade III	grade IV
<23	5	1					
24-25	22	10	45	30	30	10	30
26	39	14	36	7	21	14	58
27	61	18	30	17	33	22	28
28	79	38	48	26	26	11	37
29	85	27	32	26	22	30	22
30	98	18	33	28	6	33	
31	95	14	15	43	36	14	7
total	484	140	29	26	28	16	31

We conclude that even in this very preterm subpopulation in intensive care centres the incidence of ICH is relatively low (29%). This may be the result of the high standard of perinatal care, since most of the measures to prevent ICH as described by Szymonowicz et al (1986) were already routinely applied in the level 3 centres in the Netherlands at that time.

Of the 267 confirmed cases of ICH in the total study population, in 110 (48%) cases ICH was recorded as cause of death. As stated in chapter 11.5, any changes in mortality in this group are difficult to evaluate because of the different diagnostic procedures used nowadays; by CT-scanning and ultrasound examination of the brain, very small amounts of intracranial blood can be detected, that formerly would have gone unnoticed.

The incidence of confirmed septicaemia (12%) is again somewhat lower than reported incidences (18%) in the literature (Gérard et al, 1985; Johnson et al, 1985). This is probably, as was the case in ICH, due to the fact that our study population is unselected.

The reasons for the lack of bacteriological confirmation in the "probable" cases of septicaemia are not known. It may be conjectured that in the majority of cases a blood sample for culture has been taken (as is usual, when septicaemia is suspected), but that these cultures have remained sterile due to the small amount of blood available for culture or to earlier antibiotic treatment of mother or infant.

The four disorders described in this chapter together affected 713 infants, more than half of the total study population. Of these 713 infants, 270 (38%) died, so that 80% of all deaths occurred in this group. Of the remaining 625 infants only 70 (11%) died during the hospital stay.

Prevention of serious congenital malformations by genetic counseling, early detection and therapeutic interruption of pregnancy is, nowadays, common in the Netherlands (Thomassen, 1985) and the incidence of some defects, e.g. Down syndrome, may have decreased (Treffers et al, 1981). This matter needs further investigation.

Septicaemia can generally be treated well with antibiotic therapy. It was recorded as cause of death in 53 infants (table 11.1.1), i.e. 32% of the 165 confirmed cases of septicaemia, and 11% of the total 474 clinical cases. This is comparable to the 12 to 28% mortality in cases of confirmed neonatal septicaemia of all birthweights (Freedman et al, 1981; Placzek & Whitelaw, 1983; Bennet et al, 1985). Rarely, septicaemia was the only cause of death (24 out of 165 cases, 14%). Our findings do not support the view, that neonatal infections are an important determinant of mortality, as was reported in infants with birthweight of less than 1000 g (La Gamma et al, 1983).

However, with regard to the most important disorders, IRDS and ICH, no effective cure or preventive treatment was available for daily practice in 1983.

Any further fall in mortality and morbidity, and shortening of hospital stay of very preterm and very low birthweight infants, will have to be achieved by prevention or cure of these disorders. For that purpose, prospective randomized controlled trials are needed to test

promising hypotheses such as the effects of surfactant in the prevention and treatment of IRDS, and phenobarbital or vitamin E in the prevention of ICH.

The condition of the surviving infants at the time of discharge home is encouraging: in addition to a relatively low mortality rate, the number of serious abnormalities is rather low (3.2% of liveborn infants, 4.3% of surviving infants). In due time, the follow-up study of the surviving infants which is now in progress, will show whether the handicap rate and general health of the surviving infants is indeed satisfactory.

In chapters 14 and 15, IRDS, ICH, convulsions, septicaemia and congenital malformations will be entered in the multivariate analyses. For the sake of simplicity, only the clinical diagnoses (IRDS, ICH, septicaemia) have been included. Although in this way a small number of infants that in reality did not have the disorder may have been included, this overestimation was preferred to the considerable underestimation that would ensue from limiting the analyses to cases, confirmed by laboratory results.

For easy review, all variables that will be used in the multivariate analyses in chapters 14 and 15 ("key-variables") are listed in table 12.10.2. In addition to the observed frequencies in the total study cohort, the frequencies of the key variables in various subpopulations are presented.

Table 12.10.2 Distribution of key variables over various subpopulations (numbers adjusted to the infants: n = 1338)

chapter	key variables	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
		n %	n %	n %	n %	n %	n %	n %
5.2	maternal age <20 yr	68 (5.0)	50 (5.0)	18 (5.5)	54 (4.9)	14 (5.8)	46 (5.4)	21 (4.6)
	≧36 yr	56 (4.2)	40 (4.0)	15 (4.6)	42 (3.8)	14 (5.8)	34 (4.0)	21 (4.6)
5.4	socio-economic group	chapter 5.4	—	—	—	—	—	—
5.6	parity > 0	640 (47.8)	524 (51.9)	116 (35.7)	511 (46.6)	129 (53.5)	445 (42.4)	181 (39.9)
5.7	history of preterm birth or abortion	273 (20.4)	230 (22.8)	43 (13.2)	224 (20.4)	49 (20.3)	185 (21.7)	80 (17.6)
5.9	pre-existing maternal disease	86 (6.4)	50 (5.0)	35 (10.8)	77 (7.0)	9 (3.0)	38 (4.5)	47 (10.4)
6.4	maternal hypertensive disorders	300 (22.4)	139 (13.8)	161 (49.5)	289 (26.3)	11 (4.6)	81 (9.5)	217 (47.8)
6.5	smoking during pregnancy	387 (28.9)	267 (26.4)	119 (36.6)	329 (30.0)	58 (24.1)	227 (26.7)	155 (34.1)
6.7	medication and intoxication during pregnancy	668 (49.9)	474 (46.9)	193 (59.4)	563 (51.3)	105 (43.6)	395 (46.4)	265 (58.4)
6.9	prolonged duration of ruptured membranes	240 (17.9)	226 (22.4)	14 (4.3)	180 (16.4)	60 (24.9)	207 (24.3)	29 (6.4)
6.9	chorioamnionitis	100 (7.3)	96 (9.5)	4 (1.2)	75 (6.8)	25 (10.4)	89 (10.5)	10 (2.2)
6.10	tocolysis	591 (44.2)	533 (52.8)	58 (17.8)	445 (40.6)	146 (60.6)	469 (55.1)	114 (25.1)
6.11	glucocorticoid administration	190 (14.2)	173 (17.1)	17 (5.2)	139 (12.7)	51 (21.2)	151 (17.8)	38 (8.4)
6.12	hospital admission	1051 (78.6)	791 (78.3)	260 (80.0)	860 (78.4)	191 (79.3)	651 (76.5)	376 (82.2)
6.13	electronic monitoring:							
	abnormal CTG	365 (27.2)	187 (18.5)	177 (54.5)	336 (30.6)	28 (11.6)	112 (13.2)	249 (54.8)
	none	299 (22.3)	265 (26.2)	32 (9.8)	245 (22.3)	54 (22.4)	231 (27.1)	50 (11.1)

Table 12.10.2. Continued

chapter	total	total n = 1338	< 32 weeks n = 1010	≧ 32 weeks n = 325	< 1500 g n = 1097	≧ 1500 g n = 241	AGA/LGA n = 884	SGA n = 454
		n %	n %	n %	n %	n %	n %	n %
6.14	fetal presentation (breech)	362 (27.1)	293 (29.0)	69 (21.2)	314 (28.6)	48 (19.9)	245 (28.8)	109 (24.1)
6.15	elective delivery	333 (24.9)	155 (15.3)	178 (54.8)	306 (27.8)	27 (11.2)	85 (10.0)	243 (53.5)
6.16	mode of delivery (C.S.)	566 (42.3)	321 (31.8)	244 (75.1)	508 (46.3)	58 (24.1)	228 (25.8)	335 (73.8)
7.2	sex (male)	698 (52.2)	549 (54.4)	149 (45.8)	547 (49.9)	151 (62.7)	442 (51.9)	245 (54.0)
7.3	birthweight	table 7.3.2						
7.4	gestational age	table 7.4.2						
7.5	SGA (<10th percentile)	454 (33.9)	171 (16.9)	282 (86.8)	454 (41.3)	0	0	454 (100)
7.6	Apgar score 5 min (<7)	251 (18.8)	222 (22.0)	29 (8.9)	213 (19.4)	38 (15.8)	175 (20.6)	59 (13.0)
7.7	congenital malformation	146 (10.9)	96 (9.5)	49 (15.1)	126 (11.5)	20 (8.3)	77 (9.0)	63 (13.9)
7.8	multiple pregnancy	312 (23.3)	263 (26.0)	48 (14.8)	254 (23.2)	58 (24.1)	232 (27.3)	71 (15.6)
8.4	antenatal transport to level 3	240 (18.0)	205 (20.4)	35 (10.8)	204 (18.6)	37 (15.4)	159 (18.7)	80 (17.6)
8.3	level 1	498 (37.2)	352 (34.9)	143 (44.0)	406 (37.0)	92 (38.2)	341 (36.9)	163 (35.9)
	level 2	359 (26.8)	254 (25.1)	104 (32.0)	291 (26.5)	68 (28.2)	216 (25.4)	137 (30.2)
	level 3	481 (35.9)	404 (40.0)	78 (24.0)	400 (36.4)	81 (33.6)	321 (37.7)	154 (33.9)
8.4	neonatal transport (upgrading)	407 (30.4)	330 (32.7)	75 (23.1)	340 (30.9)	67 (27.8)	294 (34.5)	110 (24.1)
10.4	neonatal mortality	312 (23.3)	285 (28.2)	27 (8.3)	281 (25.6)	31 (12.9)	209 (24.6)	72 (15.9)
	in-hospital mortality	340 (25.4)	310 (30.7)	30 (9.2)	306 (27.8)	34 (14.1)	227 (26.7)	82 (18.1)
12.3	IRDS (clinical)	621 (46.4)	574 (56.8)	46 (14.2)	498 (45.3)	123 (51.0)	485 (57.0)	126 (27.8)
12.4	ICH (clinical)	333 (24.9)	306 (30.3)	26 (8.0)	292 (26.6)	41 (17.0)	260 (30.6)	69 (15.2)
12.4	convulsions	72 (5.4)	66 (6.5)	6 (1.8)	63 (5.7)	9 (3.7)	57 (6.7)	15 (3.3)
12.5	septicaemia (clinical)	469 (33.2)	379 (37.5)	89 (27.4)	391 (35.6)	78 (32.4)	330 (37.3)	137 (30.2)

PART 3 INFERENTIAL STATISTICS

Chapter 13 Methodology and statistical techniques

13.1 Introduction

As stated in chapter 4.6.2, multivariate statistical techniques were used to elicit associations between a number of perinatal factors on the one hand, and certain outcome measures on the other hand. This chapter offers a brief introduction to the multivariate technique that has been used in our study and the key concepts related to this technique: the logistic regression.

Some possible statistical procedures for analyses of this kind are stratification and subsequent application of the Mantel-Haenszel test statistic, linear discriminant analysis, loglinear analysis, and logistic regression analysis. Mantel-Haenszel and loglinear procedures were carried out initially, when we tried to establish the relative importance of gestational age and birthweight to mortality (Verloove & Verwey, 1986a). These procedures gave equivalent results with respect to logistic regression.

We decided against the application of the following three statistical procedures, because:

1. Stratification and application of the Mantel-Haenszel test statistic is neither appropriate nor feasible, because too many factors are involved
2. Linear discriminant analysis is a technique not suited for the analysis of discrete variables (as most of our factors are)
3. Loglinear analysis is equivalent to logistic regression if one is studying a dichotomous variable which could clearly be considered a response variable

Logistic regression is the method of our choice, because it has the following characteristics:

1. Control for confounders without the need for a (subjective) categorization of continuous variables
2. Simple determination of interaction (effect modification)
3. Simple calculation of the odds ratio as a measure in comparing risks in exposed and non-exposed groups

We applied logistic regression analysis with unconditional maximum likelihood estimation by means of the program PROC LOGIST from SAS in assessing exposure-disease relationships in our study.

In this chapter, we introduce some key concepts necessary for the understanding of the logistic regression analyses in chapters 14 and 15.

13.2 Odds and odds ratio

If we denote the probability of some event A by P(A), then the odds for this event are defined as:

$$O(A) = \frac{P(A)}{1 - P(A)}$$

The odds O(A) can be considered an alternative measure of probability besides the usual P(A). Both can be computed from each other:

$$P(A) = \frac{O(A)}{1 + O(A)}$$

Example:

Suppose the probability of neonatal mortality is 20% or .20, which is interpreted as, on the average, 1 out of 5 dies. The odds of dying can be computed as .20 / .80 = .25. In other words, expressed as an odds the chance of dying is 1 against 4. Thus, expressing the probability as a risk is talking about 1 out of how many, whereas an odds is talking about 1 against how many.

The odds ratio (OR) is a measure for the association between a (dichotomous) outcome and some (dichotomous) explanatory variable, usually called the exposure. It is defined as the ratio of two odds.

Suppose we have an exposure E and an outcome OUT, both dichotomous. Each person either has or does not have the disease OUT and is either exposed to E or unexposed. Then we have two odds to consider: O(OUT | exposed) and O(OUT | not exposed) which indicate the odds of the outcome conditional on the fact that the individual is exposed or not

exposed. Taking the ratio of these odds, we have the odds ratio for OUT with regard to the exposure E:

$$OR = \frac{O(OUT \mid E)}{O(OUT \mid \text{not } E)}$$

Hence, the odds ratio compares the odds on e.g. mortality in the exposed group against the unexposed group. An OR > 1 indicates a higher risk in the exposed group, an OR < 1 indicates a lower risk among the exposed as compared to the unexposed. Of course, statistical tests are available to test whether an OR is significantly different from 1. An OR of 1 implies both odds to be equal and hence both risks are equal too.

Another measure for such a comparison is the relative risk (RR). Just as the odds ratio is a ratio of two odds, the relative risk (or risk ratio) is a ratio of two risks:

$$RR = \frac{P(OUT \mid E)}{P(OUT \mid \text{not } E)}$$

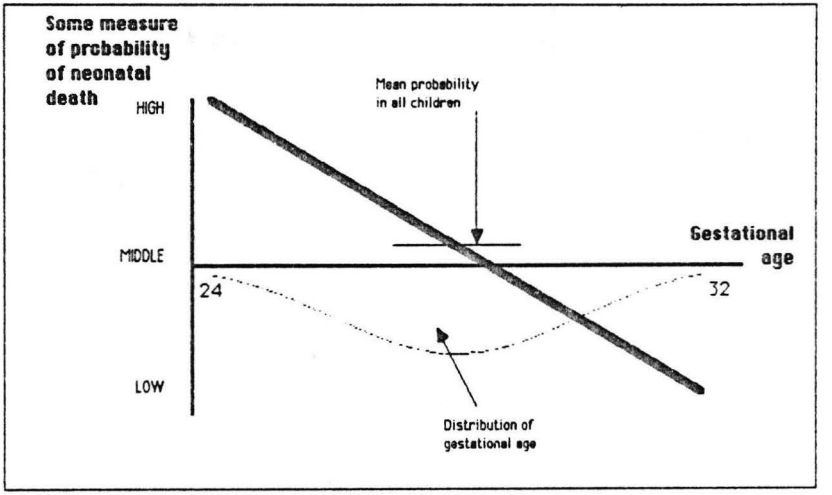
in which both probabilities are conditional probabilities. The RR and the OR are nearly equal in case the disease is rare enough. Although the RR might be easier to interpret, there is no reason to consider RR the parameter of primary interest when investigating possible associations between exposures and outcome measures. We formulate all our conclusions in terms of ORs. The OR is the normal choice when the logistic model is used: the parameters in the model have a direct interpretation in terms of ORs. Clinical interpretation of the OR is as straightforward and as easy as the interpretation of the RR. When necessary, we will also present the corresponding risks themselves for illustrative purposes. All our statistical tests will be based on the ORs.

13.3 Confounding and risk factors

In this section, we shall give a short introduction on the notion of confounding. We shall start with an example for illustrative purposes only and data used in this example have no relationship to any data presented in this thesis.

Suppose we want to study some outcome in our study population, e.g. neonatal mortality. We could estimate the probability of death by simply dividing the number of infants that died within 28 days from birth by the total number of infants in the population. Suppose furthermore, that there exists some relation between the probability of death and a specific factor, for example gestational age, which could be depicted as in the following diagram (figure 13.3.1):

Figure 13.3.1.



The continuous line depicts the relationship between the measure of probability and the gestational age for those gestational ages that are actually observed in this (hypothetical) study population. The normal curve (dotted line) is an attempt to visualize within the same diagram the distribution of gestational age within this population. We choose a normal curve for illustrative purposes only.

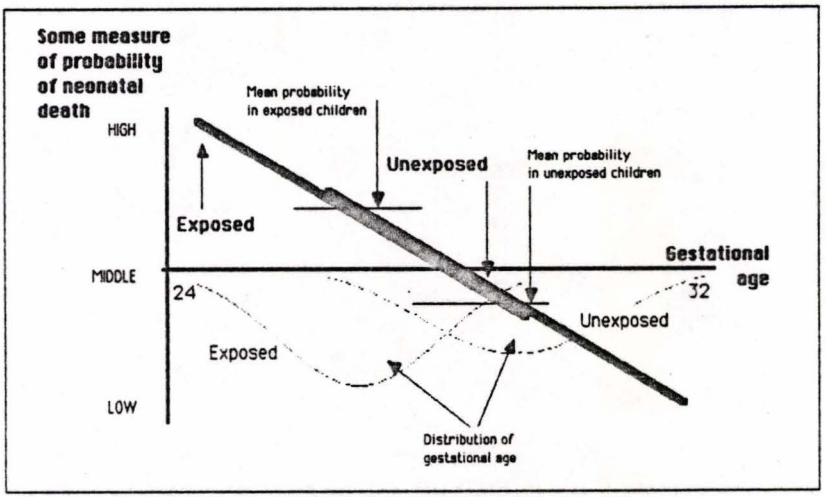
On the vertical axis, we have some measure of probability which we shall introduce later on. For the time being, it suffices to know that high values represent high probabilities and vice versa. The computed overall probability of mortality is indicated by a small horizontal line. It is evident that this diagram conveys much more information than the simple overall percentage of infants that died, by depicting the dependence of the probability of dying on gestational age.

Now suppose it is our goal to study the relationship between a certain exposure, denoted by E, and neonatal mortality. We could, of course, estimate the probability of neonatal mortality in both the exposed and unexposed group the same way we estimated the overall probability: one computes in both groups the percentage of infants that died in those groups.

Clearly, the question of clinical relevance we want to provide an answer for, is whether the exposure in itself is associated with the probability of dying. But, there are several reasons why these two

percentages (or "mean probabilities") may not be compared without due consideration. We shall try to visualize these reasons in the following diagrams:

Figure 13.3.2



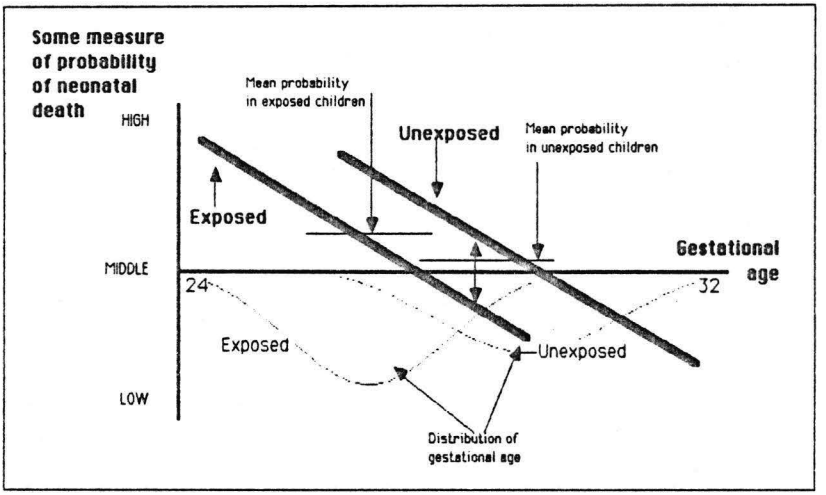
Suppose that in the population there is no causal relationship between the exposure E and the outcome. If we depict the relationship between mortality and gestational age as in figure 13.3.1, but now by two lines (one for the exposed and one for the unexposed group), these lines would coincide in this simplified situation. But if, for any reason, the distribution of gestational age, would be different in the exposed and the unexposed group, the percentages of infants dying in both groups would be different just as a result of the association between mortality and gestational age and not because of any association between exposure and outcome.

Hence, the clinically relevant question pertaining to the exposure is not the difference between the two mean probabilities, but the difference between the two lines in figure 13.3.2. Consequently, we need a technique to estimate the difference between the lines.

However, the situation could be even more complicated. In figure 13.3.3, we suppose that the exposure does, in fact, reduce the probability of mortality (line Exposed lies below line Unexposed). But due to

the fact that infants in the exposed group happen to have a lesser gestational age on the average, the exposed group has a higher mean probability for neonatal death.

Figure 13.3.3



It is evident that the reverse can occur as well: an exposure factor could result in a higher risk, but due to differences in the distribution of gestational age in both groups, it would appear to induce lower risks. In this situation, we say that gestational age is a confounder for the relation between the exposure and neonatal mortality. Hence we cannot estimate the effect of this exposure by comparing the exposed and unexposed infants by their respective observed mortality percentages, but only by the observed relationships between mortality and all factors which could possibly act as confounders.

In clinical terminology: to obtain information on the relationship between an exposure and some outcome variable, we should make corrections for differences in the distribution of other variables that may be associated with the outcome, or more precisely, that may influence the outcome-exposure relationship.

Now we will proceed with the concept of confounding. Kleinbaum et al (1982) defined a risk factor as:

"Any variable that the investigator determines to be "causally related" and antecedent to illness outcome status on the basis of substantive knowledge or theory and/or previous research findings."

Kleinbaum et al also gave a "working definition" of a confounder:

"A confounder is a risk factor for the disease under study whose control in some appropriate way will reduce or completely correct a bias when estimating the (true) exposure-disease relationship."

Hence in the (multivariate) study of risk factors, some (or all) risk factors should be considered as possible confounders when estimating the association between a factor and the outcome under consideration. Regarding the use of risk factors as (possible) confounders, Kleinbaum et al (1982) cautioned:

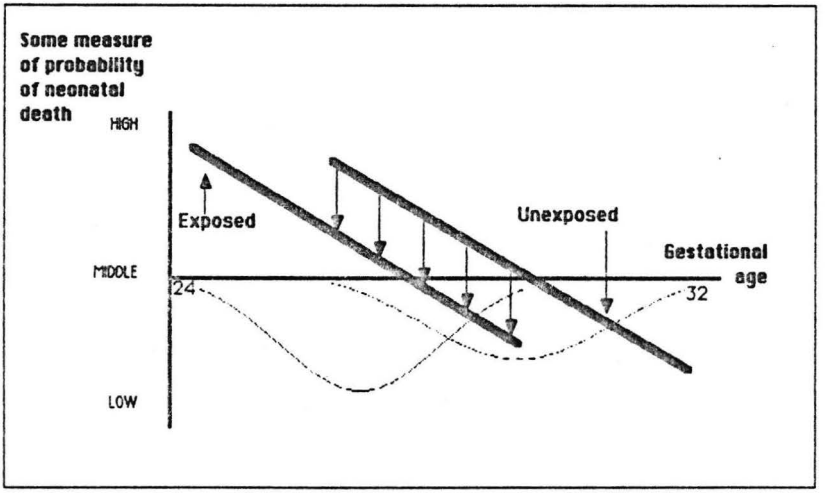
"A list of risk factors should be restricted to variables that cannot be characterized in causal terms as intervening in the causal pathway between exposure and disease. A pure intervening variable should not be considered as a potential confounder, since its control can spuriously reduce or eliminate any manifestation of a true association between Exposure and Outcome in the population." (See also "time related arrangement of perinatal factors", chapter 14.1.1).

A well known example is the following: suppose one investigates the relation between smoking (exposure) and lung cancer (outcome) and one considers "yellow fingertips" as a risk factor. If yellow fingertips would be considered a confounder for the exposure-disease relationship, then it would indeed change this relationship: after correction for yellow fingertips a true smoking-lung cancer relation would probably disappear, simply because non-smokers do not have yellow fingertips. In other words, the introduction of "yellow fingertips" as a confounder results in trying to answer the question whether there is a difference in risk between smokers and non-smokers apart from differences induced by (or associated with) yellow fingertips. Clearly, this is not a question of medical relevance. This effect is due to the fact that yellow fingertips are in no way - as far as we know - a plausible causal factor for lung cancer but simply a consequence of the exposure considered.

13.4 Interaction

The concept of interaction is introduced by another example. Consider the same situation as in the previous section, i.e. one risk factor (the exposure), a dichotomous outcome variable (neonatal mortality), and one confounder for the relation between the exposure E and the outcome (gestational age). We want to consider the differences between two diagrams, figures 13.4.1 and 13.4.2.

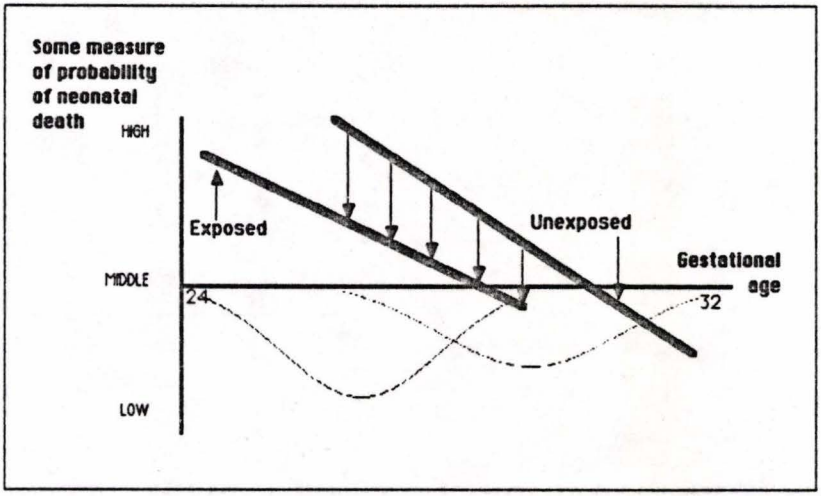
Figure 13.4.1



In figure 13.4.1, the lines that indicate the relationships between neonatal mortality and gestational age in both risk groups are more or less parallel. In figure 13.4.2, we suppose that the exposed and unexposed groups differ in the way the outcome is associated with the confounder in each group.

In the previous section we pointed out that, to answer the clinically relevant question, we had to compare the lines which depict the probabilities in both the exposed and unexposed group. In figure 13.4.1, the answer is straightforward: one can define the distance between two parallel lines and interpret this distance as a difference in risk. Because we considered lines, we made an implicit correction for differences in gestational age in both risk groups.

Figure 13.4.2



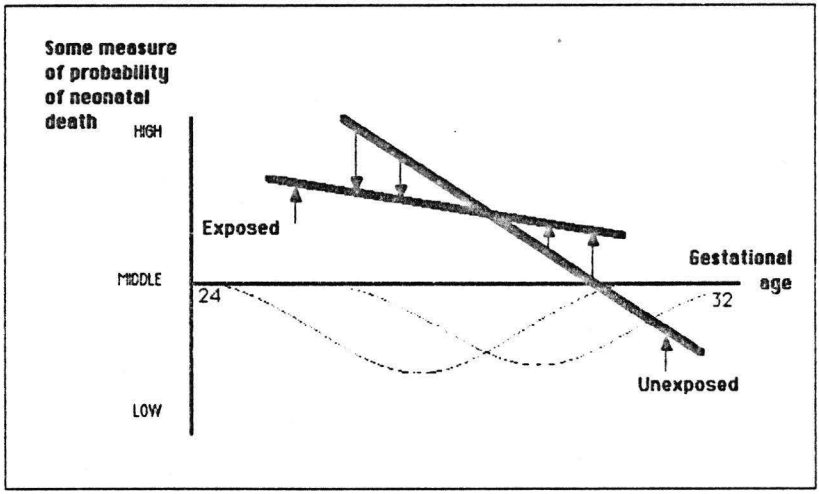
In general, for a specific gestational age represented in the figure, the difference in risk for infants in both groups can be viewed as the difference between both lines at that specific gestational age. However, in figure 13.4.1, this difference is the same for each gestational age by virtue of the parallelism of the lines, and can be given by one number, independent of gestational age. But in figure 13.4.2, this difference depends on the particular gestational age under consideration. Thus, no single number can be an answer to the clinical question. This number varies with the value of the confounder (gestational age) and hence an answer to the question should be a description of the relationship between confounder and exposure.

This phenomenon, where the relationship between outcome and exposure is modified by a confounder, is called effect modification. When present in the data under investigation, it is called interaction.

When interaction is present in the data, one can still compute a difference between the two lines by "forcing" them in some way to be parallel and thus providing a sort of "mean difference" between both risk groups. However, this "mean difference" is not a good estimate of the differences in risk between exposed and unexposed infants when one considers a particular value of the confounder. Similarly, an overall mortality percentage is not a good estimate of the mortality risk itself when considering a particular value of gestational age (if mortality depends considerably on gestational age), although the overall difference may be worth knowing.

Figure 13.4.3 depicts another example of interaction. Contrary to figure 13.4.2, where the magnitude of the difference between exposed and unexposed varied, in this situation not only the magnitude, but also the direction of the effect changes from positive to negative. Obviously, in this situation a "mean difference" between those lines is an unreliable and probably useless description of the situation.

Figure 13.4.3



13.5 The logistic regression equation

In ordinary linear regression, one models through a linear equation the expected value of some dependent variable, measured on a numerical scale, as a function of one or more other independent variables. One supplies a formula by which the expected value of e.g. the variable OUT is estimated, by measuring one or more other variables, such as GA (gestational age):

$$\text{expected value of OUT} = a + b.GA$$

In this formula, a and b are numbers chosen in such a way that this linear function is as close as possible a description of "reality".

The logistic regression deals with dependent variables which are not measured on a numerical scale (as are length, age or weight), but which

are dichotomous and can have only 2 values (yes/no, with/without some disease, dead/alive). In a logistic regression equation, one does not model the expectation of the outcome variable itself, but the probability that this outcome has one of the two possible values.

The logistic counterpart of the above linear regression equation for a dichotomous variable OUT (which we suppose to be some real "outcome", in the sense that it can be viewed as a consequence of the independent variables) would be:

$$\log(\text{odds}(OUT)) = a + b.GA$$

The reason that we do not model P(OUT) is that the above equation has very desirable mathematical properties[1] and that the parameters (values such as a and b) in such an equation have a direct and simple clinical interpretation[2].

The log(odds(OUT)) is exactly the measure referred to in our diagrams in the preceding sections on confounding and interaction (OUT is the outcome variable, in this example: neonatal mortality). If we use the vertical axis to measure the log(odds), then figure 13.3.1 can be described by this logistic equation:

$$\log(\text{odds}(OUT)) = a + c.GA$$

where in our case c is negative since the probability, and hence the odds, of dying decreases with increasing GA (gestational age).

[1] One of these is the following: choosing in our diagrams not the log(odds) as a probability measure, but the risk itself, straight lines (i.e. a linear model) would have been impossible, because risks under 0% or above 100% are impossible. Modelling in such cases can lead to uninterpretable results. Since the log(odds) can vary between minus and plus infinity, no such thing can happen. In the same way, relative risks can become uninterpretable (e.g., an RR of 2 is impossible if the base category already has a risk above 50%), but odds ratios cannot.

[2] However, one can easily calculate P(OUT) from log(odds(OUT)) and vice versa: suppose log(odds(OUT)) = .6, then by definition of the logarithm, odds(OUT) = exp(.6) = 1.82 and hence P(OUT) = (odds(OUT) / (1+odds(OUT))) = 1.82/2.82 = .65 (=65%). Alternatively, suppose P(OUT) = 20% = .2, then odds(OUT) = P(OUT) / (1-P(OUT)) = .2 / .8 = .25; hence log(odds(OUT)) = log(.25) = -1.39

Next, consider the logistic model:

$$\log(\text{odds}(OUT)) = a + b.E + c.GA \qquad \text{(equation 0)}$$

in which the exposure E can have a value of either 0 (unexposed) or 1 (exposed), and OUT is the outcome variable. Substituting both values in this equation leads to two formulas for the calculation of the odds on mortality:

exposed: $\log(\text{odds}(OUT)) = a + b + c.GA$ (equation 1)
unexposed: $\log(\text{odds}(OUT)) = a + c.GA$ (equation 2)

If b would equal 0, then both lines would coincide (have a distance 0) and hence there would be no exposure effect. This corresponds exactly to figure 13.3.2.

On the other hand, if b would be less than 0, both lines would be parallel (they would have the same slope c) and would only differ in height by an amount of (a+b) - (a) = ...b. This coefficient b is exactly what we were looking for. The number b is the distance between the two lines, measured as log(odds), so b is a measure for a difference in probability of the outcome between the exposed and the unexposed.

Looking at it in an other way, we have 2 equations which model the log(odds) as a function of gestational age, one for the exposed and one for the unexposed (both derived from the one equation 0). Subtract equation 2 from 1. The left hand side becomes:

$$\log(\text{odds}(OUT \mid \text{exposed})) - \log(\text{odds}(OUT \mid \text{unexposed}))$$

which equals[3]:

$$\log\left(\frac{\text{odds}(OUT \mid \text{exposed})}{\text{odds}(OUT \mid \text{unexposed})}\right) \underset{\text{def.}}{=} \log(OR_E(OUT))$$

The right hand side becomes:

$$(a + b.1 + c.GA) - (a + b.0 + c.GA) = b$$

for any value of GA.

[3] By virtue of the general property of logarithms:
$\log(a) - \log(b) = \log(a/b)$ for any a and b.

Hence the coefficient b is quite simply equal to the logarithm of the odds ratio with respect to the exposure E and the outcome OUT and thus we have:

$$OR_E(OUT) = e^b$$

Conclusion: a statistical test for the null hypothesis that the coefficient b equals 0 is exactly an answer to the (clinical) question whether there is evidence in the data that the exposure E is associated with the disease OUT after correction for possible differences in the distribution of gestational ages in both groups.

This concept can be generalized: suppose $R_1, R_2, \ldots\ldots R_n$ are (generally acknowledged or supposed) risk factors for the disease OUT. Then, the probability of the occurrence of the disease can be modelled as:

$$\log(\text{odds}(OUT)) = a + b_1.R_1 + b_2.R_2 + \ldots\ldots b_n.R_n$$

The b_i can be considered as the individual contributions of the risk factors R_i, adjusted for the other Rs, to the log(odds(OUT)): just let R_i play the role of exposure E and let the other risk factors act as confounders, subject to the restrictions imposed by the definition of a confounder as stated before[4]. By renumbering the remaining risk factors, the equation can be written as:

$$\log(\text{odds}(OUT)) = a + b.E + b_1.C_1 + \ldots\ldots\ldots b_{n-1}.C_{n-1}$$

By subtracting the equations one gets, substituting E=1 for exposed and E=0 for unexposed:

$$\log(OR_E(OUT)) = b$$

which is a mathematical formulation of this "individual" contribution.

Now for the interaction. We return to figures 13.4.1 and 13.4.2, and consider the following equations:

exposed:	$\log(\text{odds}(OUT)) = a + b + (c+d).GA$	(equation 4)
unexposed:	$\log(\text{odds}(OUT)) = a + \quad (c\ ).GA$	(equation 5)

We repeat that the coefficient of GA is, in fact, the slope of the regression line. Therefore, we suppose that for the unexposed there is a

[4] This implies that some of those Rs must be deleted because they cannot be considered a true confounder (e.g. because of the time-related arrangement of factors) for the association OUT-E.

line with slope c and for the exposed another line with slope c+d for some value of d. Hence figure 13.4.1 corresponds to the situation in which d equals 0, and figure 13.4.2 to the one in which d > 0. If both lines coincide, then both b and d equal 0. We can combine these two equations into one equation by introducing the exposure E into the equation[5]:

$$\log(\text{odds}(OUT)) = a + b.E + c.GA + d.E.GA \quad \text{(equation 3)}$$

This equation differs from equation (0) by the term d.E.GA, the product of the parameter d, the exposure (1 or 0), and the confounder GA (gestational age). Hence a statistical test for the null hypothesis:

$$d = 0$$

is the same as a test on interaction or (clinically speaking) an answer to the question whether the odds ratio varies with GA.

A bit more mathematically: if we subtract equation 5 from equation 4, we get:

$$\log(OR_E(OUT)) = b + d.GA$$

This means that the OR amounts to some value b, to which one should add d.GA for each gestational age considered[6]. If d equals 0, the OR does not vary anymore with varying GA and is just one number, b.

In summary: a logistic regression equation which models the effect of an exposure factor E on an outcome variable OUT, in which we make adjustments for (possible) confounders C_1, C_2,....C_n, has the following general form:

$$\log(\text{odds}(OUT)) = a + b.E + c_1.C_1 + \ldots + c_n.C_n + d_1.E.C_1 + \ldots + d_n.E.C_n$$

If all d_i can be supposed to equal 0 (e.g. by some statistical testing method), the equation reduces to:

$$\log(\text{odds}(OUT)) = a + b.E + c_1.C_1 + \ldots + c_n.C_n$$

and hence we have: $\log(OR) = b$

[5] Substituting a value of 0 for E yields the equation for the unexposed. A value of 1 yields the equation for the exposed.

[6] Note that the coefficient b in itself has no clinical interpretation here.

If for example, d_1 and d_2 cannot be supposed to equal 0, the equation would be:

$$\log(OR) = b + d_1.C_1 + d_2.C_2$$

and hence the OR can be computed from this model by specifying the values of both C_1 and C_2.

13.6 Coding of factors in logistic regression equation

The following coding scheme may facilitate the interpretation of the coefficients in the logistic regression equation. We applied this coding scheme to all our analyses. Variables, which are by their very nature dichotomous, are coded with the values 0 and 1. The absence of a factor is always coded as 0, the presence as 1.[7]

Variables which are measured on a numerical scale (e.g. gestational age and birthweight) are coded as such.

Variables which are coded on an ordinal scale can be treated as numerical ones. However, in that case, the equation is forced to have the same "impact" on a difference between e.g. category 1 and 2 as on the difference between e.g. category 4 and 5. When this is undesirable, either a recoding should take place, or the procedure should be followed as described for the next type of variables[8].

Variables which are coded by more than 2 values on a categorical scale (e.g. religion) are substituted by a set of so called dummy variables,

[7] We even adopted the convention of formulating the description of all our risk factors in such a way, that the value 0 (absence) may be considered the "desirable" of the two coding possibilities, thus allowing an easy and consistent interpretation of all coefficients (OR) in the equation.

[8] An example of such a type of variable is parity. Coded as 0,1,2,...., the "difference" between an 0- and an 1-mother is the same (with regard to the outcome) as between a 3- and a 4-mother. When studying parity, we are mainly interested in the difference between 0-mothers and all others. Therefore, this variable may be recoded into a 0-1 variable, which takes the value 0 (to indicate a 0-value for parity) or the value 1 (to indicate all other parities). If always entered into or deleted from the equations together with the variable coded on a ordinal scale, this procedure allows the model some more flexibility with respect to this variable.

each a 0-1 variable, which together represent exactly the information contained in the original variable[9]. This set of dummies is always treated as an entity during analysis[10].

When a factor has many missing values in the data, inclusion of this factor in the regression equation would result in a substantive loss of information (because cases with one or more missing values are deleted from the analysis) which is not acceptable. Alternatively, omitting the factor from the analysis (which is done very often) entails the danger of introducing a substantial bias if the factor should happen to be a strong confounder for the exposure-outcome relationship under consideration. One should at least try to circumvent these drawbacks in the following way: whenever a (dichotomous) factor has a lot of "missing values", one creates an extra variable which indicates for each infant whether or not the value of this factor was known (available), assigning the value 0 if the value is known, or 1 if it is unknown. The factor itself is then recoded in the following way: if the factor is unknown or unexposed, the value 0 is assigned; if the factor belongs to the category "exposed", a value of 1 is assigned. Although each of these 2 variables on its own provides incomplete information, considering both factors together, one can always tell what the "original" value was (e.g. the combination 0-1 indicates exposed, 0-0 indicates unexposed, and 1-0 indicates unknown; 1-1 is logically impossible).

The process is a special case of creating dummy variables as described above. By considering these two variables as a pair in the logistic regression analysis, one can indeed take into account a possible confounding effect of the risk factor itself and of the absence-presence effect of the risk factor (which can be very important), thus preventing selection bias by missing values as much as possible.

[9] It should be noted that some computer programs compute these dummies automatically during the logistic regression analysis (e.g. BMDP). In other programs the user has to define them.

[10] An example: Suppose the variable R has codes 0,1,2 and 3 as possible values. We make 3 dummy variables, R_1, R_2, and R_3, defined as follows: R_1, R_2, and R_3 are all 0 if R equals 0. If R = 1, only R_1 = 1 (R_2 = R_3 = 0). If R = 2, then R_2 = 1 (the others are 0), and the same applies to R_3. Now we have the following possible combinations (the only ones): R_1, R_2, R_3 = (0,0,0) / (1,0,0) / (0,1,0) / (0,0,1), corresponding to R = 0/1/2/3. After this process and upon entering these dummies as a set into the logistic regression equation, each dummy-coefficient has its interpretation in terms of comparing the base category (R = 0) to the category described by this dummy.

13.7 Calculation of an odds ratio for a combination of a specific factor and a specific outcome variable

For each exposure under consideration in chapter 14 and 15, an odds ratio (OR) with 95% confidence interval (CI) has to be calculated from a logistic regression equation for each outcome variable. This will provide a measure for the association of this (perinatal) factor and the outcome, while adjusting (correcting) for other factors (confounders).

Firstly, we shall give the general procedure to obtain the OR for a certain exposure. In our opinion, this is the preferred approach (also in terms of computing time) when the number of exposures is small with respect to the number of confounders considered (especially in case one studies an exposure's effect and wants to adjust for confounders)[11]. To obtain a regression equation from which the OR for an exposure under consideration is to be derived, we recommend the strategy nr. 4, as proposed by Kleinbaum et al (1982)[12]. We will add a (preliminary) step to this procedure which we shall discuss after we have outlined this approach.

E denotes the perinatal risk factor under consideration as the exposure, and OUT the outcome. Furthermore, C_1, C_2 denote the other perinatal factors[13] which can be considered as possible confounders for the E-OUT association. The actual selection of these confounders in our study is described in chapter 14.

[11] However, in case one wants to estimate the "effects" of nearly all confounders (as is the case in our study), applying this procedure over and over again for each exposure is far more costly than the (equivalent) method of establishing the logistic regression equation which does not only incorporate all confounders themselves, but also all products of confounders. The coefficients simply determine the odds ratios, even in the case of interaction.

[12] Because we are in the special situation that each risk factor in turn plays the role of an exposure, we shall combine the results of this strategy in each case, in order to reduce the amount of computing time. Essentially, we compute only one equation from which we can derive all odds ratios in one step.

[13] Strictly speaking a C_i could also be a product of other confounders. For example, apart from birthweight and gestational age, it might be necessary to consider the product of these two confounders as a third confounder. We refer to chapter 13.3 for the definition of a confounder.

After choosing the potential confounders C_1, C_2,....C_n, the product is formed with E to obtain first order interaction terms:

$$E.C_1,\ E.C_2,\ .....\ E.C_n$$

The logistic regression equation models the odds as a function of the exposure, the confounders, and the interactions as follows:

$$\log(\text{odds}(OUT)) = a + b.E + c_1.C_1 + ... + c_n.C_n + d_1.E.C_1 + ...$$

By using a backward stepwise algorithm, the interaction terms must be considered for exclusion from the model on the basis of a statistical significance test. We chose a significance level (α) of 0.01. This value of α was chosen for two reasons:

Firstly, the underlying statistical question is whether there is any interaction at all; but the answer is obtained in a stepwise fashion, thus by multiple testing. In order to minimize type I errors, we chose a lower level for α compared to the one advised by Kleinbaum (1982). However, in the case he describes, there is only 1 exposure, while we have many.

Secondly, the purely clinical interpretation of the interaction terms (effect modifiers) is important, but can be very difficult. In our opinion, the advantage (in terms of possibility of reasonable interpretations) of choosing an $\alpha = 0.01$ and thus retaining only very strong (and very few) possible effect modifiers outweighs the disadvantage that important effect modifiers might be overlooked. The only consequence is that an overall OR will be stated instead of a (different) OR for each category of the effect modifier.

As to the interpretation of "interaction", we repeat that if an interaction term, e.g. $E.C_i$, in the logistic regression equation is found to be significant, this means that (in the data) the OR of the exposure under investigation cannot be supposed to be constant over all values of the factor C_i. The ratio of the odds for the exposed versus unexposed is significantly different in the category $C_i = 0$ from the category $C_i = 1$ (for dichotomous factors; the same holds mutatis mutandis for continuous factors).

This leads to the possibility of effect modification in the population, in which case the relationship between the exposure and the outcome is modified by the variable C_i and cannot be described by a single OR.

After deleting as many interaction terms as possible, the coefficient of E provides the estimated OR for the exposure (or, in case of one or more interaction terms $E.C_i$, the combination of those coefficients).

In our case, P-values for testing the null hypothesis of the OR equaling 1, were provided by the computer program PROC LOGIST.

We calculated approximate confidence intervals (95%) based on the standard error of the coefficient in the regression equation.

When no interaction is present, the coefficient of E provides the odds ratio comparing the odds in the exposed and unexposed groups. When interaction is present, the OR can only be given for each category as defined by the combination of factors retained in the backward selection process. This OR is computed from the coefficients of both the exposure and the significant interaction terms. Confidence intervals are computed using the estimated covariance matrix (e.g. produced by PROC LOGIST). This concludes the outline of strategy nr. 4 from Kleinbaum et al (1982).

In the initial process of selecting the confounders C_1.....for the relationship E-OUT, one should enter all possible confounders into the equation, but not every possible interaction term $E.C_i$. We did not consider these terms eligible for inclusion into the equation if this product had limited dispersion. Dispersion is defined as:

$$\frac{\text{mean(E.C)-minimum(E.C)}}{\text{range(E.C)}}$$

and it is said to be limited if it is either less than 5% or greater than 95%. Therefore, we excluded interaction terms for which the above expression is near to 0 or to 1. This can happen when there are some "outliers" among the values of E.C, predominantly at one side of the distribution. Remember that the coefficient of E.C tells us how much the OR varies with the confounder C. If we would allow such a term into the equation, on the one hand there would be little chance that it has any influence at all, but on the other hand, if the few "outliers" would all happen to be in the same OUT-category (so happen to be dead or alive), then this term would suddenly be highly significant, but of no practical clinical meaning. To avoid such difficult to interpret coefficients, we adopted this "pre-screening" of the $E.C_i$ terms.

We also calculated the overall OR, even in the presence of interaction. We considered an overall OR, even when we know it to be modified by the values some other factor(s) assume, a useful measure for comparing risks in the exposed and unexposed groups.

13.8 Prediction of risks; prediction sets

Based upon the logistic regression analysis, the risk for a certain outcome variable (e.g. mortality) can be estimated for each possible combination of risk factors under consideration. The regression equation used for calculation of the OR provides us with an estimate of the risk,

conditionally on the choice of a value for all factors considered (including the exposure which plays the same role as the other risk factors in this case). In appendix J, we describe the construction of a prediction set containing a limited number of predicting variables.

Chapter 14 Factors studied in relation to mortality

14.1 Introduction

In this chapter and chapter 15, we shall analyse the relationships between 31 perinatal factors and mortality (both neonatal mortality and in-hospital mortality) as well as morbidity (IRDS, ICH and septicaemia).

The 31 factors were chosen for their generally accepted or disputed influence on mortality and morbidity (table 14.1.1).

As a measure of the association between a dichotomous factor and an outcome, odds ratios have been calculated by means of logistic regres-

sion analysis (chapter 13). For perinatal factors that were included as continuous variables (maternal age, gestational age, birthweight), no odds ratios were calculated. However, these factors have been included as potential confounders.

14.1.1 Time-related arrangement of perinatal factors

We divided the 31 perinatal factors into 4 distinct categories based on a chronological order of events:

1. pre-pregnancy and pregnancy related factors
2. delivery related factors
3. factors emerging immediately after birth
4. factors related to the neonatal period

These four "time-categories" are instrumental in fitting a logistic regression equation to the POPS-data. As described in chapter 13, such an equation models the expected log(odds) on a dichotomous outcome, e.g. mortality, as a function of certain perinatal factors. The coefficient of a particular factor can be interpreted as the "contribution" of that factor (or exposure) to the total risk, adjusted for all other factors contained in the equation. The other factors act as potential confounders for the outcome-exposure relation. The choice of the factors to be included into the equation is of great importance. One should be careful not to adjust for any factor which could not possibly be a confounder in the true sense (chapter 13). For instance, by adjusting for a factor (e.g. elective delivery) that can be a consequence of the exposure under study (e.g. hypertensive disorders during pregnancy), the association between the outcome (mortality) and the exposure (maternal hypertensive disorders) may diminish or disappear as an artifact.

To avoid such artifacts, the four sequential time-categories mentioned above have been used to form four separate logistic regression equations for each of the outcome variables considered:

1. In order to analyse the effect of an exposure in time-category 1 (pre-pregnancy and pregnancy related factors), a logistic regression equation containing only the category 1 factors as potential confounders was fitted.
2. To analyse time-category 2 factors (delivery related factors), a logistic regression equation containing all factors from categories 1 and 2 was fitted.
3. In the third sequential category (factors emerging after birth), the factors have been analysed by fitting a logistic regression equation including all factors from time-categories 1, 2 and 3.

4. The factors in time-category 4 (related to the neonatal period) have been analysed by fitting a logistic regression equation including all 31 perinatal factors.

Thus, we circumvented the problem of inadvertently adjusting for factors which definitely occurred later in time (e.g. elective delivery) and which might be a result of the exposure (e.g. hypertensive disorders during pregnancy).

14.1.2 Missing data

As described in chapters 5 and 6, the factors socio-economic status, smoking during pregnancy, and cardiotocography had a considerable number of missing data. According to the procedure in chapter 13.6, an extra (dummy) variable was included, indicating for each infant whether or not these data were available. By including the factor with an extra variable, "known versus unknown", all infants could be retained in the analysis. At the same time, the potential confounding effect of such a factor was accounted for as much as possible.

However, due to the large number of missing data, no ORs were calculated for these three factors. The fact in itself that these data were frequently missing while generally the percentage of missing data was very low in this survey, is highly suggestive of selection which might bias the results. For instance, in the case of cardiotocography (CTG) this was evident: the neonatal mortality-OR for CTG-unknown versus CTG-known was significantly increased ($p < 0.005$) in a separate analysis in which only the dichotomous factor "unknown" versus "known" was considered. This means that cases in which no predelivery CTG was recorded died more often than cases in which a CTG had been made, regardless of whether these CTGs were normal or abnormal. This phenomenon was observed as well by Yu et al (1986b). Therefore, calculation of a mortality-OR for CTG abnormal versus normal would be useless and misleading. When extrapolated to the whole population, any conclusion from such an analysis (Sporken, 1986) must necessarily be biased.

14.1.3 Interactions

Apart from the 31 perinatal factors considered, some products of these factors have been included in the sequential equations, but only if the associated coefficients were significantly different from 0 at a 1% level in a regression equation containing all possible products (see chapter 13). In addition to the variables gestational age and birthweight, their product and squares were also included. This significantly

increased the fit of the models (Verloove et al, 1986a).

Interaction is present when a risk factor is included both as an exposure and in one or more product terms. The effect of the exposure is then modified by the other factor in the product term. Odds ratios have been computed together with their confidence intervals for each stratum as defined by the effect modifiers. In such situations, an overall odds ratio has been computed from a separate logistic regression equation in which all product terms containing the exposure (but only those) have been deleted.

14.2 Results

For practical purposes, the computed adjusted odds ratios for neonatal mortality and in-hospital mortality have been listed in table 14.2.1 together with the 95% confidence intervals. An odds ratio is significantly different from 1 at the 5% level if, and only if, its 95% confidence interval does not include 1. An odds ratio greater than 1 indicates a higher risk; an odds ratio smaller than 1 indicates a lower risk for the exposed infants compared to the non-exposed infants. The odds ratios will be discussed in detail in the next sections.

All forthcoming conclusions in chapter 14.3-14.19 are based on a logistic regression equation including factors from time-category 1.

14.3 Pre-existing maternal disease

The presence of a pre-existing maternal disease carries an increased risk for mortality of the infant (table 14.3.1). Crude mortality rates were equal for infants born to mothers with or without pre-existing maternal disease. However, these crude mortality rates do not reflect the true risks, because confounding factors (e.g. gestational age) have not been accounted for. In the present analysis, the infants of mothers with pre-existing maternal disease belonged mostly to higher gestational age groups. This is illustrated in table 14.3.2. After correction for gestational age and all other potential confounding variables, pre-existing maternal disease was found to be associated with a higher mortality risk. This example illustrates the potential pitfall of comparing crude mortality rates, because the true influence of a factor may remain hidden. The opposite may occur as well: clearly different crude mortality rates may prove not significant in the multivariate analysis. In the remainder of chapters 14 and 15, this phenomenon occurs frequently. We shall refrain from repetitive elaborate explanations.

Table 14.3.1 Adjusted odds ratios and crude mortality rates for pre-existing maternal disease

outcome	OR	CI	crude mortality rates pre-existing maternal disease present % n	absent % n
neonatal mortality	2.55	(1.22-5.34)*	23.3 (20/86)	23.3 (292/1252)
in-hospital mortality	1.83	(0.88-3.82)	23.3 (20/86)	25.6 (320/1252)

* $p < 0.05$

Table 14.3.2 Pre-existing maternal disease in successive gestational age categories

gestational age (weeks)	number of infants	pre-existing maternal disease n	%
≤23	8	0	-
24-25	67	3	3.5
26-27	180	10	11.8
28-29	307	14	16.5
30-31	448	21	24.7
≥32	325	35	41.2
total	1335	85	100.0

14.4 Parity

Multiparity of the mother does not affect the mortality risk of the infant (table 14.4.1). Multiparity has been associated with an increase in incidence of preterm birth (chapter 5.6). However, we are not aware of any reports demonstrating an increase in mortality risk in preterm infants of multiparous mothers.

Table 14.4.1 Adjusted odds ratios and crude mortality rates for parity

outcome	OR	CI	crude mortality rates multiparous %	n	nulliparous %	n
neonatal mortality	1.02	(0.70-1.50)	25.8	(165/640)	21.0	(146/694)
in-hospital mortality	1.17	(0.81-1.71)	28.9	(185/640)	22.2	(154/694)

14.5 History of preterm birth or abortion

Unexpectedly, we found a lower mortality risk for infants of mothers with a history of previous preterm birth and (or) recurrent abortions. (table 14.5.1).

It has been claimed that a history of preterm birth is the best single indicator of the likelihood of preterm birth (Hobel et al, 1973; Keirse et al, 1978) or growth retardation (Miller & Jekel, 1985) in the current pregnancy (chapter 5.7). However, the effect of such an obstetrical history on the eventual outcome (e.g. mortality) of the ensuing preterm or growth retarded infants has not been studied.

The results of the present analysis indicate a lower mortality risk in such infants, compared to infants of the same gestational age and birthweight whose mothers did not have a history of preterm birth or recurrent abortion.

Table 14.5.1 Adjusted odds ratios and crude mortality rates for history of preterm birth or abortion

outcome	OR	CI	crude mortality rates history of preterm or abortion present %	n	absent %	n
neonatal mortality	0.58	(0.36-0.92)*	21.6	(59/273)	23.8	(253/1065)
in-hospital mortality	0.61	(0.39-0.95)*	25.3	(69/273)	25.4	(271/1065)

* $p < 0.05$

We hypothesize, that this difference may be the result of the underlying cause of preterm birth. In cases with a history of previous preterm birth, there is a high probability of "maternal causes" whereas in cases without such a history, "fetal causes" may be more pronounced. In these latter cases, a higher mortality risk is to be expected.

14.6 Infants' sex

Logistic regression analysis did not show any difference in mortality risk between boys and girls (table 14.6.1). Equal mortality risks in

Table 14.6.1 Adjusted odds ratios and crude mortality rates for sex

outcome	OR	CI	crude mortality rates male % n	female % n
neonatal mortality	1.05	(0.74-1.50)	23.8 (166/698)	22.4 (142/635)
in-hospital mortality	1.14	(0.81-1.61)	26.2 (183/698)	24.1 (153/635)

boys and girls have been found before (Perkins, 1981), but are contrary to the popular and well-publicized belief that preterm and VLBW boys have a higher mortality risk than girls. Most of the studies that report such a difference between the sexes originate from neonatal intensive care centres with highly selected study populations (Kollée et al, 1984; Brothwood et al, 1986). Considerable selection bias in such study populations may have been introduced by referral patterns.

Some studies are based on autopsies, without mentioning the autopsy rate in boys and girls, which may also result in selection bias (Naeye et al, 1971).

Khoury et al (1985), studying a geographically defined population and adjusting for several perinatal and labour-related factors, also reported an excess neonatal mortality in males. However, adjustments were made for birthweight only (by comparing sex-specific neonatal mortality rates within each birthweight category) and not for gestational age, because gestational age was unknown in more than 40% of the deaths.

Paneth et al (1982a) calculated an odds ratio of 1.62 ($p < 0.001$) for neonatal mortality of male infants compared to female infants. Although

their study population also was geographically defined, its cut-off point was by birthweight (501-2000 g). In the logistic regression model, adjustment was made for birthweight (by stratification) and "gestation-for-birthweight" (quartiles), but not for gestational age and birthweight as separate variables.

Yu et al (1986b) found a significantly lower percentage of females among deaths than among survivors (48% versus 65%; p = 0.0309, chi-square analysis with Yates' correction) in an inborn extremely low birthweight population (500-999 g), but the difference in mean gestational age between deaths and survivors (25 versus 27 weeks) was not taken into account. In VLBW infants, Brothwood et al (1986) reported an infant mortality of 41% in boys and 19% in girls. In addition to being a partly referred population, again the difference in mean gestational age of one week between boys and girls was not taken into account.

In our opinion, the above mentioned differences in mortality risk between boys and girls are merely caused by methodological problems. From the fetal growth charts (Kloosterman, 1969) it is evident that at equal gestational age boys tend to have a higher birthweight than girls. All studies classifying infants by birthweight alone surely must show this bias: in all birthweight categories boys have lower gestational ages than girls, and inherently higher mortality rates. Kloosterman (1969) already drew attention to this methodological pitfall, when calculating mortality risk, as did Hall et al (1982) more recently.

In our study, differences in birthweight as well as gestational age have been taken into consideration by using the logistic regression technique. It is unlikely that other variables, that might be responsible for differences in mortality risk between the sexes, have been overlooked and omitted as potential confounders from the analysis.

Therefore, we conclude that there is no difference in risk for mortality between boys and girls in very preterm or VLBW infants.

14.7 Medication and intoxications during pregnancy

This composite index (chapter 6.7) includes all cases that have been exposed to potential hazardous chemical influences during pregnancy. This group comprises alcohol, narcotic drugs, smoking and medication (n=668). Although it may be argued that in all cases a pharmacologically active compound was present in the infant, the agents involved are so different that opposite effects might be expected. We, therefore, refrained from calculating odds ratios or crude risks. The factor was included in the analysis as a potential confounder.

14.8 Maternal hypertensive disorders

Infants of mothers with hypertension have a significantly lower mortality risk (table 14.8.1). Hypertension is a well known risk in pregnancy, associated with impaired placental function (Lin et al, 1982). The most severe cases result in intra-uterine death which is not included in this study.

Table 14.8.1 Adjusted odds ratios and crude mortality rates for maternal hypertensive disorders

outcome	OR	CI	crude mortality rates hypertension present % n	absent % n
neonatal mortality	0.36	(0.19-0.67)*	9.0 (27/300)	27.5 (285/1038)
in-hospital mortality	0.43	(0.24-0.78)*	11.0 (33/300)	29.6 (307/1038)

* $p < 0.05$

In less severe cases, changes occur in the placenta leading to an increased vascular resistance (Keirse & Kanhai, 1984d; Huisman, 1986; Khong et al, 1986). It is speculated that this higher placental vascular resistance necessitates a gradual adaptation in the fetus similar to that which usually takes place immediately after birth, when the loss of the placenta with its low vascular resistance triggers the adaptation process. Thus, fetuses who survived an intra-uterine period with placental vascular changes may have a better chance to survive the transition from intra-uterine to extra-uterine life at an untimely moment. The same association between maternal hypertension and mortality or survival has been reported by Yu et al (1986b). They ascribed this phenomenon to more mature enzyme systems, as a result of chronic stress in utero.

In our study cohort, infants of hypertensive mothers are well represented in the advanced gestational age groups. Therefore, the lower crude mortality rates are not surprising.

However, after correction for gestational age and other potential confounding factors, the odds for mortality are still much lower in the hypertensive group.

We hypothesize that factors involved in the fetal adaptation process exert an influence beyond the date of delivery.

14.9 Congenital malformations

Testing for interaction revealed a significant (1%-level) modification of the effect of congenital malformations on mortality by the factor gestational age. In table 14.9.1, separate mortality odds ratios are shown, calculated for the different categories of gestational age.

Table 14.9.1 Adjusted odds ratios and crude mortality rates for congenital malformations, by gestational age

outcome	OR	CI	crude mortality rates malformed % n	normal % n
neonatal mortality	1.91	(1.2- 3.2)*	32.2 (47/146)	22.2(265/1192)
gestational age (weeks)				
26	0.4	(0.2- 0.8)	44.4 (4/ 9)	61.8(42/ 68)
27	0.6	(0.3- 1.1)	66.7 (4/ 6)	41.2(40/ 97)
28	0.9	(0.5- 1.6)	8.8 (1/ 12)	29.8(37/ 124)
29	1.5	(0.9- 2.4)	26.3 (5/ 19)	19.1(29/ 152)
30	2.3	(1.4- 3.8)	38.1 (8/ 21)	14.2(26/ 183)
31	3.7	(2.1- 6.4)	29.2 (7/ 24)	7.3(16/ 220)
32	5.8	(3.0-11.2)	30.6 (15/ 49)	4.3(12/ 276)
in-hospital mortality	2.20	(1.3 - 3.6)*	36.3 (53/146)	24.1(287/1192)
gestational age (weeks)				
26	0.4	(0.2 - 0.9)	44.4 (4/ 9)	64.7(44/ 68)
27	0.7	(0.4 - 1.3)	66.7 (4/ 6)	44.3(43/ 97)
28	1.1	(0.6 - 1.8)	16.7 (2/ 12)	35.5(44/ 124)
29	1.6	(1.1 - 2.6)	26.3 (5/ 19)	21.1(32/ 152)
30	2.5	(1.6 - 4.0)	47.6 (10/ 21)	15.5(28/ 183)
31	3.9	(2.3 - 6.6)	33.3 (8/ 24)	8.2(18/ 220)
32	5.9	(3.1 -11.2)	32.6 (16/ 49)	5.1(14/ 276)

* $p < 0.05$

The mortality odds ratios of congenital malformation vary with gestational age: in the higher gestational age categories, infants with congenital malformations have a higher mortality risk than infants without malformations. In the lower gestational age categories the opposite is found: infants with congenital malformations have a lower mortality risk than normal infants. This is to be expected, because, as a result of the entry criteria of our study, lethal congenital malformations were more frequently present in the higher gestational age groups (table 12.2.2: < 32 weeks: 13 out of 1010 = 1.3%; ≥ 32 weeks: 15 out of 325 = 4.6%).

14.10 Hospital admission during pregnancy

For infants whose mother had been admitted to hospital during pregnancy for a period of more than 24 hours prior to the onset of labour, the mortality risk was not different from those whose mother had not (table 14.10.1). This factor comprises a variety of conditions. A number of these have been entered as such into the logistic regression analysis and corrections have been made for their effects. Consequently, after adjusting for these and other confounders, an influence of the factor "hospital admission" itself on the mortality risk could not be demonstrated.

Table 14.10.1 Adjusted odds ratios and crude mortality rates for hospital admission during pregnancy

outcome	OR	CI	crude mortality rates hospital admission present % n	absent % n
neonatal mortality	1.22	(0.73-2.03)	22.8 (240/1051)	25.1 (72/287)
in-hospital mortality	1.10	(0.67-1.81)	24.8 (261/1051)	27.5 (79/287)

14.11 Multiple pregnancy

Infants born as a result of multiple pregnancy had a considerably higher mortality risk than singletons (table 14.11.1). An easy explanation for such a discrepancy in crude mortality rates (as was found by

Table 14.11.1 Adjusted odds ratios and crude mortality rates for multiple pregnancy

outcome	OR	CI	crude mortality rates multiple %	n	singleton %	n
neonatal mortality	1.78	(1.19-2.67)*	30.4	(95/312)	21.2	(217/1026)
in-hospital mortality	1.83	(1.23-2.73)*	33.0	(103/312)	23.1	(237/1026)

* $p < 0.05$

Yu et al, 1986b) is the difference in gestational age: the median gestational age in multiple births was one week shorter than in singletons in our study population.

However, in the logistic regression analysis gestational age and many other potential confounders (table 14.1.1) have been taken into account. Still, the mortality odds ratios are significantly increased. This may be due partly to the increased risk of IRDS in infants of multiple pregnancies (chapter 15.2.4).

14.12 Antenatal transport

Antenatal transport to a level 3 hospital was associated with a lower mortality risk (table 14.12.1).

Table 14.12.1 Adjusted odds ratios and crude mortality rates for antenatal transport

outcome	OR	CI	crude mortality rates antenatal transport present %	n	absent %	n
neonatal mortality	0.60	(0.39-0.94)*	25.7	(63/245)	22.8	(249/1093)
in-hospital mortality	0.68	(0.44-1.04)	29.4	(72/245)	24.5	(268/1093)

* $p < 0.05$

At first glance, these crude mortality rates suggest an increased mortality after maternal transport. However, due to the limited capacity in tertiary care centres, cases for maternal transfer were selected carefully: only cases with distinct fetal-maternal pathology were considered eligible. This may have caused substantial negative selection.

In the logistic regression analysis, confounding by such a selection bias is counteracted, so like is compared with like. The adjusted odds ratios for mortality are distinctly lower than 1, confirming the beneficial effect of planned and immediately instituted intensive care in a tertiary centre reported by others (Harris et al, 1978).

14.13 Tocolysis

Administration of tocolytic drugs to the mother for more than 24 hours was not associated with a different mortality risk (table 14.13.1).

Table 14.13.1 Adjusted odds ratios and crude mortality rates for tocolysis

outcome	OR	CI	crude mortality rates tocolysis present % n	absent % n
neonatal mortality	0.92	(0.59-1.42)	24.0 (142/591)	22.8 (170/747)
in-hospital mortality	1.02	(0.67-1.56)	26.2 (155/591)	24.8 (185/747)

The objective of tocolysis is to increase gestational age, thereby increasing the infant's chances of survival. However, a correction is made for the effect of gestational age by including this factor in the logistic regression analysis, so the influence of tocolysis on mortality, as expressed in the odds ratio, reflects the difference in mortality risk of infants of equal gestational age at birth with and without tocolysis. A difference still present after such a correction would then be inherent to the procedure of tocolysis itself. Since no such difference was obtained, tocolytic drug treatment as a procedure is apparently not associated with a change in mortality risk.

14.14 Administration of glucocorticoids

The administration of glucocorticoids to the mother in an attempt to accelerate fetal lung maturation was associated with a lower mortality risk (table 14.14.1).

Table 14.14.1 Adjusted odds ratios and crude mortality rates for administration of glucocorticoids

outcome	OR	CI	crude mortality rates glucocorticoids present % n	absent % n
neonatal mortality	0.58	(0.34-0.99)*	16.8 (32/190)	24.2 (277/1143)
in-hospital mortality	0.49	(0.29-0.83)*	17.9 (34/190)	26.5 (303/1143)

* $p < 0.05$

Contrary to the administration of tocolytic drugs (chapter 14.13), glucocorticoid administration in itself is associated with a lower mortality risk. No interaction with gestational age was found, suggesting a similar effect of glucocorticoid treatment at different gestational ages.

Liggins and Howie (1972) first reported a beneficial effect of antenatally administered glucocorticoids on the incidence and severity of IRDS in the neonatal period. The results of a randomized prospective trial in the Netherlands by Schutte (1981) indicated an advantageous effect of betamethasone on neonatal mortality and the incidence of IRDS. In contrast to reported adverse effects of chronic glucocorticoids administration during pregnancy, the one-day treatment with betamethasone has not been associated with short or long term ill-effects in the infants (de Graeff & Wit, 1986).

Nevertheless, fear for yet unknown long term ill-effects on the infants (Oosterbaan & Swaab, 1987) dissuades many obstetricians from administering glucocorticoids to mothers with impending preterm delivery. The results of the present study show a substantially lower mortality risk for infants treated with glucocorticoids. These results and the reduction in mortality previously reported in randomized controlled trials call for a reappraisal of glucocorticoid administration in the Netherlands.

14.15 Prolonged duration of ruptured membranes

A prolonged duration of the period between the moment of membrane rupture and the onset of labour affected the mortality risk, although not significantly (table 14.15.1).

Table 14.15.1 Adjusted odds ratios and crude mortality rates for prolonged duration of ruptured membranes

outcome	OR	CI	crude mortality rates prolonged ruptured membranes present % n	absent % n
neonatal mortality	0.66	(0.40-1.08)	22.1 (53/240)	23.6 (259/1098)
in-hospital mortality	0.66	(0.40-1.06)	23.8 (57/240)	25.8 (283/1098)

Previous studies have mentioned a lower neonatal mortality risk associated with prolonged duration of ruptured membranes (Bada et al, 1977; Perkins, 1982). The literature, however, is beset with methodological difficulties: especially the differences in the selection of cases preclude comparison of similar cases. Although randomized trials of management protocols have been carried out (Barrett & Boehm, 1982; Cotton et al, 1984), the factor "early membrane rupture" cannot be randomized.

The results of the multivariate analysis of data from the present study support the clinical view that a conservative management is justified; mortality risk is lower (though not significantly) after prolonged duration of ruptured membranes.

14.16 Chorioamnionitis

Chorioamnionitis was not significantly associated with mortality risk (table 14.16.1). Chorioamnionitis is an infection of the placenta, membranes and fetus, expressing itself in maternal symptoms such as fever and leucocytosis. It is strongly associated with neonatal septicaemia (Garite & Freeman, 1982) (chapter 15.4.1).

However, modern antibiotic therapy has reduced the role of septicaemia as a major cause of death (chapter 12.10). The fact that no relationship

Table 14.16.1 Adjusted odds ratios and crude mortality rates for chorioamnionitis

outcome	OR	CI	crude mortality rates chorioamnionitis present % n	absent % n
neonatal mortality	1.35	(0.73-2.50)	27.0 (27/100)	22.9 (283/1234)
in-hospital mortality	1.22	(0.66-2.26)	28.0 (28/100)	25.1 (310/1234)

between chorioamnionitis and mortality could be demonstrated in the present study is in agreement with such considerations.

14.17 Fetal presentation

Breech and transverse fetal presentation are associated with a higher mortality risk (table 14.17.1).

Regardless of the mode of delivery, in this study the infants in non-vertex presentation had a significantly higher mortality risk than infants in vertex presentation. This is in agreement with previous findings (Goldenberg & Nelson, 1977; Yu et al, 1986b).

As described in chapter 6.14, the failure of some infants to assume the vertex presentation before birth is associated with the presence of

Table 14.17.1 Adjusted odds ratios and crude mortality rates for fetal presentation

outcome	OR	CI	crude mortality rates breech and transverse % n	vertex and unknown % n
neonatal mortality	1.57	(1.09-2.26)*	29.6 (107/362)	21.0 (205/976)
in-hospital mortality	1.38	(0.96-1.97)	30.9 (112/362)	23.3 (228/976)

* $p < 0.05$

fetal abnormalities. Recent studies have focused on the association between fetal abnormalities and eventual adverse outcome, irrespective of the mode of delivery (Nelson & Ellenberg, 1986). Furthermore, breech presentation carries an increased risk, because of possible technical complications during delivery (both vaginal delivery and caesarean section).

Fetal presentation strongly influences the obstetrician's decision regarding mode of delivery. Therefore, we calculated the adjusted mortality odds ratios for breech versus vertex presentation in two groups of infants: those born vaginally and those born after a caesarean section (table 14.17.2).

Table 14.17.2 Adjusted odds ratios for fetal presentation according to mode of delivery

outcome	OR	CI	crude mortality rates breech %	n	vertex %	n
neonatal mortality						
vaginal delivery	2.48	(1.54-3.99)*	41.3	(81/196)	25.5	(147/576)
caesarean section	0.80	(0.40-1.94)	15.1	(25/166)	14.7	(59/400)
in-hospital mortality						
vaginal delivery	2.00	(1.26-3.20)*	42.3	(83/196)	27.7	(160/576)
caesarean section	0.87	(0.45-1.38)	17.5	(29/166)	17.0	(68/400)

* $p < 0.05$

The present data are based on a national survey comprising many different hospitals with varying policies regarding mode of delivery of preterm infants presenting by the breech. Given the present obstetric policies, the crude mortality rates and the result of the logistic regression analysis suggest that, in cases eventually born after a caesarean section, the mortality risk for infants in breech presentation is equal to that of infants in vertex presentation. However, in cases that were born vaginally, breech presentation is associated with a significantly increased mortality risk. Since other factors (e.g. the obstetrician's estimate of the infant's viability) may have influenced

the decision regarding mode of delivery, the result of this analysis should be interpreted with care. The dilemma of the optimal mode of delivery for very preterm infants presenting by the breech, should be answered with a prospective randomized trial.

14.18 Gestational age and birthweight

The importance of gestational age and birthweight in relation to mortality in our study population has been discussed elsewhere (Verloove et al, 1986a). Both gestational age and birthweight were inversely associated with mortality. In a separate, stepwise logistic regression analysis, gestational age proved to be a better predictor of mortality than birthweight. Based upon the results of all analyses hitherto performed, we conclude that gestational age is by far the strongest determinant of mortality in the POPS population.

In the present study, the factors gestational age and birthweight were, therefore, included in all analyses as continuous variables. No odds ratios have been calculated, but the factors were included as potential confounders.

In figure 14.18.1, (the smoothed) relationship between neonatal mortality, gestational age and birthweight is illustrated. This model was obtained from a separate logistic regression analysis of the data and comprises the full range of gestational age and birthweight. The same applies to in-hospital mortality. The reverse, the chance of being discharged from hospital alive, was depicted in a chart (Verwey et al, 1986; appendix K).

14.19 Small for gestational age

Infants with a birthweight below the 10th percentile for gestational age, according to the Amsterdam growth charts (Kloosterman, 1969), showed a higher mortality risk compared to infants with an appropriate weight for gestation, but the increase in mortality is statistically not significant (table 14.19.1).

Although gestational age and birthweight were included as separate factors in the logistic regression analyses, we included the factor SGA as well. It appeared that, especially at the extremes of birthweight-for-gestational age, this improved the fit of the statistical model. Due to the special condition of the infant, there might be additional clinical effects of SGA on mortality besides the accumulated effects of gestational age and birthweight. The odds ratios obtained from the analysis do indeed suggest such a mechanism.

Figure 14.18.1 POPS 1983: Graphic display of the model showing the relation between neonatal mortality and gestational age and birthweight groupings

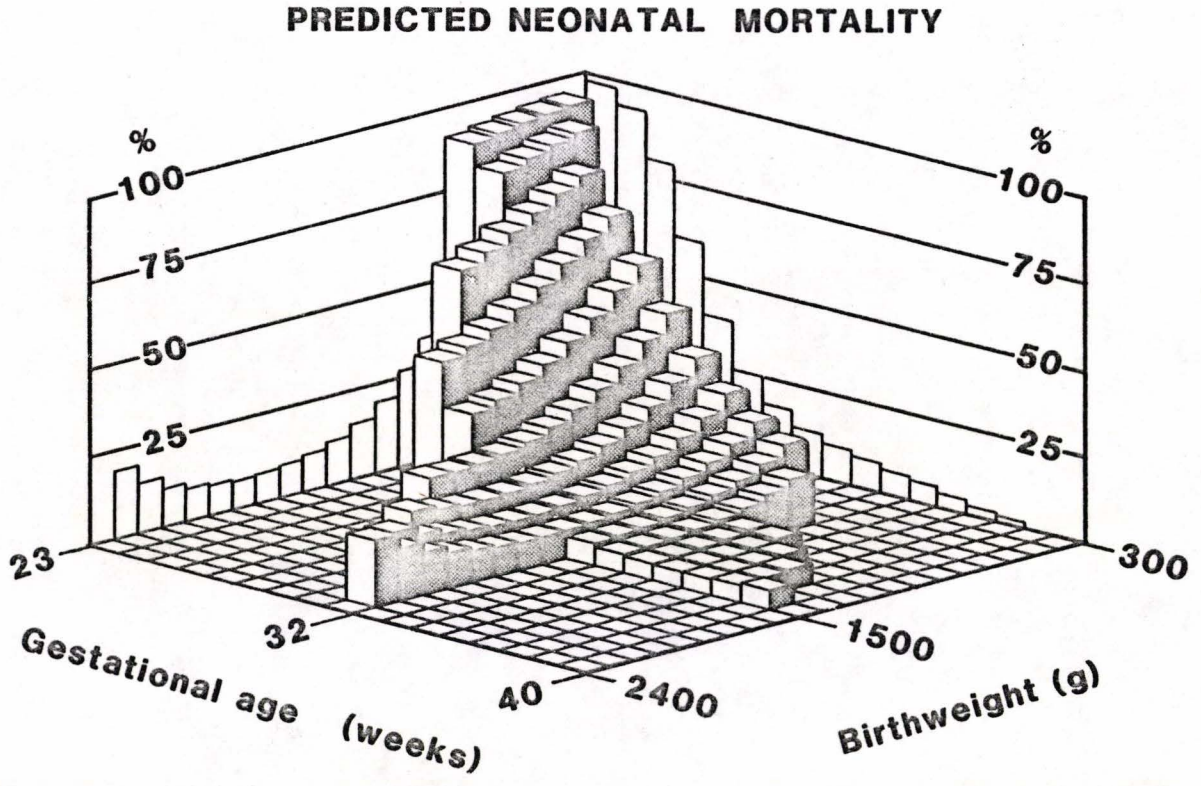


Table 14.19.1 Adjusted odds ratios and crude mortality rates for small for gestational age

outcome	OR	CI	crude mortality rates SGA %	n	AGA/LGA %	n
neonatal mortality	1.87	(0.94-3.71)	15.9	(72/454)	24.6	(209/851)
in-hospital mortality	1.45	(0.75-2.82)	18.1	(82/454)	26.7	(227/851)

In total hospital populations of newborn infants (term and preterm), perinatal mortality as well as neonatal morbidity is reported to be higher in SGA infants (Huisjes, 1981). However, in publications concerning VLWB infants, SGA is reported to be a condition that favours survival (Hoskins et al, 1983; Goldenberg et al, 1985b; Yu et al, 1986a; Yu et al, 1986b). Within such birthweight-defined populations this obviously is true: an SGA-infant of 900 g and 32 weeks gestation has a lower mortality risk than an AGA infant of 900 g and 27 weeks gestation. The clinical impression that very preterm, SGA infants have a relatively better chance of survival than AGA infants of the same gestational age (due to accelerated maturation caused by intra-uterine stress) has, to our knowledge, never been confirmed. In a population op preterm non-malformed infants, Heinonen et al (1985) found that intrauterine growth retardation (defined as birthweight, birthlength, or ponderal index being more than two standard deviations below the expected mean for gestational age) was associated with poor neonatal outcome. Mortality (as well as morbidity) was higher than in appropriately grown preterm infants of corresponding gestational age.

We conclude that, after correction for confounding by "favourable" factors such as hypertension and gestational age, the factor SGA itself is not associated with a lower mortality risk.

The conclusions in sections 14.20 - 14.23 are based upon a logistic regression equation, including the factors in time-category 1 and 2.

14.20 Hospital level of care

The level of care provided in the hospital of birth of the infants appeared to be related to in-hospital mortality; infants born in level 1 hospitals as well as infants born in level 2 hospitals had a significantly higher mortality risk than those born in level 3 hospitals (perinatal intensive care centres in university hospitals, chapter 8.3). Neonatal deaths occurred more often as well, but no statistical significance could be demonstrated (table 14.20.1).

The actual number of deaths in infants born in level 1, 2 and 3 is presented in table 14.20a,b,c, according to gestational age and birthweight (the total number of infants is less than 1338 because infants for whom data on one or more of the potential confounding factors were missing, have been omitted from the final analysis).

The calculated odds ratios in our study show the same kind of difference between hospital levels of care as were found in New York by Paneth et al (1982b): the odds ratio for mortality during the first 3 months of life for infants born in level 1 hospitals, compared to level 3 hospitals, is 1.27 (95% CI 1.08-1.49), and for infants born in level 2 hospitals it is 1.32 (95% CI 1.16-1.52). This result supports the hypothesis that perinatal and newborn intensive care are effective in lowering mortality. The same conclusion was drawn concerning obstetric care (Kiely et al, 1985) and neonatal care for preterm infants of longer gestational age and normal birthweight (Paneth et al, 1986). Since Paneth's and the present analysis included 13 and 25 potential confounding factors respectively, appropriately representing the condition of the infants, the excess mortality in level 1 and 2 hospitals is probably not due to bias in the population, but to the level of care itself. In a recent study including all gestational age and birthweight categories, Paneth et al (1987) found in preterm infants a significantly higher neonatal mortality risk in level 1 and 2 hospitals compared to level 3 hospitals: at birthweights of 1251-2250 g and over 2250 g, the relative risks amounted to 1.38-1.72. For term infants, higher mortality risks were found in level 1 and 2- born low birthweight infants only. They concluded that intrauterine referral of preterm or growth retarded infants to tertiary care settings "has the potential to reduce neonatal mortality by almost 12%". However, in their study of term, normal birthweight infants, no difference in mortality risk was found between the three levels of care, and no benefit in survival was expected from delivery in a tertiary care setting.

Table 14.20.a LEVEL 1: In-hospital mortality rate (%) by gestational age in completed weeks and birthweight in 100 g categories
Actual number of infants in parentheses (dead/liveborn)

GA (wks)	≤24	25	26	27	28	29	30	31	32	33	34	35	total
BW (g)													
≤1500					(1/ 3)	30 (3/10)	23 (7/30)	10 (5/49)					17 (16/ 92)
1250-1499			(1/ 1)	(2/ 4)	19 (3/16)	24 (5/21)	7 (2/29)	12 (3/26)	4 (1/24)	0 (0/17)	7 (1/15)	10 (1/10)	12 (19/163)
1000-1249		(2/ 3)	(5/ 8)	33 (5/15)	52 (11/21)	23 (3/13)	40 (4/10)	27 (4/15)	(2/ 9)	(1/ 9)	9 (1/11)	(2/ 3)	34 (40/117)
750- 999	(2/ 2)	80 (8/10)	(3/ 5)	53 (8/15)	27 (3/11)	(1/2)	(2/ 3)	(1/ 7)	(4/ 6)	(0/ 2)	(1/ 1)	(0/ 1)	51 (33/ 65)
500- 749	(8/ 8)	(2/ 3)	(3/ 3)	(2/ 2)		(0/ 1)	(0/ 2)			(1/ 1)			80 (16/ 20)
<500	(1/ 1)												(1/ 1)
Total	100 (11/11)	75 (12/16)	71 (12/17)	47 (17/36)	35 (18/51)	26 (12/47)	20 (15/74)	13 (13/97)	18 (7/39)	7 (2/29)	11 (3/27)	21 (3/14)	27 (125/458)

Rates are based on at least 10 infants.

Table 14.20.b LEVEL 2: In-hospital mortality rate (%) by gestational age in completed weeks and birthweight in 100 g categories
Actual number of infants in parentheses (dead/liveborn)

GA (wks)	≤24	25	26	27	28	29	30	31	32	33	34	35	total
BW (g)													
≤1500					(1/ 2)	(2/ 7)	32 (6/19)	2 (1/40)					15 (10/ 68)
1250-1499			(1/ 1)	(1/ 3)	36 (5/14)	25 (4/16)	9 (2/23)	9 (1/11)	30 (3/10)	0 (0/12)	0 (0/12)	(0/ 4)	16 (17/106)
1000-1249			(4/ 6)	(4/ 5)	20 (3/15)	27 (3/11)	40 (4/10)	8 (1/13)	(0/ 7)	(1/ 9)	(0/ 3)		25 (20/ 79)
750- 999		(8/ 9)	(4/ 9)	(2/ 6)	(2/ 4)	(2/ 6)	(2/ 8)	(0/ 2)	(0/ 7)	(1/ 3)			39 (21/ 54)
500- 749	(1/ 1)	(2/ 2)	(1/ 1)	(1/ 1)	(2/ 2)	(1/ 1)	(1/ 1)			(1/ 2)			91 (10/ 11)
<500	(1/ 1)												(1/ 1)
Total	(2/ 2)	91 (10/11)	59 (10/17)	53 (8/15)	35 (13/37)	29 (12/41)	25 (15/61)	5 (3/66)	13 (3/24)	12 (3/26)	0 (0/15)	(0/ 4)	25 (79/319)

Rates are based on at least 10 infants.

Table 14.20.c LEVEL 3: In-hospital mortality rate (%) by gestational age in completed weeks and birthweight in 100 g categories
Actual number of infants in parentheses (dead/liveborn)

GA (wks)	≤24	25	26	27	28	29	30	31	32	33	34	35	total
BW (g)													
≤1500			(0/ 1)	(0/ 1)	(0/ 1)	0 (0/11)	8 (2/24)	14 (6/43)					10 (8/ 81)
1250-1499				(3/ 6)	20 (4/20)	13 (3/23)	14 (3/21)	0 (0/14)	20 (2/10)	8 (1/13)	(0/ 6)	(0/ 2)	14 (16/115)
1000-1249		(1/ 2)	59 (10/17)	30 (7/23)	35 (6/17)	15 (5/34)	0 (0/12)	17 (2/12)	13 (2/15)	10 (1/10)	(0/ 4)	(0/ 2)	23 (34/148)
750- 999	(1/ 1)	94 (16/17)	61 (14/23)	50 (8/16)	(5/ 8)	36 (4/11)	(1/ 7)	(1/ 9)	(0/ 3)	(0/ 2)			52 (50/ 97)
500- 749	(4/ 4)	(2/ 2)	(2/ 2)	(4/ 6)	(0/ 2)	(1/ 4)	(2/ 5)	(1/ 3)	(0/ 3)				52 (16/ 31)
<500	(1/ 1)												(1/ 1)
Total	(6/ 6)	90 (19/21)	60 (26/43)	42 (22/52)	31 (15/48)	16 (13/83)	12 (8/69)	12 (10/81)	13 (4/31)	8 (2/25)	0 (0/10)	(0/ 4)	26 (125/473)

Rates are based on at least 10 infants.

Table 14.20.1 Adjusted odds ratios[1] and crude mortality rates for level of care

outcome	OR CI level 1 versus level 3	crude mortality rates level 1 % n	level 3 % n
neonatal mortality	1.55 (0.94-2.56)	23.9 (119/498)	24.3 (117/481)
in-hospital mortality	1.80 (1.09-2.95)*	25.9 (129/498)	26.4 (127/481)
	level 2 versus level 3	level 2 % n	level 3 % n
neonatal mortality	1.57 (0.93-2.67)	21.2 (76/359)	24.3 (117/481)
in-hospital mortality	1.90 (1.13-3.20)*	23.4 (84/359)	26.4 (127/481)

* $p < 0.05$

A carefully balanced appraisal is needed when interpreting the results from such a multifactorial issue. The substantial number of upgrading neonatal transports (chapter 8) suggests that the staff at level 1 hospitals have a liberal approach to neonatal transfer. In 1983, the policy of predelivery maternal transport in high risk cases had not yet been adopted by all hospitals. Nearly 500 (37%) of all very preterm or very low birthweight infants were born in level 1 hospitals. It is plausible that part of these could have been referred antenatally, since about 70% of the pregnant women were hospitalized at some time before delivery. By further regionalization and centralization of intensive care, mortality in this group of infants may decrease even more. Ideally, patient selection for delivery in level 1 should be such that overall crude mortality is much lower than in level 3 (Peddle et al, 1983; Hein & Lathrop, 1986).

[1] Note that the odds ratios are obtained from one and the same regression equation based on the total population. The factor "level" consisting of two dummy variables was demonstrated to be significant by comparing the log likelihoods for two models (one containing both dummy variables, the other none).

In level 2 hospitals the situation is slightly different. Most of these hospitals have (limited) facilities for perinatal intensive care. Maternal referrals to level 3 are rare, and neonatal transports are only effectuated in highly selected cases. Under these circumstances, the mortality risk for infants born in level 2 hospitals appears to be higher than for infants born in level 3 hospitals, while ideally this should be the same, and crude mortality should be lower. Two options to achieve such an optimal situation are: centralization of the care for these infants into the existing level 3 hospitals, together with extension of these NICUs to prevent further overcrowding, or creating full facilities in a number of the level 2 hospitals, thereby upgrading these to level 3. A combination of these management policies is presently being considered by experts and public authorities in the Netherlands.

14.21 Elective delivery

Infants born after elective delivery (chapter 6.15) had a mortality risk similar to other infants (table 14.21.1).

Table 14.21.1 Adjusted odds ratios and crude mortality rates for elective delivery

outcome	OR	CI	crude mortality rates elective % n	spontaneous % n
neonatal mortality	1.03	(0.54-1.95)	13.8 (46/333)	26.5 (266/1005)
in-hospital mortality	1.06	(0.58-1.96)	15.9 (55/333)	28.6 (287/1005)

Elective delivery at an early gestational age only occurs in selected cases, since Dutch obstetrical traditions are rather conservative. Therefore, it would be reasonable to expect a higher mortality rate in these cases: 74% showed signs of fetal distress (abnormal CTG-tracing, chapter 6.15). However, the crude mortality rates are much lower. As stated in chapter 6, elective deliveries are not evenly distributed over various gestational age categories and other potential confounding factors. The obtained adjusted odds ratios showed virtually equal mortality risks.

We assume that at least part of the elective deliveries have prevented

fetal death. Huisman et al (1983) showed indeed a lower perinatal mortality risk in cases with elective delivery. Unfortunately, we cannot evaluate the effect of elective delivery on perinatal mortality, since data on fetal death were not included in this study.

The equal adjusted mortality odds for liveborn infants indicate that once born alive, these electively born infants have a mortality risk equal to that of infants born spontaneously.

14.22 Mode of delivery

Caesarean section as such was not related to a lower mortality risk (table 14.22.1).

Table 14.22.1 Adjusted odds ratios and crude mortality rates for mode of delivery

outcome	OR	CI	crude mortality rates caesarean section %	n	vaginal %	n
neonatal mortality	0.87	(0.53-1.42)	14.8	(84/566)	29.5	(228/772)
in-hospital mortality	0.86	(0.53-1.39)	17.1	(97/566)	31.5	(243/772)

In this analysis, the effect of caesarean section is compared to vaginal delivery. Caesarean sections comprise elective and emergency cases. As in the associated variable, elective delivery (chapter 14.21), one would expect a higher mortality rate (negative selection of cases). However, the crude mortality rates are lower for cases with caesarean section (table 14.22.2). From this table it is evident that the "effect" of mode of delivery depends on gestational age and fetal presentation. This holds true for other factors as well, such as birthweight and congenital malformations. By including these factors in the logistic regression analysis, the influence of the variable "mode of delivery" as such can be estimated more accurately. The adjusted mortality odds were not different at the 5% level. As was the case in "elective delivery", this still leaves the possibility that under many circumstances, caesarean section may be a life-saving procedure. Again, data on antenatal death were not included in our study, rendering evaluation of the relation with perinatal mortality impossible.

Table 14.22.2 Neonatal mortality according to gestational age, fetal presentation and mode of delivery

gestational age (weeks)	vertex				breech			
	vaginal		section		vaginal		section	
	%	n	%	n	%	n	%	n
≤25	82	(42/ 51)	100	(1/ 1)	100	(23/ 23)	-	
26-27	43	(44/103)	55	(12/ 22)	67	(30/ 45)	40	(4/ 10)
28-29	21	(32/153)	19	(12/ 64)	29	(14/ 48)	33	(14/ 42)
30-31	11	(23/204)	15	(18/119)	19	(12/ 62)	6	(4/ 63)
≥32	10	(6/ 63)	8	(16/193)	11	(2/ 18)	6	(3/ 51)
total	26	(147/574)	15	(59/399)	41	(81/196)	15	(25/166)

The conclusions in section 14.23 are based on a logistic regression equation including factors from time-categories 1, 2 and 3.

14.23 Apgar score

The Apgar score at 5 minutes after birth was closely related to both neonatal and total in-hospital mortality (table 14.23.1).

Infants with a low Apgar score obviously have a far greater risk to die than infants with a high Apgar score, even when a variety of potential confounders is taken into consideration.

Table 14.23.1 Adjusted odds ratios and crude mortality rates for Apgar score

outcome	OR	CI	crude mortality rates			
			AS < 7		AS ≥ 7	
			%	n	%	n
neonatal mortality	4.77	(3.17-7.18)*	54.2	(136/251)	16.2	(176/1087)
in-hospital mortality	4.58	(3.04-6.89)*	56.6	(142/251)	18.2	(198/1087)

* $p < 0.05$

In term infants, the predictive abiiity of the Apgar score for mortality (and morbidity) has been questioned (Sykes et al, 1982; 1983; Rosen, 1985; Silverman et al, 1985; Dijxhoorn et al, 1986). However, it appears to have a strong relation to mortality in VLBW infants (Yu & Wood, 1978; Paul et al, 1979; Yu & Hollingsworth, 1979b; Nelson & Ellenberg, 1981; Perkins, 1981; Cordero et al, 1982; Rosen, 1985; Yu et al, 1986b).

Since the estimation of "viability" by the attending clinician may have been influenced strongly by the Apgar score, this parameter may act as a "self-fulfilling prophecy": clinicians may have refrained from resuscitating infants with low Apgar scores. To investigate this possibility, we studied the infants who died separately. In those who had a low Apgar score, in 56% (78/140) of the infants "intensive treatment was withheld or withdrawn" (Whitelaw, 1986) (table 4.4.1, item 81),while in infants with a high Apgar score this was 51% (75/146). However, the relatively large number of missing data on Apgar score in infants that died (n=54) precludes any conclusion.

The conclusions in sections 14.24-14.28 are based on a logistic regression equation including factors from time-categories 1-4.

14.24 Neonatal transport

Testing for interaction disclosed a significant (1%-level) modification of the effect of neonatal transport by gestational age: the mortality odds ratios of neonatal transport vary with gestational age (table 14.24.1).

The most obvious factors that could have caused confounding by indication (congenital malformation, IRDS, ICH, septicaemia) have been included in the logistic regression analysis. However, indications for neonatal transport may have been different at various gestational ages: e.g. a rather good condition at 27 weeks gestation may have been the indication for neonatal transport while a deteriorating clinical condition may have been a contra-indication at that gestational age. At a more advanced gestational age, the situation was probably the reverse: only the sickest infants may have been transported.

The ratios in table 14.24.1 suggest that at the lower gestational ages, neonatal transport of otherwise similar infants is associated with a lower mortality risk, while at more advanced gestational ages it is associated with a higher mortality risk. We speculate that this reflects the policy employed by the attending paediatricians.

Table 14.24.1 Adjusted odds ratios and crude mortality rates for neonatal transport, by gestational age

outcome	OR	CI	crude mortality rates neonatal transport present % n	absent % n
neonatal mortality	0.59	(0.3- 1.0)	25.6 (104/407)	22.3 (208/931)
gestational age (weeks)				
26	0.19	(0.1- 0.4)	40.0 (8/ 20)	66.7 (38/ 57)
27	0.28	(0.1- 0.5)	38.5 (15/ 39)	45.3 (29/ 64)
28	0.40	(0.2- 0.7)	29.8 (17/ 57)	26.6 (21/ 79)
29	0.58	(0.3- 1.0)	29.8 (14/ 47)	16.1 (20/124)
30	0.83	(0.5- 1.5)	23.3 (20/ 86)	11.9 (14/118)
31	1.20	(0.6- 2.2)	10.4 (7/ 67)	9.0 (16/177)
32	1.74	(0.8- 3.5)		
33	2.51	(1.1- 5.8)	20.0 (15/ 75)	4.8 (12/250)
34	3.63	(1.4- 9.5)		
in-hospital mortality	0.69	(0.4- 1.1)	29.0 (118/407)	23.8 (222/931)
gestational age (weeks)				
26	0.22	(0.1- 0.5)	40.0 (8/ 20)	70.1 (40/ 57)
27	0.32	(0.2- 0.6)	43.6 (17/ 39)	46.9 (30/ 64)
28	0.45	(0.3- 0.8)	36.8 (21/ 57)	31.6 (25/ 79)
29	0.65	(0.4- 1.1)	29.8 (14/ 47)	18.5 (23/124)
30	0.93	(0.5- 1.6)	26.7 (23/ 86)	12.7 (15/118)
31	1.33	(0.7- 2.4)	13.4 (9/ 67)	9.6 (17/177)
32	1.90	(0.9- 3.8)		
33	2.72	(1.2 -6.1)	21.3 (16/ 75)	5.6 (14/250)
34	3.89	(1.5-10.0)		

14.25 Idiopathic respiratory distress syndrome

Testing for interaction (1% level) disclosed effect modification by the factor Apgar score: in infants with a low Apgar score, the fact whether or not IRDS ensued was irrelevant. However, in infants with a high Apgar score, the mortality odds of IRDS-cases was 4 times the odds of non-IRDS cases (table 14.25.1).

Since IRDS is one of the major causes of death in the study population (chapter 11), this result is not unexpected. It confirms the well-known association between IRDS and mortality risk, because in the multivariate analysis adjustments were made for potential confounding factors such as gestational age or multiple pregnancy. This would imply that prevention of IRDS, regardless of gestational age, may lower mortality considerably.

Table 14.25.1 Adjusted odds ratios and crude mortality rates for IRDS, by Apgar score

outcome	OR	CI	crude mortality rates IRDS present %	n	absent %	n
neonatal mortality	2.43	(1.6-3.7)*	34.0	(211/621)	14.1	(101/717)
Apgar score 5 min.						
≥ 7	4.39	(2.4-8.0)	25.4	(103/406)	4.4	(25/565)
< 7	0.75	(0.3-1.6)	53.2	(82/154)	55.6	(54/ 97)
in-hospital mortality	2.64	(1.8-4.0)*	37.4	(232/621)	15.1	(108/717)
Apgar Score 5 min.						
≥ 7	3.88	(2.2-6.7)	28.6	(116/406)	5.7	(32/565)
< 7	0.95	(0.4-2.1)	57.1	(88/154)	55.7	(54/ 97)

* $p < 0.05$

14.26 Intracranial haemorrhage

Infants in whom the clinical diagnosis ICH (chapter 12.4) was made showed a considerably increased odds for neonatal as well as in-hospital mortality (table 14.26.1).

Table 14.26.1 Adjusted odds ratios and crude mortality rates for intracranial haemorrhage

outcome	OR	CI	crude mortality rates ICH present % n	ICH absent % n
neonatal mortality	2.59	(1.68-3.98)*	43.8 (146/333)	16.5 (166/1005)
in-hospital mortality	2.37	(1.56-3.59)*	47.4 (158/333)	18.1 (182/1005)

As was the case in IRDS (chapter 14.25), ICH itself is closely associated with mortality, at all gestational ages and in the presence of other factors as well. Since "convulsions" are included as a potential confounding factor in this analysis, part of the effect of ICH itself may have been corrected for inadvertedly. In reality the association is probably even stronger. Thus, prevention of ICH may lower mortality as well.

14.27 Septicaemia

Testing for interaction showed a significant (1% level) modification of the effect of septicaemia by birthweight: in infants with a relatively low birthweight the mortality risk was lower in septicaemia-cases, while in the higher birthweight categories the mortality risk was higher (table 14.27.1).

The explanation of the interaction of septicaemia and birthweight with respect to mortality may be simple. Although the time of onset of septicaemia was not recorded in this study, it is likely that cases of septicaemia are a mixed group: on the one hand, "early onset" septicaemia caused by micro-organisms such as group B-haemolytic streptococcus, occurring at all gestational ages and birthweights and, on the other hand, septicaemia at a later time during the hospital admission

period. A separate investigation of the data has shown that septicaemia often occurred in infants who were treated with total parenteral nutrition for longer periods of time, i.e. infants with a relatively low birthweight. The causative organisms in these cases of septicaemia were mainly staphylococci, and the associated mortality was low (Beganovic et al, 1986). This phenomenon may explain the lower mortality risk in cases with septicaemia versus cases without septicaemia in the lower birthweight categories.

Table 14.27.1 Adjusted odds ratios and crude mortality rates for septicaemia, by birthweight.

outcome	OR	CI	crude mortality rates septicaemia present %	n	absent %	n
neonatal mortality	0.77	(0.5 -1.1)	20.5	(96/469)	24.0	(209/869)
birthweight (g)						
750-999	0.39	(0.2 -0.7)	20.0	(15/ 75)	53.5	(76/142)
1000-1249	0.70	(0.5 -1.1)	27.1	(38/140)	23.0	(50/217)
1250-1499	1.26	(0.8 -2.0)	15.5	(21/135)	9.3	(29/311)
1500-1749	2.24	(1.2 -4.3)				
1750-1999	4.01	(1.6 -9.9)	20.5	(16/ 78)	9.2	(15/163)
in-hospital mortality	0.86	(0.6 -1.3)	23.7	(111/469)	25.5	(222/869)
birthweight (g)						
750-999	0.53	(0.3 -0.9)	26.6	(20/ 75)	57.7	(82/142)
1000-1249	0.82	(0.5 -1.2)	30.7	(43/140)	24.0	(52/217)
1250-1499	1.28	(0.8 -2.0)	16.3	(22/135)	10.3	(32/311)
1500-1749	1.99	(1.1 -3.8)				
1750-1999	3.09	(1.3 -7.5)	23.1	(18/ 78)	9.8	(16/163)

14.28 Convulsions

The odds ratio for neonatal and in-hospital mortality of infants who have had convulsions during hospitalization was significantly increased, when compared to infants without convulsions (table 14.28.1).

Table 14.28.1 Adjusted odds ratios and crude mortality rates for convulsions

outcome	OR	CI	crude mortality rates convulsions present % n	absent % n
neonatal mortality	2.09	(1.07-4.07)*	48.6 (35/72)	21.9 (277/1266)
in-hospital mortality	2.71	(1.40-5.26)*	55.6 (40/72)	23.7 (300/1266)

Since the factor ICH has been included in this analysis as a potential confounding factor, part of the effect of "convulsions" may have been corrected for; in reality the association between convulsions and mortality is probably stronger.

As was the case in "bad Apgar score", the relation between convulsions and mortality may be the result of the clinician's tendency to refrain from further treatment of infants who are considered severely neurologically damaged following convulsions (Whitelaw, 1986). To investigate this possibility, we studied the infants who died separately. We calculated the percentage of infants with and without convulsions, in which further treatment was withheld or withdrawn. Forty in-hospital deaths had shown convulsions. In 72% of these (n=29) further treatment had been withheld or withdrawn. In only 50% of the infants who died without having had convulsions (149 out of 295 cases) treatment had been discontinued (chi-square 5.98; $p < 0.05$). This confirms the hypothesis that convulsions often occurred in infants whose outcome was considered to be probably death or severe handicap and, therefore, the clinician withdrew intensive treatment (Bissenden, 1986). Still, convulsions are strong indicators of serious and life-threatening conditions and the increased mortality risks are therefore not surprising.

14.29 Conclusions

Factors, associated with an increased mortality risk, are pre-existing maternal disease, multiple pregnancy, breech presentation, birth outside a tertiary care centre, low Apgar score, neonatal transport (at relatively high gestational age), IRDS (in infants with a high Apgar score), ICH, septicaemia (in infants with a relatively high birthweight), and convulsions.

Factors, associated with a decreased mortality risk, are history of preterm birth or abortion, maternal hypertension, antenatal transport to a tertiary care centre, glucocorticoid administration before delivery, neonatal transport (at relatively low gestational age), and septicaemia (in infants with a relatively low birthweight).

Table 14.1.1 Definition of 31 factors used in the logistic regression analysis (in chronological order of occurrence and in categories of concurrent factors)

Time-category 1

socio-economic class	1 (low) to 6 (high) (van Westerlaak, 1975)
maternal age	in years (chapter 5.2)
pre-existing maternal disease	any versus none (chapter 5.9)
parity	>0 versus 0 (chapter 5.6)
history of preterm birth or abortion	>1 abortion and (or) ≥1 preterm birth versus none or 1 abortion (chapter 5.7)
infants' sex	male versus female (chapter 7.5)
smoking during pregnancy	any versus none (chapter 6.5)
medication and intoxication	any (medication, alcohol, soft or hard drugs, smoking) versus none (chapter 6.7)
maternal hypertensive disorders	any versus none (chapter 6.4)
congenital malformation	any versus none (chapter 12.2)
hospital admission during pregnancy	1 or more days versus none or less than 24 hours (chapter 6.12)
multiple pregnancy	yes versus no (chapter 7.8)
antenatal transport to level 3	yes versus no (chapter 8.4.1)
tocolysis	≥24 h. versus none or <24 h. (chapter 6.10)
glucocorticoid administration	>24 h. versus none (chapter 6.11)

prolonged duration of ruptured membranes	≥24 h. versus none or <24 h. (chapter 6.9)
chorioamnionitis	yes versus no (chapter 6.9)
cardiotocography during pregnancy	abnormal versus normal tracing (chapter 6.13)
fetal presentation	breech and transverse presentation versus vertex (chapter 6.14)
gestational age	in days (chapter 7.2)
birthweight	in gram (chapter 7.3)
small for gestational age	<10th percentile versus ≥10th percentile (Kloosterman, 1969) (chapter 7.3)
Time-category 2	
hospital level 1	level 1 versus level 3 (chapter 8.3)
hospital level 2	level 2 versus level 3 (chapter 8.3)
elective delivery	yes versus no (chapter 6.15)
mode of delivery	caesarean section versus vaginal (chapter 6.16)
Time-category 3	
Apgar score 5 min.	<7 versus ≥7 (chapter 7.6)
Time-category 4	
neonatal transport to level 2,3	yes versus no (chapter 8.4.)
IRDS	clinical versus none (chapter 12.3)
ICH	clinical versus none (chapter 12.4)
septicaemia	clinical versus none (chapter 12.5)
convulsions	clinical versus none (chapter 12.4)

Table 14.2.1 Adjusted odds ratios (OR), 95% confidence intervals (CI) for neonatal and in-hospital mortality [1]

	neonatal mortality		in-hospital mortality	
	OR	CI	OR	CI
1. socio-economic class	-	-	-	-
2. maternal age	-	-	-	-
3. pre-existing mat. disease	2.55	(1.22-5.34)*	1.83	(0.88-3.82)
4. parity	1.02	(0.70-1.50)	1.17	(0.81-1.71)
5. hist.preterm or abortion	0.58	(0.36-0.92)*	0.61	(0.39-0.95)*
6. infants' sex	1.05	(0.74-1.50)	1.14	(0.81-1.61)
7. smoking	-	-	-	-
8. medication and intoxication	-	-	-	-
9. maternal hypertension	0.36	(0.19-0.67)*	0.43	(0.24-0.78)*
10. congenital malformation	interaction gest. age (table 14.9.1)			
11. hospital admission pregnancy	1.22	(0.73-2.03)	1.10	(0.67-1.81)
12. multiple pregnancy	1.78	(1.19-2.67)*	1.83	(1.23-2.73)*
13. antenatal transport	0.60	(0.39-0.94)*	0.68	(0.44-1.04)
14. tocolysis	0.92	(0.59-1.42)	1.02	(0.67-1.56)
15. glucocorticoids	0.58	(0.34-0.99)*	0.49	(0.29-0.83)*
16. prol. dur. rupt. membranes	0.66	(0.40-1.08)	0.66	(0.40-1.06)
17. chorioamnionitis	1.35	(0.73-2.50)	1.22	(0.66-2.26)
18 cardiotocography	-	-	-	-
19. fetal presentation	1.57	(1.09-2.26)*	1.38	(0.96-1.97)
20. gestational age	-	-	-	-
21. birthweight	-	-	-	-
22. SGA	1.87	(0.94-3.71)	1.45	(0.75-2.82)
23. hospital of birth: level 1	1.55	(0.94-2.56)	1.80	(1.09-2.95)*
level 2	1.57	(0.93-2.67)	1.90	(1.13-3.20)*
24. elective delivery	1.03	(0.54-1.95)	1.06	(0.58-1.96)
25. mode of delivery	0.87	(0.53-1.42)	0.86	(0.53-1.39)
26. Apgar score 5 min.	4.77	(3.17-7.18)*	4.58	(3.04-6.89)*
27. neonatal transport	interaction gest. age (table 14.25.1)			
28. IRDS	interaction Apgar sc. (table 14.26.1)			
29. ICH	2.59	(1.68-3.98)	2.37	(1.56-3.59)*
30. septicaemia	interaction birthw. (table 14.28.1)			
31. convulsions	2.09	(1.07-4.07)*	2.71	(1.40-5.26)*

* $p < 0.05$

[1] For factors that were included in the logistic regression analysis as continuous variables (maternal age, gestational age, birthweight), factors with a large number of missing data (socio-economic class, smoking, cardiotocography) and factors with equivocal effects (medication and intoxication) no adjusted odds ratios were calculated.

Chapter 15 Factors studied in relation to morbidity

15.1 Introduction

The procedure, used to study mortality in chapter 14, was also employed to investigate the relation between various perinatal factors on the one hand and disorders in the neonatal period on the other

hand. These disorders were selected because of the potential life-threatening character: idiopathic respiratory distress syndrome (IRDS), intracranial haemorrhage (ICH) and septicaemia. In the future, the collected data on other disorders in the neonatal period will be studied separately.

Each perinatal factor (table 14.1.1) was considered in turn as an exposure (independent variable), with all others included as potential confounding factors. Odds ratios for IRDS, ICH, and septicaemia (dependent variable) were calculated from the four logistic regression equations. The results from the analyses are presented in the next sections.

In time-category 4, no morbidity odds ratios were calculated for the factor neonatal transport. In many cases the disorders that are the outcome measures (IRDS, ICH, septicaemia) have been the indication for transport. Hence an odds ratio significantly greater than 1 may only signify bias by indication, and not a higher "risk". These odds ratios were therefore omitted.

No tests for interaction were performed. Practical considerations precluded such a procedure.

15.2 The relation between IRDS and perinatal factors

The adjusted odds ratios for IRDS (clinical diagnosis, chapter 12.3) are listed in table 15.2.1. The actual percentage of infants with IRDS is presented for each perinatal factor as well. Only factors for which an adjusted odds ratio (significantly) different from 1 was obtained, will be discussed here.

15.2.1 Parity

The risk of IRDS was greater for infants of multiparous mothers than for infants of nulliparous women, but this difference was not significant at the 5% level.

The increased risk of IRDS for infants born to multiparous mothers was an unexpected finding. We know of no previous reports focusing on the association between a mother's parity and neonatal respiratory distress syndrome. We cannot offer an explanation for it, and this finding may well be the result of coincidence.

15.2.2 Infants' sex

Contrary to mortality (chapter 14.6), the risk of IRDS was higher in boys than in girls. This finding is consistent with the literature

(Khoury et al, 1985; Stark & Frantz, 1986), showing a higher incidence of IRDS due to a delay in lung maturation in boys, without a clinically more severe illness or a higher case-fatality ratio. Probably due to modern intensive care techniques, such a higher incidence apparently does not necessarily lead to a higher death rate in boys.

15.2.3 Hospital admission during pregnancy

The risk of IRDS was significantly lower when the mother had been hospitalized for some time during pregnancy. This lower risk was present even after correction for other perinatal factors in the same time-category, indicating the importance of a well prepared delivery of the infant. No information on L/S-testing, prior to delivery, was available in our study. Although this lack of information hampers the interpretation of the results, we want to emphasize that immediate adequate care of the newborn reduces the possibility to develop IRDS (Strauss et al, 1985; Stark & Frantz, 1986).

15.2.4 Multiple pregnancy

The risk of IRDS was greater for infants of multiple pregnancies than for singleton infants, even after correction for potential confounders such as gestational age. This suggests that the factor multiple pregnancy by itself increases the risk of developing IRDS. The underlying pathophysiological mechanism is yet unknown and requires further investigation. This increased risk of IRDS may partially explain the increased mortality risk for infants of multiple pregnancies (chapters 14.11 and 14.25).

15.2.5 Antenatal transport

Infants whose mothers had been transferred to a level 3 hospital before delivery had a significantly lower risk of IRDS. Since adjustments have been made for all concurrent factors such as gestational age (time-category 1, table 14.1.1) by including these factors in the logistic regression analysis, the adjusted odds ratio reflects more accurately the effect of antenatal transport itself.

The lower risk of IRDS may well be the result of the intensive perinatal care provided in level 3 hospitals. The better condition of the newborn infant and adequate resuscitation of asphyxiated preterm infants lowers the incidence (and severity) of IRDS (Cooke, 1983; Stark & Frantz, 1986).

15.2.6 Tocolysis

Infants born after tocolytic treatment of more than 24 hours duration had a significantly greater risk of IRDS than infants whose mother did not receive tocolytic treatment. To our knowledge, such a significant association has not yet been reported. Most studies evaluating the effect of tocolytic treatment are beset by methodological difficulties. Although the pregnancy may be prolonged by a few days or weeks (Falck Larsen et al, 1986; Leveno et al, 1986), the effect of beta-mimetics on the infants is less well documented. Studies reporting on outcome of infants after tocolytic treatment are often difficult to interpret because of differences in gestational age at birth (Leveno et al, 1986), or concurrent glucocorticoid administration (Salvat et al, 1978). In one study (Kristoffersen et al, 1979), ritodrine treatment was associated with an increased incidence of IRDS, but the number of cases was small.

We conclude that the indiscriminate use of beta-mimetic drugs in preterm labour needs reappraisal.

15.2.7 Administration of glucocorticoids

Infants whose mother had been given a short course of glucocorticoids during pregnancy had a significantly lower risk of IRDS than infants born to mothers without such a treatment. This finding is in agreement with previous reports on the efficacy of glucocorticoid treatment to accelerate pulmonary maturation (Schutte, 1981).

According to current treatment protocols, the administration of glucocorticoids is restricted to a limited number of pregnancies. Therefore, a separate analysis was performed: after excluding cases not eligible for glucocorticoid treatment (gestational age either < 26 weeks or ≥ 32 weeks), the resulting adjusted odds ratio for IRDS was even lower: OR 0.51; CI 0.29-0.89 (Koppe et al, 1986). The administration of glucocorticoids to pregnant mothers with threatening preterm labour is still a matter of debate in the Netherlands (chapter 14.14). Nevertheless, the present study strongly supports a more liberal use of glucocorticoids in well selected cases.

15.2.8 Gestational age

In table 15.2.2, the crude percentages of IRDS-cases in successive gestational age categories are presented. The well known relation between low gestational age and the occurrence of IRDS (Stark & Frantz, 1986) is demonstrated once again. The low incidence of IRDS in cases with a gestational age of 24 weeks or less is due to the fact that many

Table 15.2.2 IRDS in successive gestational age categories

gestational age (weeks)	number of infants	IRDS n	IRDS %
≤23	8	1	12.5
24	19	6	31.6
25	48	31	64.6
26	77	48	62.3
27	103	69	67.0
28	136	92	67.6
29	171	111	64.9
30	204	113	55.4
31	244	103	42.2
≥32	325	46	14.2
total	1335	620	46.4

of these infants died very soon after birth with a "diagnosis" of "immaturity" (chapter 11.5). The low incidence in cases with a gestational age of 32 weeks or more does not reflect the true incidence at those gestational ages, because of the patient selection (< 1500 g) in this study.

15.2.9 Birthweight

Table 15.2.3 presents the crude percentages of IRDS-cases in successive birthweight categories.No obvious relationship between birthweight and IRDS is discernable.

15.2.10 Mode of delivery

In the study population, infants delivered by caesarean section had a significantly greater risk of IRDS than infants born vaginally. This finding is especially important, since in the logistic regression analysis corrections were made for all perinatal factors in time-categories 1 and 2 (table 14.2.1). The adjusted odds ratio of 1.72 thus indicates the excess risk of IRDS in cases born by caesarean section.

During the last decades, other authors focused on the association

Table 15.2.3 IRDS in successive birthweight categories

birthweight (g)	number of infants	IRDS n	IRDS %
<500	5	0	-
500-599	14	6	42.9
600-699	33	15	45.5
700-799	51	25	49.0
800-899	88	44	50.0
900-999	101	58	57.4
1000-1099	124	70	56.5
1100-1199	139	54	38.8
1200-1299	161	77	47.8
1300-1399	179	76	42.5
1400-1499	202	73	36.1
≥1500	241	123	51.0
total	1338	621	46.4

between caesarean section, particularly elective caesarean section, and an increased incidence and severity of IRDS (Usher, 1971; Fedrick & Butler, 1972). However, in a separate analysis of the present data the odds of IRDS for infants born by elective and emergency caesarean section were equal.

Although mortality due to IRDS has decreased in recent years, IRDS is still the main cause of death and morbidity in the neonatal period. The increased incidence of IRDS in infants born by caesarean section is the most obvious detrimental effect of a procedure that is otherwise considered beneficial.

The hypothetical benefit of an atraumatic delivery by caesarean section may well be counteracted by IRDS and its consequences. This may relate to the finding in the present study (chapter 14.23) that caesarean section is not associated with a lower mortality risk.

15.2.11 Apgar score

Infants with a low Apgar score at 5 minutes after birth showed an increased risk of IRDS. This association is in agreement with previous reports (Cooke, 1983; Strauss et al, 1985; Stark & Frantz, 1986). The

pathophysiological mechanism is not yet fully understood. While asphyxia after birth may be a factor contributing to IRDS, it may as well be a consequence of the underlying surfactant deficiency. In both situations, immediate intensive care may reduce the severity of IRDS and its consequences (Drew, 1982; Szymonovicz et al, 1986).

15.2.12 Intracranial haemorrhage

The association between ICH and IRDS is well-known (chapters 11 and 12), and is reconfirmed by the results of this analysis.

15.2.13 Conclusions

The relationship between IRDS and gestational age is obvious. We found an excess risk of IRDS for several perinatal factors: male sex, multiple pregnancy, tocolysis, caesarean section, low Apgar score and ICH. The mother's hospitalization during pregnancy, antenatal transport and glucocorticoid administration to the mother were associated with a significantly lower risk of IRDS.

We speculate that the incidence of IRDS may be reduced by the administration of glucocorticoids to well-selected cases. Whenever necessary, tocolysis may be practiced to gain time, necessary for this treatment. In eligible cases such a course should also be considered before performing an elective caesarean section. The possible beneficial effect of antenatal transport has already been discussed in chapter 14 with respect to mortality, and is shown again for IRDS.

15.3 The relation between ICH and perinatal factors

The adjusted odds ratios for ICH (clinical diagnosis, chapter 12.4) are listed in table 15.3.1. The actual percentage of infants with ICH is presented for each perinatal factor as well. Only factors for which an adjusted odds ratio was obtained which differed (significantly) from 1, will be discussed here.

15.3.1 Maternal hypertensive disorders

The risk of ICH was lower in infants of mothers with hypertension during pregnancy, although the difference was statistically not significant. The risk of IRDS was not lower for infants of hypertensive mothers (table 15.2.1), therefore, the well-known relationship between IRDS and

ICH did not affect this finding.

In a previous analysis, including only data on infants within the study population with a gestational age of less than 32 weeks, admitted to 6 NICUs (van de Bor et al, accepted for publication), the adjusted odds ratio for ICH for the factor maternal hypertension was significantly lower than 1 (OR 0.5; CI 0.3-0.8). These findings suggest that maternal hypertensive disorders may influence the fetus' (circulatory) adaptation to extrauterine life (chapter 14.8), especially as far as brain blood flow is concerned. We speculate that "chronic" maternal hypertension may prevent the loss of autoregulation of brain blood flow that is generally assumed to be an aetiologic factor in the occurrence of ICH (Brubakk et al, 1985), or that it plays a role in the maturation of the cerebrovascular system (Low et al, 1986).

15.3.2 Multiple pregnancy

The risk of ICH was higher for infants from multiple pregnancies than for singletons, but not significantly at the 5% level. There may well be a relationship with the increased risk of IRDS in infants from multiple pregnancies (chapter 15.2.4).

15.3.3 Gestational age and birthweight

In a separate study, gestational age and the occurrence of ICH were shown to be closely associated (van de Bor et al, accepted for publication). This finding is consistent with previous reports (Shinnar et al, 1982; Baerts, 1984). No association with birthweight was found.

15.3.4 Hospital level of care

Infants born in level 2 hospitals had a significantly lower risk of ICH than infants born in level 3 hospitals. Infants born in level 1 hospitals showed a risk of ICH similar to that in infants born in level 3 hospitals.

At least two explanations can be offered for this phenomenon. If we accept the fact that ICH occurred less frequently in infants born in level 2 hospitals, this may either have been due to better (preventive) care or to some (positive) selection bias unaccounted for in the analysis. Both explanations are improbable, since the mortality risk was significantly higher for infants born in level 2 hospitals than in level 3 hospitals (chapter 14.20). On the other hand, as stated in chapter 12, ultrasound examination of the brain was not performed routinely in level

2 and level 1 hospitals. This may have led to underreporting of ICH, especially in infants born in level 2 hospitals, since neonatal transport to a level 3 hospital was rare. Many infants born in level 1 hospitals were transferred to a level 3 hospital, where the presence of ICH was routinely investigated by ultrasound examination of the brain.

However, on the basis of the present data no conclusion can be reached in this respect. Only when ultrasound or an equivalent examination is performed routinely at all levels of care, any difference in risk for ICH can be evaluated.

15.3.5 Apgar score

Infants with a low Apgar score at 5 minutes after birth had a higher risk of ICH than those with a high Apgar score. The same association between low Apgar scores and ICH has been found by others (Tejani et al, 1984; Strauss et al, 1985).

As described in chapter 15.2.11, a low Apgar score is strongly associated with IRDS. In view of the well-known association between IRDS and ICH, the increased risk of ICH could be expected.

15.3.6 Idiopathic respiratory distress syndrome

In cases with IRDS, the adjusted odds for ICH were considerably higher than in cases without IRDS. This confirms once again the well-known association between these disorders (as in chapter 15.2.12).

15.3.7 Septicaemia

Infants with a diagnosis of septicaemia had a significantly higher risk of ICH than infants without septicaemia, and vice versa (chapter 15.4.4). Septicaemia is generally considered a risk factor for ICH, due to the adherent systemic hypotension. Although this relationship could not be confirmed by Levene et al (1982) and Sinha et al (1985), Low et al (1986) did demonstrate an association between major infections (such as septicaemia and meningitis) and ICH. Nevertheless, other mechanisms may have played an important role as well: infants with ICH are generally in a worse condition and require prolonged periods of total parenteral nutrition, which, in turn, is associated with septicaemia (Beganovic et al, 1986).

15.3.8 Convulsions

Convulsions are a symptom of a disturbance of the brain. The relationship between convulsions and ICH is, therefore, evident.

15.3.9 Conclusions

The association between ICH and low gestational age has been shown elsewhere (van de Bor et al, accepted for publication). In the present analyses, only a few other perinatal factors appeared to be significantly associated with a higher risk of ICH: a low Apgar score, IRDS, septicaemia and convulsions. No association was found between ICH and obstetrical factors such as fetal presentation or mode of delivery.

Apart from the prevention of IRDS, no clear preventive strategies for ICH can be deduced from this survey. The unexpected finding of a lower risk of ICH for infants born to hypertensive mothers invites further study.

15.4 The relation between septicaemia and perinatal factors

The adjusted odds ratios for septicaemia are listed in table 15.4.1. The actual percentage of infants with septicaemia is presented for each perinatal factor. Only factors for which an adjusted odds ratio (significantly) different from 1 was obtained, will be discussed here.

15.4.1 Prolonged duration of ruptured membranes

Infants born after prolonged duration of ruptured membranes had a higher risk of septicaemia than infants born after a short period of ruptured membranes. This association is well-known and well publicized. However, the question whether an infection is the cause or the effect has not yet been answered definitely (Perkins, 1982; Nelson et al, 1985a). Either an infection may cause a rupture of the membranes (Thomsen et al (1987) or the micro-organisms penetrate after and by means of the rupture.

15.4.2 Hospital level of care

As was the case for ICH (chapter 15.3.4), the risk of septicaemia appeared to be lower for infants born in level 2 hospitals compared to those born in level 3 hospitals. No difference was found between infants

born in level 1 and level 3 hospitals. A similar explanation can be offered as for ICH: either there is a truly lower risk of septicaemia in infants, born in level 2 hospitals, or there is a problem of underreporting. In the case of septicaemia, however, the latter is unlikely: the clinical diagnosis of septicaemia is generally accepted; blood cultures are available in all hospitals, and are taken on a large scale.

The lower frequency of septicaemia in level 2 hospitals is probably due to fewer and relatively shorter periods of invasive procedures (IPPV, total parenteral nutrition, intravascular monitoring).

15.4.3 Intracranial haemorrhage

The relation between ICH and septicaemia has been discussed in chapter 15.3.9.

15.4.4 Convulsions

The risk of septicaemia was considerably higher for infants with convulsions than for infants without convulsions. By including all perinatal factors in the logistic regression equation from which the odds ratio was obtained, adjustments were made for the presence or absence of ICH. Nevertheless, an adjusted odds ratio significantly greater than 1 was obtained. Apparently, the convulsive disorder itself or some factor inherent to a convulsive disorder (e.g. the need for prolonged total parenteral nutrition because of nutritional problems) is associated with septicaemia. This needs further study (chapter 15.3.7).

15.4.5 Conclusions

Prolonged duration of ruptured membranes is the only prenatal factor significantly associated with the occurrence of septicaemia in the infants. Delivery in a level 2 hospital appeared to have lower risk of septicaemia. Whether this is due to better prevention of infections or to other factors, such as fewer and shorter periods of invasive procedures, remains to be studied. The occurrence of ICH and convulsions is significantly related to septicaemia. The reason for this finding may be the need for prolonged periods of intensive care.

Table 15.2.1 Adjusted odds ratios (OR), 95% confidence intervals (CI) and crude rates of IRDS [1]

	OR	CI	factor present % n	factor absent % n
1. socio-economic class	-	-	-	-
2. maternal age	-	-	-	-
3. pre-existing mat.dis.	1.21	(0.71-2.07)	39(34/ 86)	47(587/1252)
4. parity	1.33	(0.99-1.79)	51(328/ 640)	42(290/ 694)
5. hist.preterm or abort.	1.00	(0.71-1.40)	50(138/ 273)	45(483/1065)
6. infants' sex	1.40	(1.08-1.82)*	51(356/ 698)	42(264/ 635)
7. smoking	-	-	-	-
8. medication and intox.	-	-	-	-
9. maternal hypertension	0.93	(0.61-1.40)	30(89/ 300)	51(532/1038)
10. cong. malformation	0.94	(0.62-1.43)	41(60/ 146)	47(561/1192)
11. hospital adm. pregn.	0.58	(0.39-0.85)*	44(463/1051)	55(158/ 287)
12. multiple pregnancy	1.56	(1.14-2.13)*	58(180/ 312)	43(441/1026)
13. antenatal transport	0.69	(0.50-0.96)*	46(114/ 245)	46(507/1093)
14. tocolysis	1.49	(1.07-2.08)*	53(312/ 591)	41(309/ 747)
15. glucocorticoids	0.56	(0.39-0.81)*	44(83/ 190)	47(534/1143)
16. prol.dur.rupt.membr.	0.78	(0.55-1.10)	50(121/ 240)	45(500/1098)
17. chorioamnionitis	0.88	(0.54-1.44)	51(51/ 100)	46(569/1234)
18. cardiotocography	-	-	-	-
19. fetal presentation	1.06	(0.80-1.41)	50(181/ 362)	45(440/ 976)
20. gestational age	-	-	-	-
21. birthweight	-	-	-	-
22. SGA	1.17	(0.70-1.95)	28(126/ 454)	56(495/ 884)
23. hospital of birth				
level 1 vs. level 3	1.27	(0.88-1.84)	47(233/ 498)	46(222/ 481)
level 2 vs. level 3	1.36	(0.93-2.01)	46(166/ 359)	46(222/ 481)
24. elective delivery	0.91	(0.59-1.42)	30(99/ 331)	52(522/1007)
25. mode of delivery	1.72	(1.18-2.51)*	39(222/ 566)	52(399/ 772)
26. Apgar score 5 min.	1.61	(1.15-2.27)*	61(154/ 251)	43(467/1087)
27. neonatal transport	-	-	61(249/ 407)	40(372/ 931)
28. IRDS	-	-	-	-
29. ICH	2.81	(2.00-3.97)*	73(242/ 333)	38(379/1005)
30. septicaemia	1.13	(0.84-1.50)	51(240/ 469)	44(381/ 869)
31. convulsions	1.11	(0.60-2.08)	72(52/ 72)	45(569/1266)

Table 15.3.1 Adjusted odds ratios (OR), 95% confidence intervals (CI) and crude rates of ICH [1]

	OR	CI	factor present %	n	factor absent %	n
1. socio-economic class	-	-	-		-	
2. maternal age	-	-	-		-	
3. pre-existing mat.dis.	1.36	(0.75-2.46)	26(	22/ 86)	25(	311/1252)
4. parity	0.73	(0.52-1.01)	26(	167/ 640)	24(	165/ 694)
5. hist.preterm or abort.	1.13	(0.77-1.64)	28(	76/ 273)	24(	257/1065)
6. infants' sex	0.99	(0.74-1.33)	25(	177/ 698)	25(	156/ 635)
7. smoking	-	-	-		-	
8. medication and intox.	-	-	-		-	
9. maternal hypertension	0.62	(0.39-1.00)	15(	46/ 300)	28(	287/1038)
10. cong. malformation	1.23	(0.78-1.92)	27(	39/ 146)	25(	294/1192)
11. hospital adm. pregn.	0.97	(0.64-1.48)	24(	254/1051)	27(	79/ 287)
12. multiple pregnancy	1.37	(0.98-1.91)	30(	95/ 312)	23(	238/1026)
13. antenatal transport	0.95	(0.67-1.36)	30(	73/ 245)	24(	260/1093)
14. tocolysis	0.88	(0.61-1.26)	27(	157/ 591)	24(	176/ 747)
15. glucocorticoids	0.75	(0.49-1.14)	22(	42/ 190)	25(	290/1143)
16. prol.dur.rupt.membr.	0.95	(0.64-1.41)	28(	67/ 240)	24(	266/1098)
17. chorioamnionitis	1.20	(0.71-2.01)	32(	32/ 100)	24(	301/1234)
18. cardiotocography	-	-	-		-	
19. fetal presentation	1.18	(0.87-1.60)	29(	106/ 362)	23(	227/ 976)
20. gestational age	-	-	-		-	
21. birthweight	-	-	-		-	
22. SGA	0.62	(0.35-1.10)	15(	69/ 454)	30(	264/ 884)
23. hospital of birth						
level 1 vs. level 3	1.05	(0.70-1.55)	26(	130/ 498)	31(	147/ 481)
level 2 vs. level 3	0.45	(0.29-0.70)*	16(	56/ 359)	31(	147/ 481)
24. elective delivery	1.09	(0.66-1.81)	17(	56/ 333)	27(	277/1005)
25. mode of delivery	1.39	(0.93-2.08)	22(	123/ 566)	27(	210/ 772)
26. Apgar score 5 min.	1.49	(1.04-2.12)*	35(	89/ 251)	22(	244/1087)
27. neonatal transport	-	-	38(	155/ 407)	19(	178/ 931)
28. IRDS	2.76	(1.96-3.90)*	39(	242/ 621)	13(	91/ 717)
29. ICH	-	-	-		-	
30. septicaemia	2.25	(1.63-3.12)*	36(	171/ 469)	18(	161/ 869)
31. convulsions	7.79	(4.05-14.99)*	76(	55/ 72)	22(	278/1266)

* $p < 0.05$

Table 15.4.1 Adjusted odds ratios (OR), 95% confidence intervals (CI) and crude rates of septicaemia [1]

	OR	CI	factor present %	n	factor absent %	n
1. socio-economic class	-	-	-		-	
2. maternal age	-	-	-		-	
3. pre-existing mat.dis.	1.09	(0.65-1.82)	31(27/	86)	33(417/	1243)
4. parity	0.81	(0.60-1.08)	32(206/	636)	34(238/	689)
5. hist.preterm or abort.	1.37	(0.98-1.92)	36(99/	273)	33(345/	1056)
6. infants' sex	1.17	(0.86-1.44)	34(233/	694)	33(210/	630)
7. smoking	-	-	-		-	
8. medication and intox.	-	-	-		-	
9. maternal hypertension	0.90	(0.62-1.31)	31(93/	298)	34(351/	1031)
10. cong. malformation	1.09	(0.73-1.62)	34(50/	145)	33(394/	1184)
11. hospital adm. pregn.	0.77	(0.53-1.11)	33(347/	1046)	34(97/	283)
12. multiple pregnancy	1.00	(0.73-1.35)	34(105/	307)	33(339/	1022)
13. antenatal transport	0.98	(0.70-1.36)	36(89/	244)	33(355/	1085)
14. tocolysis	1.01	(0.72-1.40)	35(204/	589)	32(240/	740)
15. glucocorticoids	1.16	(0.80-1.67)	37(70/	190)	33(372/	1134)
16. prol.dur.rupt.membr.	1.44	(1.01-2.06)*	41(98/	238)	32(346/	1091)
17. chorioamnionitis	1.17	(0.72-1.90)	43(43/	100)	33(400/	1227)
18. cardiotocography	-	-	-		-	
19. fetal presentation	1.28	(0.97-1.68)	37(133/	359)	32(311/	970)
20. gestational age	-	-	-		-	
21. birthweight	-	-	-		-	
22. SGA	0.69	(0.43-1.13)	30(137/	454)	35(307/	875)
23. hospital of birth						
level 1 vs. level 3	0.81	(0.57-1.15)	33(164/	695)	38(184/	479)
level 2 vs. level 3	0.61	(0.42-0.89)*	27(96/	355)	38(184/	479)
24. elective delivery	0.94	(0.63-1.41)	30(100/	331)	34(344/	998)
25. mode of delivery	1.25	(0.87-1.77)	34(195/	565)	33(249/	764)
26. Apgar score 5 min.	1.25	(0.90-1.74)	37(91/	246)	33(353/	1083)
27. neonatal transport	-	-	42(170/	407)	30(274/	922)
28. IRDS	1.15	(0.86-1.54)	39(240/	621)	29(204/	708)
29. ICH	2.19	(1.59-3.01)*	51(171/	332)	27(273/	997)
30. septicaemia	-	-	-		-	
31. convulsions	2.23	(1.28-3.88)*	60(43/	72)	32(401/	1257)

* $p < 0.05$

[1] For factors that were included in the logistic regression analysis as continuous variables (maternal age, gestational age, birthweight), factors with a large number of missing data (socio-economic class, smoking, cardiotocography), factors with equivocal effects (medication and intoxication) and factors for which the outcome variable may have caused bias by indication (neonatal transport) no adjusted odds ratios were calculated.

Chapter 16 Summary, conclusions and recommendations

In chapter 1, the concepts of (very) low birthweight, (very) preterm birth, and intensive care are discussed. Notwithstanding recommendations by the WHO and the FIGO to classify newborn infants by gestational age and birthweight categories, the literature shows that it is still the prevailing practice to define study populations only by birthweight, often in dissimilar categories. Thus a comparison of studies becomes highly inaccurate and often the results do not differentiate between various aetiological subpopulations such as intrauterine growth retarded and very preterm infants.

We recommend that the WHO- and FIGO categorization be used in future reports, and that the study populations be defined by both gestational age and birthweight.

In the Netherlands, failure to record routinely the gestational age and weight of all births and first year deaths is a serious drawback for perinatal epidemiological research. To calculate mortality rates in birthweight or gestational age categories, data on birthweight and gestational age are required for all infant deaths (numerator) as well as for all stillborn and liveborn infants (denominator). As yet only in cases of first week death, birthweight and gestational age are recorded.

We recommend firstly, that a mandatory registration of all births from 22 weeks gestational age onwards (stillborn as well as liveborn) should be established. The record should contain gestational age and birthweight. Secondly, all first year deaths should be reported by gestational age and birthweight. This requires only a small change in the registration form (yellow B-form).

In chapter 2, the current literature on VLBW or very preterm infants is reviewed. However inaccurate comparisons may be, this review allows several conclusions:

- the mortality decreased considerably during the last decades in all birthweight categories including the extremely low birthweight infants. The major handicap rate remained virtually unchanged. Consequently, the percentage of surviving, normal infants increased almost threefold.
- trials, preferably randomized, controlled, double blind trials, are the instrument of choice for evaluation of the effectiveness of specific measures of care. Before being introduced in routine perinatal care, all new treatment schemes or practices should be evaluated following such a procedure. However, since some procedures are difficult to randomize and impossible to blind, observational studies are needed as well to evaluate certain aspects of perinatal care.

-regional studies, including all cases in a geographically well defined area, provide useful epidemiological data without selection bias by referral systems between hospitals. Regionalization programs within such areas have shown the beneficial effect of centralizing high risk deliveries in tertiary care centres.

In chapter 3, the objectives of the present study are stated. In addition to establishing incidences, mortality and morbidity rates, we have investigated the relationships between outcome and perinatal factors as far as pregnancy, delivery, and hospitalization of the infants are concerned.

Chapter 4 describes the study design. In a prospective, collaborative, longitudinal survey, data were collected on infants born alive during 1983 with a gestational age of less than 32 weeks and (or) a birthweight of less than 1500 g. After discharge home, follow-up data were recorded during out-patient visits at the corrected age of 3, 6, 12 and 24 months. In addition to a descriptive analysis of the collected data (in this thesis limited to the perinatal period), the use of multivariate statistical techniques allowed estimation of exposure-disease relationships, while controlling (adjusting) for the effects of many other factors.

The study population includes 1338 infants, born to 1214 mothers and comprises 94% of all such infants born alive in the Netherlands in 1983. The sex of the infants was female in 48% and male in 52% of all cases.

In chapter 5, relevant characteristics of the 1214 mothers of the study infants are presented. The vast majority of mothers were healthy women prior to the index pregnancy. Low as well as high maternal age was associated with a higher incidence of very preterm or VLBW births. Marital status and parity did not differ from that in the general population. However, nearly one third of the study mothers had a history of one or more previous preterm births. In the first part of the POPS-study, data on socio-economic class were to insufficiently recorded to render reliable results. Because the relation between socio-economic class and the incidence and outcome of preterm and VLBW birth is well known, we recommend that these data should be fully recorded in future studies.

In chapter 6, obstetrical data on the index pregnancies and deliveries are presented. The incidence of maternal hypertensive disorders in the cohort was high (22.8%), especially in pregnancies of infants born after 32 weeks gestation with a birthweight of less than 1500 g (49%). External factors with a potentially deleterious influence during pregnancy were frequently recorded: smoking 29%, abuse of alcohol 0.5%, soft drugs 0.4%, hard drugs 0.3%, medication during pregnancy 59% and during labour and delivery 65%. Premature rupture of the membranes occurred in 39% of the cases; nearly half of these had a latent period of more than 24 hours between membrane rupture and the onset of labour. Chorioamnionitis occurred more frequently with increasing length of the latent period.

Tocolysis of more than 24 hours duration, was recorded for mothers of 44% of the study infants. In a third of these, glucocorticoids had also been administered for the acceleration of fetal pulmonary maturation.

Breech presentation occurred in 329 infants (25%); more than half of these were born after a spontaneous vaginal breech delivery. Caesarean section was performed electively in 22% of all cases. Another 20% was born after an emergency caesarean section, resulting in an overall caesarean section rate of 42%.

Chapter 7 describes the main characteristics of the 1338 study infants. Gestational age was recorded in all but 3 cases and varied from 22 to 40 weeks: median gestational age 30 weeks and 2 days. Of the study population, 1010 infants had a gestational age of less than 32 completed weeks. In addition, 58 such infants were born in non-participating hospitals and were not included in the study cohort. Therefore, the observed incidence of very preterm birth in the Netherlands was 0.63%.

Birthweight was recorded for all cases and varied from 420 to 2780 g: median birthweight 1250 g. Of the study population, 1097 infants had a birthweight of less than 1500 g. In addition, 67 such infants were born in non-participating hospitals and were not included in the study cohort. Therefore, the observed incidence of VLBW in 1983 was 0.68%.

According to the Amsterdam growth charts, 17% of the study infants with a gestational age of less than 32 weeks, were SGA. This percentage obviously exceeds the expected 10%. Therefore, either the standards are no longer applicable, or the study population comprises an excess of growth retarded cases. Further study of the present data is warranted to elucidate criteria for (very) preterm intrauterine growth retardation.

In this study, the Apgar score was found to be the only useful parameter of an infant's condition after birth. In 19% of the cases, the Apgar score at 5 minutes after birth was 6 or less.

In 188 mothers, multiple pregnancy was present, resulting in 312 infants (23%) that were part of a twin, triplet or quadruplet.

In chapter 8, the hospitals involved in the study are described. The hospitals were classified into 3 levels of care:

1. hospitals with limited or no facilities for the treatment of very preterm and (or) very low birthweight infants (n=106)
2. hospitals with facilities for obstetric as well as neonatal special care, but only short term intensive care (n=19)
3. perinatal intensive care centres (n=8)

Because of centralization, 36% of the study infants were born in the perinatal intensive care centres (level 3). This centralization is largely due to antenatal transport (n=240), especially of infants under 32 weeks gestational age. However, the additional number of neonatal (intensive care) transports (n=427) indicates that most of the study infants did need such intensive neonatal care that was not available at the hospital of birth. In 78 cases long distance, intensive care transports were necessary because of overcrowding of the nearest NICU. In all, 86% of the neonatally transported infants that survived the neonatal period were transferred back to a hospital in a lower level.

In chapter 9, we present the results of an inquiry, conducted in the non-participating hospitals. The study population comprises 94% of all infants born alive with a gestational age of less than 32 weeks and (or) with a birthweight of less than 1500 g in the Netherlands in 1983. Comparison with data from other available sources (LVR, Eurocat, CBS) confirmed the completeness of the cohort. Discrepancies existed only at the extremely short gestational ages. We would like to stress the importance of a mandatory registration of gestational age and weight for all births (stillborn and liveborn), especially since the Netherlands is one of the very few West-European countries without such a registration.

In chapter 10, mortality in the study cohort is discussed. The most important mortality rates are as follows:

-first day mortality (24 hours):	11.0%
-early neonatal mortality (7 days):	19.9%
-neonatal mortality (28 days):	23.3%
-total in-hospital mortality:	25.4%
-infant mortality (first year):	27.2%

Comparison of mortality according to the usual birthweight-defined categories showed that in the Netherlands, mortality in VLBW infants is relatively low. Most of the deaths in the study cohort occurred during

the first week (73%), but a substantial number (8%) occurred only after the first 28 days of life.

We recommend that newborn mortality be reported not only as neonatal mortality but also as total in-hospital mortality (including all cases dying before discharge home) and as infant mortality (including all cases dying after discharge home).

In 1983, 37% of all first week deaths in the Netherlands was attributable to the study population, as was 34% of all the neonatal deaths and 25% of all infant deaths. In order to achieve a further decrease of these mortality rates in the Netherlands, sustained efforts to improve the perinatal care for this high-risk group of infants are warranted.

Chapter 11 lists the causes of death in the 340 infants that died during hospitalization. IRDS was the main cause of death (n=122) in the study population, often accompanied by ICH (n=116). Congenital malformations were less important as a cause of death (n=36). The "diagnosis" of immaturity was recorded frequently (n=55) as a cause of death. We suggest abolishing this practice, since it does not promote an understanding of the aetiology and pathophysiology of the neonatal disorders that may lead to death.

Postmortem examinations were performed in a large number of cases (63%). In the present study 15% of the autopsies changed or expanded the clinical diagnosis. Therefore, we advise that autopsy should always be performed, preferably according to a (perinatal) protocol.

In chapter 12, the most important disorders in the neonatal period are discussed. The incidence of IRDS (clinical 46%, confirmed 33%) as well as of ICH (clinical 25%, confirmed 20%) is low compared to the literature. Although modern intensive care has lowered the fatality rate considerably, especially of IRDS, no really effective cures or preventive measures are as yet available as routine treatment. We recommend that promising treatments be evaluated properly in prospective randomized trials (surfactant, vitamin E, phenobarbital) before being introduced in daily practice.

The incidence of congenital malformations (major malformations 9.3%; total 10.9%) is high, especially in the subpopulation of SGA infants (13.9%). The effect of current preventive measures is unknown. We favour a continuous registration of all congenital malformations on a national scale to monitor trends in the incidence of congenital defects. Such a registration may either be incorporated in a continuous registration of neonatal morbidity ("Landelijke Neonatale Registratie") or in a separate registration system.

In chapter 13, the methodology of the multivariate statistical technique used in this study (the logistic regression analysis) is explained. By using multivariate statistical techniques, the influence of a specific perinatal factor (exposure) can be calculated while adjusting for several potentially confounding factors. We conclude that such a procedure is essential to the proper evaluation of perinatal data, because of the differences in the distribution of perinatal factors.

In chapter 14, the relationship between mortality and a number of perinatal risk factors is examined by the application of logistic regression analysis.

Perinatal factors associated with a lower risk for mortality were: history of preterm birth or abortion, maternal hypertensive disorders, prolonged duration of ruptured membranes, antenatal transport and the administration of glucocorticoids.

Perinatal factors not associated with mortality risk were: mother's parity, hospitalization during pregnancy, tocolysis, chorioamnionitis, elective delivery, mode of delivery and sex of the infant.

Perinatal factors associated with an increased risk for mortality were: pre-existing maternal disease, congenital malformations, multiple pregnancy, breech or transverse presentation, birth outside a perinatal intensive care centre, low Apgar score, SGA, IRDS, ICH and convulsions.

Some of these findings are in contrast with generally accepted views. To our surprise, maternal hypertensive disorders were associated with a significantly lower mortality risk. Although the underlying pathophysiological mechanism is not yet fully understood, we hypothesize that maternal hypertension changes the feto-placental circulation, facilitating the adaptation process after birth. This hypothesis needs further study.

The finding of a lower adjusted mortality risk for infants born after glucocorticoid administration to the mother confirms the previously reported results from randomized controlled trials. In view of the limited number of cases treated with glucocorticoids, a reappraisal of this treatment is needed for the Netherlands.

We found no difference in the adjusted mortality risk between boys and girls in our study population. The previously reported excess-risk for boys in birthweight defined studies is caused by their shorter gestational age in comparable birthweight categories.

Elective delivery and caesarean section are interventions that are restricted to cases with a strong medical indication. These techniques are used only in cases with increased risk. Since we found no association between these factors and the adjusted mortality risk, we conclude

that once born alive, these infants have a mortality risk equal to that of infants born after a spontaneous or vaginal delivery.

Breech presentation was associated with a significantly increased risk for mortality, suggesting that the failure of an infant to assume the vertex presentation before birth is in itself an important prognostic factor. However, fetal presentation strongly influences the mode of delivery. Therefore, we calculated the adjusted odds ratio for mortality for infants delivered by caesarean section and for vaginal deliveries separately. In the caesarean section group, the mortality risks of breech presentation and vertex presentation were almost the same: odds ratio 0.80 (95% confidence limits 0.40-1.94). However, in vaginally born infants, breech presentation was associated with a significantly increased mortality risk: odds ratio 2.48 (95% confidence limits 1.54-3.99). Since other factors beyond the scope of this study, may have influenced the mode of delivery of the infants, the results of this analysis should be interpreted with care. The dilemma of the optimal mode of delivery for very preterm infants in breech presentation, should be faced with a prospective, randomized trial.

Different mortality risks for very preterm and/or VLBW infants were found in the three levels of care provided at the hospitals of birth and the related factors antenatal and neonatal transport. Although causal relationships cannot be established by the present study, it is likely that the differences in adjusted mortality risk can be reduced by improving the perinatal care delivery system for these vulnerable infants. Therefore, we recommend further centralization of births of very preterm infants with an expected very low birthweight to hospitals providing perinatal intensive care. The obvious limiting factor is the continuous shortage of intensive care accommodation, necessitating overcrowding of the intensive care units and restricted admittance of antenatal and neonatal transfers. Public health care authorities should assign high priority to the expeditious implementation of the decree issued by the Ministry of Welfare, Public Health and Cultural affairs ("concept planningsbesluit inzake de intensieve zorg voor pasgeborenen") proposing an increase of the total number of "intensive care incubators" from 60 to 100 and of "high care incubators" from 72 to 140.

In chapter 15, the relationship between neonatal morbidity and a number of perinatal risk factors is examined by the application of logistic regression analysis.

Perinatal factors associated with a lower risk for IRDS were: mother's admission to hospital during pregnancy, antenatal transport and glucocorticoid administration. The lower risk of IRDS after hospitalization of the mother during pregnancy and after antenatal transport indicates

the importance of a well-prepared delivery and of immediate adequate care of the newborn. This emphasizes again the need for improving the perinatal care delivery system for these infants. The lower risk of IRDS after glucocorticoid administration to the mother reinforces the above mentioned need for reappraisal of this treatment in the Netherlands.

Perinatal factors associated with an increased risk of IRDS were: male sex, multiple pregnancy, tocolysis, caesarean section, low Apgar score and ICH. The finding that male sex is associated with a higher risk for IRDS is in agreement with previous reports. Apparently, this does not lead to a higher mortality rate in boys. The association between IRDS and caesarean section or low Apgar score has been described previously. However, in multiple pregnancy and cases treated with tocolysis, the underlying mechanisms are yet unknown and require further investigation.

Maternal hypertensive disorders were associated with a lower risk of ICH. This suggests that such disorders may influence the fetus' (circulatory) adaptation to extra-uterine life, especially with regard to brain blood flow. The underlying pathophysiological mechanism is yet unknown and further study is needed.

Perinatal factors associated with an increased risk of ICH were: low Apgar score, IRDS, septicaemia and convulsions. This confirms generally accepted views.

Few perinatal factors were associated with the risk for septicaemia. Birth in a level 2 hospital was associated with a lower risk for septicaemia. This may be due to fewer and shorter periods of the use of invasive procedures.

Prolonged duration of ruptured membranes was associated with an increased risk for septicaemia. This relationship is well known, although the causality has not yet been established.

The associations between IRDS, ICH and septicaemia, present in our study population, confirm the often observed sequential occurrence of these disorders in many infants.

In recapitulation, we present the following recommendations, concerning:

Future perinatal research in the Netherlands

-mortality in newborn infants should at least be reported as neonatal mortality as well as postneonatal (infant) mortality.
-the relevance of the Amsterdam weight-for-gestational-age charts should be evaluated for very preterm infants.
-a collaborative randomized trial is needed to determine the optimal mode of delivery for (very) preterm infants in breech presentation.
-further study is needed to understand the pathophysiological mechanism involved in maternal hypertensive disorders (associated with lower adjusted risks for mortality and ICH), multiple pregnancy (associated with higher adjusted risks for mortality and IRDS) and tocolysis (associated with a higher adjusted risk of IRDS).
-data on socio-economic class should be fully recorded, notwithstanding the current reluctance to ask such questions.

Health care delivery in the Netherlands

-all births, stillborn as well as liveborn, should be registered from 22 gestational weeks onwards, including gestational age and birthweight.
-all first year deaths should be recorded by gestational age and birthweight.
-health care authorities should assign high priority to the extension of neonatal intensive care facilities.
-the administration of glucocorticoids in well selected pregnancies to accelerate fetal lung maturation requires reappraisal.

A national perinatal surveillance system should be established for the stimulation of such perinatal epidemiological research projects and for the evaluation of perinatal health care delivery.

References

Alberman E. Sociologic factors and birthweight in Great Britain. In: Reed DM, Stanley FJ, eds. The Epidemiology of Prematurity. Baltimore: Urban and Schwarzenberg, 1977; 146-156.

Alberman E, Benson J, Evans S. Visual defects in children of low birthweight. Arch Dis Child 1982a; 57: 818-822.

Alberman E, Benson J, McDonald A. Cerebral palsy and severe educational subnormality in low-birthweight children: a comparison of births in 1951-53 and 1970-73. Lancet 1982b; i: 606-608.

Alberman E. Low birthweight. In: Bracken MB, ed. Oxford: Oxford University Press, 1984: 86-98.

Alden ER, Mandelkorn T, Woodrum DE, Wennberg RP, Parks CR, Hodson WA. Morbidity and mortality of infants weighing less than 1,000 grams in an intensive care nursery. Pediatrics 1972; 50: 40-49.

Allen MC, Jones M jr. Medical Complications of Prematurity. Obstet Gynecol 1986; 67: 427-437.

Alley J, Terry J. Underreporting of Neonatal Deaths - Georgia,1974-1977. U.S. Department of Health, Education, and Welfare/Public Health Service. Morb Mort Weekl Rep 1979; 28: 253-254.

American Academy of Pediatrics. Committee on Fetus and Newborn. Nomenclature for duration of gestation, birthweight and intra-uterine growth. Pediatrics 1967; 39: 935-939.

American Academy of Pediatrics, The American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care. 1983. ISBN: 0-91076-1-04-3.

Amiel-Tison C, Pilla Grossi S, Laroche JC, Royon M, Tchobrousky C, Henrion R. Mortalité et morbidité néonatales. Les nouveaux objectifs de la prévention. Arch Fr Pediatr 1981a; 38: 281-290.

Amiel-Tison C, Lebrun F. Mortalité et Pronostic Cérébral des nouveau-nés de très faible poids de naissance. Rev Prat 1981b; 31: 367-374.

Anonymous. The Fate of the Baby under 1501 g at Birth. Editorial: Lancet 1980; i: 461-463.

Anonymous. Perinatal Pathology. Editorial: Lancet 1984; i: 431-432.

Anonymous. 10 jaar intercollegiale toetsing in het Catharina Ziekenhuis, 1986.

Apgar V. A proposal for new method of evaluation of the newborn infant. Anesth Analg 1953; 32: 260-265.

Astbury J, Orgill AA, Bajuk B, Yu VYH. Determinants of developmental performance of very low-birthweight survivors at one and two years of age. Dev Med Child Neurol 1983; 25: 709-716.

Bada HS, Alojipan LC, Andrews BF. Premature Rupture of Membranes and Its Effect on the Newborn. Pediatr Clin North Am 1977; 24: 491-500.

Baedorf K. Zur Frage des "Aufzuchtwertes", besonders der geistigen Entwicklung Unreifgeborener unter 1700 g Geburtsgewicht. Zeitschr Kinderheilkd 1937; 59: 218-235.

Baerts W. Intracraniële bloedingen bij preterm geborenen; een echografische studie. Thesis, Erasmus University, Rotterdam, 1984. pp 239.

Bajuk B, Kitchen WH, Lissenden JV, Yu VYH. Perinatal factors affecting survival of very low birthweight infants - a study from two hospitals. Aust Paediatr J 1981; 17: 277-280.

Bakketeig LS. The risk of repeated preterm or low birth-weight delivery. In: Reed DM, Stanley FJ, eds. The Epidemiology of Prematurity. Baltimore: Urban and Schwarzenberg, 1977: 231-241.

Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight on successive births. Am J Obstet Gynecol 1979; 135: 1086-1103.

Bakketeig LS, Hoffman HJ. Epidemiology of preterm birth: results from a longitudinal study of births in Norway. In: Elder MG, Hendricks CH, eds. Preterm Labor. London: Butterworths International Medical Reviews, 1981; 17-46.

Ballard JL, Kazmaier Novak K, Driver M. A simplified score for assessment of fetal maturation of newly born infants. J Pediatr 1979; 95: 769-774.

Barrett JM, Boehm FH. Comparison of aggressive and conservative management of premature rupture of fetal membranes. Am J Obstet Gynecol 1982; 144: 12-16.

Barrett JM, Boehm FH, Vaughn WK. The Effect of Type of Delivery on Neonatal Outcome in Singleton Infants of Birth Weight of 1,000 g or Less. JAMA 1983; 250: 625-629.

Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr 1967; 71: 159-163.

Bavikatte K, Bull MJ, Bryson CQ, Schreiner RL, Lemons JA, Gresham EL. Dramatically Improved Outcome of Extremely Low Birth Weight Infants: Experience in Indiana in 1977. J Indiana State Med Assoc 1980: 234-237.

Bax M. Looking at learning disorders. Devel Med Child Neurol 1982; 24: 731-732.

Bax M. Following up the small baby. Devel Med Child Neurol 1983; 25: 415-116.

Bax M. Perinatal care - success of failure? Devel Med Child Neurol 1986; 28: 277-278.

Beckwitt Turkel S, Miller CA, Guttenberg ME, Radovich Moynes D, Hodgman JE. A Clinical Pathological Reappraisal of Kernicterus. Pediatrics 1982; 69: 267-272.

Beckwitt Turkel SB, Sims ME, Guttenberg ME. Postponed Neonatal Death in the Premature Infant. AJDC 1986; 140: 576-579.

Beganovic N, Verloove-Vanhorick SP, Brand R, Ruys JH. Total Parenteral Nutrition and. Presented at the Xth Congress of Perinatal Medicine, Leipzig, 12-16 August 1986.

Behrman RE, Babson GS, Lessel R. Fetal and Neonatal Mortality in White Middle Class Infants. Mortality Risks by Gestational Age and Weight. Am J Dis Child 1971; 121: 486-489.

Bennebroek Gravenhorst J, Overbeeke MAM, Dijk BA van. Problemen bij de anti-rhesus (D)-immunoprofylaxe. Ned Tijdschr Geneeskd 1984; 128: 1005-1009.

Bennet R, Eriksson M, Melen B, Zetterström R. Changes in the Incidence and Spectrum of Neonatal Septicemia during a Fifteen-year period. Acta Paediatr Scand 1985; 74: 687-690.

Bennett FC, Robinson NM, Sells CJ. Hyaline Membrane Disease, Birth Weight, and Gestational Age. Effects on Development in the First Two Years. Am J Dis Child 1982; 136: 888-891.

Bennett FC, Robinson NM, Sells CJ. Growth and Development of Infants Weighing Less Than 800 Grams at Birth. Pediatrics 1983; 71: 319-323.

Bennett-Britton S, Fitzhardinge PM, Ashby S. Is intensive care justified for infants weighing less than 801 gm at birth? J Pediatr 1981; 99: 937-943.

Bergman I, Hirsch RP, Fria TJ, Shapiro SM, Holzman I, Painter MJ. Cause of hearing loss in the high-risk premature infant. J Pediatr 1985; 106: 95-101.

Bhat R, Raju TNK, Vidyasagar D. Immediate and long-term outcome of infants less than 1000 grams. Crit Care Med 1978; 6: 147-150.

Bierich, JR. Praenatale Schaedigungen durch Alkohol. Der Gynaekologe, 1978; 11: 142-150.

Bissenden JG. Ethical aspects of neonatal care. Arch Dis Child 1986; 61: 639-641.

Bjerkedal T, Bakketeig L, Lehmann EH. Percentiles of birth weights of single live births at different gestation periods. Acta Paed Scand 1973; 62: 449-457.

Blegen SD. The premature child. The incidence, aetiology, mortality and the fate of the survivors. Acta Paediatr 1953; 42: suppl 88.

Bodmer B, Benjamin A, McLean FH, Usher RH. Has use of cesarean section reduced the risks of delivery in the preterm breech presentation? Am J Obstet Gynaecol 1986; 154: 244-250.

Bonte JTP, Friden LM, Berg JWH van den. De statistiek van de doodsoorzaken. Ned Tijdschr Geneeskd 1985; 129: 1421-1429.

Bor M van de, Verloove-Vanhorick SP, Brand R, Keirse MJNC, Ruys JH. Incidence and prediction of periventricular-intraventricular hemorrhage in very preterm infants. Accepted for publication J Perinat Med, 1987.

Bosch Ch, Kowalewski S. Ergebnisse neurologischer Nachuntersuchungen im Alter von 1-7 Jahren bei Fruehgeborenen mit Geburtsgewichten unter 1500 Gramm. Monatsschr Kinderheilkd 1981; 129: 274-278.

Bowes WA jr, Halgrimson M, Simmons MA. Results of the Intensive Perinatal Management of Very-Low-Birth Weight Infants (501 to 1,500 Grams). J Reprod Med 1979; 23: 245-250.

Bowes WA jr, Simmons MA. Improved outcome in very low-birth weight infants. Am J Obstet Gynecol 1980; 136: 1080-1081.

Bowes WA jr. A review of perinatal mortality in Colorado, 1971 to 1978, and its relationship to the regionalization of perinatal services. Am J Obstet Gynecol 1981; 141: 1045-1052.

Boyle MH, Torrance GW, Sinclair JC, Horwood SP. Economic Evaluation of Neonatal Intensive Care of Very-Low Birth-Weight Infants. N Engl J Med 1983; 308: 1330-1337.

Brander T. Besteht ein Zusammenhang zwischen dem Geburtsgewicht und dem Intelligenzquotienten bei Fruehgeborenen? Monatsschr Kinderheilkd 1935; 63: 341-350.

Brans YW, Escobedo MB, Hayashi RH, Huff RW, Kagan-Hallet KS, Ramamurthy RJ. Perinatal mortality in a large perinatal center: Five-year review of 31,000 births. Am J Obstet Gynecol 1984; 148: 284-289.

Braun FHT, Jones KL, Smith DW. Breech presentation as an indicator of fetal abnormality. J Pediatr 1975; 86: 419-421.

Brothwood M, Wolke D, Gamsu H, Benson J, Cooper D. Prognosis of the very low birthweight baby in relation to gender. Arch Dis Child 1986; 61: 559-564.

Brown ER, Taeusch HW. Intensive care and the very low birthweight infant. Lancet 1979; ii: 362-363.

Brubakk AM. Brain blood flow in the neonate. Thesis, University of Leiden, 1985. 171 pp.

Bryce RL, Enkin MW. Six myths about controlled trials in perinatal medicine. Am J Obstet Gynecol 1985; 151: 707-710.

Bucci SP, Colarizi P, Di Tullio F, Panero A, Iannetti P, Santillo C, Moreno A, De Lucia ML, Bucci G. Prognosi a distanza di bambini con peso alla nascita di 1500 g o meno. Ital J Ped 1979; 5: 593-601.

Buckell EWC, Wood BSB. Wessex Perinatal Mortality Survey 1982. Br J Obstet Gynaecol 1985; 92: 550-558.

Buckwald S, Zorn WA, Egan EA. Mortality and Follow-up Data for Neonates Weighing 500 to 800 g at Birth. AJDC 1984; 138: 779-781.

Buncher CR. Cigarette smoking and duration of pregnancy. Am J Obstet Gynecol 1969; 103: 942-946.

Butler NR, Alberman ED, Goldstein H. Maternal factors affecting duration of pregnancy, birthweight and fetal growth. In: Butler NR & Alberman ED. Perinatal Problems. Edinburgh: E. and S. Livingstone Ltd, 1969: 47-65.

Calame A, Prod'hom LS. Pronostic vital et qualité de survie des prématurés pesant 1500 g et moins à la naissance, soignés en 1966-1968. Schweiz Med Wochenschr 1972; 102: 65-70.

Calame A, Ducret S. Jaunin L, Plancherel B. High risk appropriate for gestational age (AGA) and small for gestational age (SGA) preterm infants. Neurological handicap and developmental abnormalities at five years of age. Helv Paediatr Acta 1983; 38: 39-50.

Campbell AGM. Which infants should not receive intensive care? Arch Dis Child 1982; 57: 569-571.

Capper A. Progress in Pediatrics. The fate and development of the immature and of the premature child. Review of the Literature and Study of Cerebral Hemorrhage in the New-Born Infant. Part I. Am J Dis Child 1928a; 35: 262-288.

Capper A. Progress in Pediatrics. The fate and development of the immature and of the premature child. Review of the Literature and Study of Cerebral Hemorrhage in the New-Born Infant. Part II. Am J Dis Child 1928b; 35: 443-491.

Carr-Hill RA, Hall MR. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985; 92: 921-928.

Centraal Bureau voor de Statistiek. Perinatale sterfte: waarin opgenomen de relatie met de plaats van bevalling. 1979.

Centraal Bureau voor de Statistiek. Maandbericht gezondheid 84/2, 1984.

Centraal Bureau voor de Statistiek. Maandbericht gezondheid 85/7, 1985a.

Centraal Bureau voor de Statistiek. Maandstatistiek bevolking 85/10, 1985b.

Chalmers I, Mutch L. Are current trends in perinatal practice associated with an increase or a decrease in handicapping conditions? Lancet 1981; i: 1415.

Chalmers I, Sinclair JC. Promoting perinatal health: is it time for a change of emphasis in research? Early Hum Dev 1985; 10: 171-191.

Chervenak FA, Berkowitz GS, Thornton J, Kreiss C, Youcha S, Ehrenkranz RA, Hobbins JC, Berkowitz RL. A comparison of sonographic estimation of fetal weight and obstetrically determined gestational age in the prediction of neonatal outcome for the very low-birth weight fetus. Am J Obstet Gynecol 1985; 152: 47-50.

Chesley LC. Hypertensive Disorders of Pregnancy. New York: Appleton Century Crofts, 1978.

Chiswick ML. Perinatal referral: a time for decisions. Br Med J 1982; 285: 83-84.

Chiswick ML. Commentary on current World Health Organisation definitions used in perinatal statistics. Arch Dis Child 1986; 61: 708-710.

Clark CE, Clyman RI, Roth RS, Sniderman SH, Lane B, Ballard RA. Risk factor analysis of intraventricular hemorrhage in low-birth-weight infants. J Pediatr 1981; 99: 625-628.

Coelingh Bennink HJT. Zwangerschapsdiabetes. Thesis, Rijksuniversiteit Utrecht, 1980. 278 pp.

Cohen RS, Stevenson DK, Malachowski N, Ariagno RL, Kimble KJ, Hopper AO, Johnson JD, Ueland K, Sunshine P. Favorable Results of Neonatal Intensive Care for Very Low-Birth-Weight Infants. Pediatrics 1982; 69: 621-625.

Cohen SE, Sigman M, Parmelee AH, Beckwith L. Perinatal Risk and Developmental Outcome in Preterm Infants. Semin Perinatol 1982; 6: 334-339.

Commey JOO, Fitzhardinge PM. Handicap in the preterm small-for-gestational age infant. J Pediatr 1979; 94: 779-786.

Commissie Neonatologie van de Nederlandse Vereniging voor Kindergeneeskunde, 1978. Regionalisatie van de diagnostiek en behandeling van de zieke pasgeborene (curatieve neonatologie) in Nederland.

Cooke RWI. In utero transfer to specialist centres. Arch Dis Child 1983; 58: 483-484.

Cordero L, Backes CR, Zuspan FP. Very low-birth weight infant. I. Influence of place of birth on survival. Am J Obstet Gynecol 1982; 143: 533-537.

Cornel MC, Swagemakers MLS, Meerman GJ te, Haayer EJ, Kate LP ten. De EUROCAT-registratie van aangeboren afwijkingen en meerlinggeboorten; doelstellingen, werkwijze en resultaten van het Nederlandse deelproject in de periode 1981-1983. Ned Tijdschr Geneeskd 1986; 130: 1233-1237.

Cotton DB, Gonik B, Bottoms SF. Conservative versus aggressive management of preterm rupture of membranes. A randomized trial of amniocentesis. Am J Perinatol 1984; 1: 322-324.

Cox C, Kendall AC, Hommers M. Changed prognosis of breech-presenting low birthweight infants. Br J Obstet Gynaecol 1982; 89: 881-886.

Creasy RK, Liggins GC. Aetiology and management of preterm labour. In: Stallworthy J and Bourne G, eds. Recent advances in Obstetrics and Gynaecology 13. London: Churchill-Livingstone, 1979: 21-45.

Cree JE, Meyer J, Hailey DM. Diazepan in Labour: Its Metabolism and Effect on the clinical condition and thermogenesis of the newborn. Br Med J 1973; 4: 251-255.

Dahms B. The autopsy in pediatrics. AJDC 1986; 140: 335.

Daling JR, Emanuel I. Induced abortion and subsequent outcome of pregnancy. A matched cohort study. Lancet 1975; ii: 170-173.

Damstra-Wijmenga SMI. Analyse van perinatale sterfte van thuisgeborenen in 1983. The Practioner 1986: 201-210.

David RJ. Low Birth Weight (LBW) rates are declining in U.S. populations. Pediatr Res 1983a; 17: 177A.

David RJ, Siegel E. Decline in Neonatal Mortality, 1968 to 1977: Better Babies or Better Care? Pediatrics 1983b; 71: 531-540.

Davies PA, Stewart AL. Low-Birth Weight-infants: neurological sequelae and later intelligence. Br Med Bull 1975; 31: 85-91.

Davies PA. Outlook for the low birthweight baby - then and now. Arch Dis Child 1976; 51: 817-819.

Davies PA. Perinatal mortality. Arch Dis Child 1980; 55: 833-837.

Dijxhoorn MJ, Visser GHA, Fidler VJ, Touwen BCL, Huisjes HJ. Apgar Score, meconium and acidaemia at birth in relation to neonatal neurological morbidity in term infants. Br J Obstet Gynaecol 1986; 93: 217-222.

Doornik MC van, Cats BP, Versluys C, Saint-Aulaire ED de, Woord H van der. Pasgeborenen met een zeer laag geboortegewicht. T Kindergeneeskd 1980; 48: 74-85.

Douglas JWB, Blomfield JM. The Reliability of longitudinal surveys. Milbank Mem Fund Q 1955; 33: 227-252.

Douglas JWB, Gear R. Children of low birthweight in the 1946 national cohort. Behaviour and educational achievement in adolescence. Arch Dis Child 1976; 51: 820-827.

Drew JH. Immediate Intubation at Birth of the Very-Low-Birth-Weight Infant. Am J Dis Child 1982; 136: 207-210.

Drillien CM. Studies in Prematurity, Stillbirth and Neonatal Death. Part I. Factors affecting birth-weight and outcome. J Obstet Gyn 1947; 300-323.

Drillien CM. Studies in Prematurity. Part 4. Development and progress of the prematurely born child in the pre-school period. Arch Dis Child 1948; 23: 69-83.

Driscoll JM jr, Driscoll YT, Steir ME, Stark RI, Dangman BC, Perez A, Wung JT, Kritz P. Mortality and Morbidity in Infants Less Than 1,001 Grams Birth Weight. Pediatrics 1982; 69: 21-26.

Druzin ML, Fox A, Kogut E, Carlson C. The relationship of the nonstress test to gestational age. Am J Obstet Gynecol 1985; 153: 386-389.

Dubois EFL, Koppe JG, Peters GJM. Obstetrical and Neonatal predictors of perinatal and Neonatal mortality in premature infants. Presented at the IXth Congress of Perinatal Medicine, Dublin, 1984.

Dubowitz LMS, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr 1970; 77: 1-10.

Dunn HG. Sequelae of Low Birthweight: The Vancouver study. Oxford: Blackwell Scientific Publications Ltd, 1986.

Dunn PM, Speidel BD, Fleming PJ. Intensive care and the very-low-birth-weight infant. Lancet 1979; ii: 254-255.

Dunn PM. The Search for Perinatal Definitions and Standards. Acta Paediatr Scand 1985; 319: 7-16.

Duyzings AJM. Ueber die Fruehgeburt und das zu fruehgeborene Kind. Arch Gynecol 1935; 159: 524-536.

Dweck HS, Saxon SA, Benton JW, Cassady G. Early Development of the Tiny Premature Infant. Am J Dis Child 1973; 126: 28-34.

Eaves LC, Nuttall JC, Klonoff H, Dunn HG. Developmental and psychological test scores in children of low birth weight. Pediatrics 1970; 45: 9-20.

Egan EA, Buckwald S, Topper WH, Zorn WA, Johnson CB. Extreme prematurity (600-799g): Survival and early follow-up. Pediatr Res 1980; 14: 433.

Eksmyr R, Larssen K-E, Bakketeig LS, Bergsjo P, Finne P, Laurini R, Wasén G, Knoff H. Perinatal Mortality in a Swedish Country 1973-1978. Time Trends Revealed by Perinatal Audit. Acta Paediatr Scand 1986; 75: 17-23.

Elliott HR, Abdulla H, Hayes PJ. Pulmonary oedema associated with ritodrine infusion and betamethasone administration in premature labour. Br Med J 1978; II: 799-800.

Erhardt CL, Weiner L, McAvoy G. Pathological reports for mortality statistics. JAMA 1959; 171: 33-36.

Erjavec M, Pajntar M, Novak Z. Very low birth weight infants. Paper presented at the IXth Congress of Perinatal Medicine, Dublin, 1984.

Eskes TKAB, Nijdam WS, Buys RJRM, Rossum JM van. Prospectief onderzoek naar het gebruik van geneesmiddelen bij zwangeren. J Drug Research 1983; 8: 1912-1916.

Falck Larsen J, Eldon K, Lange AP, Leegaard M, Osler M, Sederberg Olsen J, Permin M. Ritodrine in the treatment of preterm labor: second Danish multicenter study. Obstet Gynecol 1986; 67: 607-613.

Fedrick J, Butler NR. Hyaline Membrane Disease. Lancet 1972; ii: 768-769.

Fedrick J, Anderson ABM. Factors associated with spontaneous pre-term birth. Br J Obstet Gynaecol 1976; 83: 342-350.

Fetter WPF, Baerts W, Borst LE. Late morbiditeit bij kinderen met een geboortegewicht van minder dan 1500 gram, geboren in de periode 1979-1983. Ned Tijdschr Geneeskd 1986; 130: 1143-1146.

Field TM, Dempsey JR, Ting GT, Hallock N, Dabiri C, Shuman HH. Respiratory Distress Syndrome: Perinatal Prediction of One Year Developmental Outcome. Semin Perinatol 1982; 6: 288-293.

FIGO. List of Gynecologic and Obstetrical Terms and Definitions. Int J Gynaecol Obstet 1976; 14: 570-576.

FIGO. Report of the FIGO Committee on Perinatal mortality and morbidity, following a Workshop on Monitoring and Reporting Perinatal Mortality and Morbidity. Geneva, 1982.

FIGO. Report of the FIGO sub-committee on Perinatal Epidemiology and Health Statistics following a Workshop in Cairo, November 11-18, 1984, on the Methodology of Measurement and Recording of Infant Growth in the Perinatal Period. FIGO, London, 1986.

Finnström O. Studies on Maturity in Newborn Infants. IX. Further Observations on the Use of External Characteristics in Estimating Gestational Age. Acta Paediatr Scand 1977; 66: 601-604.

Fischer WM, Stude I, Brandt H. Ein Vorschlag zur Beurteilung des antepartualen Kardiotokogramms. 2. Geburtsh. Perinat 1976; 180: 117-123.

Fitzhardinge PM, Ramsay M. The Improving Outlook for the Small Prematurely Born Infant. Dev Med Child Neurol 1973; 15: 447-459.

Fitzhardinge PM. Early Growth and Development in Low-Birthweight Infants Following Treatment in an Intensive Care Nursery. Pediatrics 1975; 56: 162-172.

Fitzhardinge PM, Pape K, Arstikaitis M, Boyle M, Ashby S, Rowley A, Netley C, Swyer PR. Mechanical ventilation of infants of less than 1,501 gm birth weight: Health, growth and neurologic sequelae. J Pediatr 1976a; 88: 531-541.

Fitzhardinge PM. Follow-Up Studies on the Low Birth Weight Infant. Clin Perinatol 1976b; 3: 503-516.

Fitzhardinge PM, Pape KE. Intrauterine growth retardation (IUGR): An added risk to the preterm infant. Pediatr Res 1977; 11: 562.

Fitzhardinge PM, Kalman E, Ashby S, Pape KE. Present status of the infant of very low birth weight treated in a referral neonatal intensive care unit in 1974. In: Elliot K, O'Connor M, eds. Major Mental Handicap: Methods and Costs of Prevention. Ciba Found Symp. Amsterdam: Elsevier, 1978; 59: 139-150.

Fledelius H. Inhibited growth and development as permanent features of low birth weight. A Longitudinal Study of Eye Size, Height, Head Circumference, Interpupillary Distance and Exophtalmometry, as Measured at Age of 10 and 18 Years. Acta Paediatr Scand 1982; 71: 645-650.

Fog Pedersen J, Mølsted-Pedersen L. Early growth retardation in diabetic pregnancy. Br Med J 1979; 1: 18-19.

Francis-Williams J, Davies PA. Very Low Birthweight and Later Intelligence. Dev Med Child Neurol 1974; 16: 709-728.

Freedman RM, Ingram DL, Gross I, Ehrenkranz RA, Warshaw JB, Baltimore RS. A Half Century of Neonatal Sepsis at Yale. Am J Dis Child 1981; 135; 140-144.

Galloway CAS, Robertson G. The prognosis for very low birth weight babies in the highlands of Scotland. Scott Med J 1981; 26:336-339.

Gamsu HR, Light F, Potter A, Price JF. Intensive care and the very-low-birthweight infant. Lancet 1979; ii: 736.

Garite TJ, Freeman RK. Chorioamnionitis in the Preterm Gestation. Obstet Gynecol 1982; 59: 539-545.

Gau G. The ultimate audit. Br Med J 1977; 1: 1580-1581.

Gelderen HH van, Posthuma JH, Haas JH de. Geboortegewicht en praematuritas in Nederland. Tijdschr Soc Geneesk 1954; 22: 443-454.

Gèrard P, Bachy A, Battisti O, Senterre J, Rigo J, Adam E, Beauduin P, Bartholomè J, El Bouz S. Mortality in 504 infants weighing less than 1501 g at birth and treated in four neonatal intensive care units of South-Belgium between 1976 and 1980. Eur J Pediatr 1985; 144: 219-224.

Gezondheidsraad. Advies inzake intensive-care neonatologie. Verslagen, Adviezen, Rapporten, Ministerie van Welzijn, Volksgezondheid en Cultuur. Staatsuitgeverij, 's-Gravenhage 75/1983 (ISBN 90 12 04454 5).

Gilstrap LC, Hauth JC, Bell RE, Ackerman NB, Yoder BA, Delemos R. Survival and Short-Term Morbidity of the Premature Neonate. Obstet Gynecol 1985; 65: 37-41.

Goldenberg RL, Nelson K. Iatrogenic respiratory distress syndrome. An analysis of obstetric events preceding delivery of infants who develop respiratory distress syndrome. Am J Obstet Gynecol 1975; 123: 617-620.

Goldenberg RL, Nelson KG. The premature breech. Am J Obstet Gynecol 1977; 127: 240-244.

Goldenberg RL, Humphrey JL, Hale CB, Boyd BW, Wayne JB. Neonatal deaths in Alabama, 1970-1980: An analysis of birth weight- and race-specific neonatal mortality rates. Am J Obstet Gynecol 1983a; 145: 545-552.

Goldenberg RL, Humphrey JL, Hale CB, Boyd BW, Wayne JB. Neonatal deaths in Alabama. II. Policy and research implications derived from a comparison of birth weight-specific state and medical center neonatal mortality rates. Am J Obstet Gynecol 1983b; 146: 450-455.

Goldenberg RL, Humphrey JL, Hale CB, Wayne JB. Lethal Congenital Anomalies as a Cause of Birth-Weight-Specific Neonatal Mortality. JAMA 1983c; 250: 513-515.

Goldenberg RL, Nelson KG, Hale CD, Wayne J, Bartolucci AA, Koski J. Survival of infants with low birth weight and early gestational age, 1979 to 1981. Am J Obstet Gynecol 1984; 149: 508-511.

Goldenberg RL, Nelson KG, Koski JF, Cutter G, Cassady GE. Neonatal mortality in infants born weighing 501 to 1000 grams. Am J Obstet Gynecol 1985a; 151:608-611.

Goldenberg RL, Nelson KG, Koski JF, Cutter GR. Low birth weight, intrauterine growth retardation, and preterm delivery. Am J Obstet Gynecol 1985b; 152: 980-984.

Goldenberg RL, Koski J, Ferguson C, Wayne J, Hale CB, Nelson KG. Infant mortality: Relationship between neonatal and postneonatal mortality during a period of increasing perinatal center utilization. J Pediatr 1985c; 106: 301-303.

Goldenberg RL, Hanson S, Wayne JB, Koski J. Vital Statistics Data as a Measurement of Perinatal Regionalization in Alabama, 1970-1980. South Med J 1985d; 78: 657-660.

Gordon RR. Premature baby statistics. Br Med J 1977a; 1: 1313-1315.

Gordon RR. Neonatal and "perinatal" mortality rates by birth weight. Br Med J 1977b; 2: 1202-1204.

Gordon RR. Intensive care and the very-low-birthweight infant. Lancet 1979; ii: 36.

Graeff-Meeder ER de, Wit JM. Glucocorticoïden in de zwangerschap: effecten op de foetus en de pasgeborene. Ned Tijdschr Geneeskd 1986; 130: 2168-2171.

Grassy RG, Hubbard C, Graven SN, Zachman RD. The Growth and Development of Low Birth Weight Infants Receiving Intensive Neonatal Care. Preliminary Observation on 28 Such Infants. Clin Pediatr 1976; 15: 549-553.

Gray PH, Griffin EA, Deasy PF, Duignan NM. Intensive Care and the Very Low Birth Weight Infant. Ir Med J 1983; 76: 236-239.

Guinness book of Records. Longest pregnancy. In: McWhirter N & R, eds. Guinness Book of Records. London: Superlatives Limited, 1975: 17.

Haas G, Buchwald-Saal M, Mentzel H, Michaelis R. Mortalität und neurologische Morbidität bei ehemaligen Frühgeborenen und untergewichtigen Termingeborenen. Monatsschr Kinderheilkd 1983; 131: 1-3.

Haas JH de, Haas-Posthuma JH de. Zo rookt Nederland. Brochure Stichting Volksgezondheid en roken. The Hague, 1982.

Hack M, Fanaroff AA, Merkatz IR. The Low-Birth-Weight Infant-Evolution of a Changing Outlook. N Engl J Med 1979; 301: 1162-1165.

Hack M, Merkatz IR, Jones PK, Fanaroff AA. Changing trends of neonatal and postneonatal deaths in very-low-birtweight infants. Am J Obstet Gynecol 1980; 137: 797-800.

Hack M, Fanaroff AA, Changes in the delivery room care of the extremely small infant(<750g). N Engl J Med 1986; 314: 660-664.

Haesslein HC, Goodlin RC. Delivery of the tiny newborn. Am J Obstet Gynecol 1979; 134: 192-200.

Hagberg B, Hagberg, Olow I. The changing panorama of cerebral palsy in Sweden 1954-1970. I. Analysis of the General Changes. Acta Pediatr Scand 1975; 64: 187-192.

Hall MH, Carr-Hill R. Impact of sex ratio on onset and management of labour. Br Med J 1982; 285: 401-403.

Hall MH. Incidence and distribution of preterm labour. In: Beard RW and Sharp F, eds. Preterm Labour and its consequences. Proceedings of the 13th Study Group of the RCOG. London: Royal College of Obstetricians and Gynecologists, 1985: 5-13. ISBN 0 902331 337.

Harper R, Rosenstein R, Sia C, Kierney C. Should we continue to define neonatal mortality as death within the first 28 days of life? Pediatr Res 1979; 13: 390 (abstr.).

Harris TR, Isaman J, Giles HR. Improved Neonatal Survival Through Maternal Transport. Obstet Gynecol 1978; 52: 294-300.

Hatt JJ, Flusin MF, Chavanne J.L'élevage et l'avenir des prématurés de poids égal ou inférieur à 1250 grammes. Etude portant sur 42 observations. Ann Pediat 1972; 19: 67-71.

Hawgood S, Spong J, Yu VYH. Intraventricular Hemorrhage. Incidence and Outcome in a Population of Very-Low-Birth-Weight Infants. Am J Dis Child 1984; 138: 136-139.

Hein HA, Brown CJ. Neonatal Mortality Review: A Basis for Improving Care. Pediatrics 1981; 68: 504-509.

Hein HA, Lathrop SS. The Changing Pattern of Neonatal Mortality in a Regionalized System of Perinatal Care. AJDC 1986; 140: 989-993.

Hein PR, Sporken JMJ, Boon JM, Boo Th de, Jongsma HW. Vooruitzichten bij kinderen geboren vóór de 34e zwangerschapsweek I. Sterfte. Ned Tijdschr Geneeskd 1982; 126: 857-861.

Heinonen K. Matilainen R, Koski H. Launiala K. Intrauterine growth retardation (IUGR) in pre-term infants. J Perinat Med 1985; 13: 171-178.

Hemel OJS van. Perinatologische kwaliteitsbewaking door de landelijke verloskunde registratie. In: Proceedings VIe Medisch Informatica congres 1986: 73-78. ISBN 90 5005 005 0

Hermansen MC, Hasan S. Importance of Using Standardized Birth Weight Increments to Report Neonatal Mortality Data. Pediatrics 1986; 78: 144-145.

Hernandez JA, Lazarte RA, Goldson E, Honeyfield PR, Butterfield LJ. Mortality and early morbidity in infants less than 1000 grams birth weight. Clin Research 1981; 29: 118A.

Hertzig ME. Neurological "Soft" Signs in low-birthweight children. Dev Med Child Neurol 1981; 23: 778-791.

Hess JH, Mohr GJ, Bartelme PF. The Physical and Mental Growth of Prematurily Born Children. Chicago: Univ. of Chicago Press, 1934.

Hess JH, Lundeen EC. The premature infant. Medical and Nursing Care. Philadelphia: J.B. Lippincott Comp, 1949; 1-323.

Hess JH. Experiences gained in a thirty year study of prematurely born infants. Pediatrics 1953; 11: 425-434.

Hesseldahl H. A Danish multicenter study on Ritodrine R in the treatment of pre-term labour. Dan Med Bull 1979; 26: 116-118.

Hirata T, Epcar JT, Walsh A, Mednick J, Harris M, McGinnis MS, Sehring S, Papedo G. Survival and outcome of infants 501 to 750 gm: A six-year experience. J Pediatr 1983; 102: 741-748.

Hobel CJ, Hyvarinen MA, Okada DM, Oh W. Prenatal and Intrapartum high-risk screening. I Prediction of the high-risk neonate. Am J Obstet Gynecol 1973; 117: 1-9.

Hoffman HJ, Bakketeig LS. Risk factors associated with the occurrence of preterm birth. Clin Obstet Gynecol 1984; 27: 539-552.

Hogerzeil HV, Soepatmi S, Kreijenbroek M, Treffers PE. Aan heroine verslaafde zwangeren: een overzicht over 11 jaar uit het Wilhelmina Gasthuis te Amsterdam. Ned Tijdschr Geneeskd 1982; 126: 316-320.

Hommers M, Kendall AC. The Prognosis of the Very Low birth-weight Infant. Dev Med Child Neurol 1976; 18: 745-752.

Horwood SP, Boyle MH, Torrance GW, Sinclair JC. Mortality and Morbidity of 500- to 1,499-Gram Birth Weight Infants Liveborn to Residents of a Defined Geographic Region Before and after Neonatal Intensive Care. Pediatrics 1982; 69: 613-620.

Hoskins EM, Elliot E, Shennan AT, Skidmore MB, Keith E. Outcome of very low-birth weight infants born at a perinatal center. Am J Obstet Gynecol 1983; 145: 135-140.

Howard PJ, Worrel CH. Premature infants in later life. Study of Intelligence and Personality of 22 Premature Infants at Ages 8 to 19 Years. Pediatrics 1952; 9: 577-584.

Hughes EC. Obstetric-Gynecologic Terminology. Philadelphia: Davis, 1972: 442-443.

Hughes-Davies TH. Conservative care of the newborn baby. Arch Dis Child 1979; 54: 59-61.

Huisjes HJ. Intrauterine growth retardation a question of definition. In: Huisjes HJ, ed. Aspects of perinatal morbidity. Groningen: Universitaire Boekhandel Nederland, 1981: 54-60.

Huisman A, Visser GHA, Okken A, Wagen A van der, Huisjes HJ. Intra-uteriene verwijzingen; een overzicht van vier jaar ervaring, 1978-1981. Ned Tijdschr Geneeskd 1983; 127: 1525-1530.

Huisman A. Haemorheological changes during pregnancy. Thesis, Rijksuniversiteit Groningen, 1986. 107 pp.

Hunt JV, Tooley WH, Harvin D. Learning Disabilities in Children with Birth Weights <1500 Grams. Semin Perinatol 1982; 6: 280-287.

Hutson JM, Fox HE, Driscoll JM, Driscoll YT, Steir ME. Obstetrical intensive care-improved survival for infants under 1000 grams. Ped Res 1983; 17: 319A.

Hytten FE, Leitch I. The Physiology of Human Pregnancy. Oxford: Blackwells Scientific Publications, 1971.

Hytten FE. Breech presentation: is it a bad omen? Br J Obstet Gynaecol 1982; 89: 879-880.

Jarvis SN, Holloway JS, Hey EN. Increase in cerebral palsy in normal birthweight babies. Arch Dis Child 1985; 60: 1113-1121.

Jivani SKM. Evolution of neonatal intensive care in a district general hospital. Arch Dis Child 1986; 61: 148-152.

Johnson L, Bowen FW, Abbasi S, Herrmann N, Weston M, Sacks L, Porat R, Stahl G, Peckham G, Delivoria-Papadopoulos M, Quinn G, Schaffer D. Relationship of Prolonged Pharmacologic Serum Levels of Vitamin E to Incidence of Sepsis and Necrotizing Enterocolitis in Infants with Birth Weight 1,500 Grams or Less. Pediatrics 1985; 75: 619-638.

Jones RAK, Cummins M, Davies PA. Infants of very low birth-weight: A 15-year analysis. Lancet 1979a; i: 1332-1335.

Jones RAK, Cummins M, Davies PA. Intensive care and the very-low-birth-weight infant. Lancet 1979b; ii: 523.

Jones RAK, Davies PA. The outcome for preterm infants. In: Elder MG, Hendricks CH, eds. Preterm Labor. London: Butterworths Intern. Medical Reviews: Obstet Gynecol, 1981; I: 289-316.

Jonge GA de, Klaauw MM van der. De frequentie van roken voor, tijdens en na de zwangerschap. Ned Tijdschr Geneeskd 1982; 126: 1537-1543.

Kanhai HHH. Achtergronden en konsekwenties van vroeggeboorte. Thesis, Rijksuniversiteit Leiden, 1981. 228 pp.

Karp LE, Doney JR, McCarthy T, Meiss PJ, Hall M. The premature breech: trial of labor or cesarean section. Obstet Gynecol 1979; 53: 88-92.

Keirse MJNC, Rush RW, Anderson ABM, Turnbull AC. Risk of pre-term delivery in patients with previous pre-term delivery and/or abortion. Br J Obstet Gynaecol 1978; 85: 81-85.

Keirse MJNC. Epidemiology of preterm labour. In: Keirse MJNC, Anderson ABM, Bennebroek Gravenhorst J, eds. Human Parturition. The Hague: Martinus Nijhoff Publishers, the Netherlands, 1979: 219-234.

Keirse MJNC, Kanhai HHH. An Obstetrical Viewpoint On Preterm Birth With Particular Reference To Perinatal Morbidity And Mortality. In: Huisjes HJ, ed. Aspects of Perinatal Morbidity. Groningen: Universitaire Boekhandel Nederland, 1981a: 1-35.

Keirse MJNC, Trimbos JB, Mallens TEJM, Heemst M van der. Reliability of ultrasound as compared to direct fetal electrocardiography for antepartum cardiotocography. Br J Obstet Gynaecol 1981b; 88: 391-394.

Keirse MJNC. Perinatal mortality rates do not contain what they purport to contain. Lancet 1984a; i: 1166-1169.

Keirse MJNC. Obstetrical attitudes to glucocorticoid treatment for fetal lung maturation: time for a change? Eur J Obstet Gynecol Reprod Biol 1984b; 17: 247-255.

Keirse MJNC. Epidemiology and Aetiology of the Growth Retarded Baby. Clin Obstet Gynecol 1984c; 11: 415-436.

Keirse MJNC, Kanhai HHH. Haemodynamics and pregnancy-induced hypertension. In: Kleef JW van, Burm AGL, Spierdijk J, eds. Current Concepts in Regional Anaesthesia. The Hague: Martinus Nijhoff Publishers, 1984d: 91-103.

Khong TY, Wolf F de, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by preeclampsia and by Small-for-gestational age infants. Br J Obstet Gynaecol 1986; 93: 1049-1059.

Khoury MJ, Marks JS, McCarthy BJ, Zaro SM. Factors affecting the sex differential in neonatal mortality: The role of respiratory distress syndrome. Am J Obstet Gynecol 1985; 777-782.

Kiely JL, Paneth N. Follow-up studies of low-birthweight infants: suggestions for design, analysis and reporting. Dev Med Child Neurol 1981; 23: 96-100.

Kiely J, Paneth N, Stanley F. Monitoring the Morbidity Outcomes of Perinatal Health Services. In: Stanley F and Alberman E, eds. The Epidemiology of Cerebral Palsies. London: Spastics Int Med Publ, 1984: 150-171.

Kiely JL, Paneth N, Susser M. Fetal death during labor: An epidemiologic indicator of level of obstetric care. Am J Obstet Gynecol 1985; 153: 721-727.

Kitchen WH, Ryan MM, Rickards A, Gaudry E, Brenton AM, Billson FA, Fortune DW, Keir EH, Lundahl-Hegedus EE. A Longitudinal Study of Very Low-birthweight Infants. I: Study Design and Mortality Rates. Dev Med Child Neurol 1978; 20: 605-618.

Kitchen WH, Rickards A, Ryan MM, McDougall AB, Billson FA, Keir EH, Naylor FD. A Longitudinal Study of Very Low-birth-weight Infants. II: Results of Controlled Trial of Intensive Care and Incidence of Handicaps. Dev Med Child Neurol 1979; 21: 582-589.

Kitchen WH, Ryan MM, Rickards A, McDougall AB, Billson FA, Keir EH, Naylor FD. A Longitudinal Study of Very Low-birthweight Infants. IV: An Overview of Performance at Eight Years of Age. Dev Med Child Neurol 1980; 22:172-188.

Kitchen WH, Lissenden JV, Yu VYH, Bajuk B. Collaborative study of very-low-birthweight infants: Techniques of perinatal care and mortality. Lancet 1982a; i: 1454-1457.

Kitchen WH, Orgill A, Rickards A, Ryan MM, Lissenden JV, Keith CG, Yu VYH, Ford GW, Astbury J, Russo W, Bajuk B, Nave JRM. Collaborative study of very-low-birthweight infants: Outcome of two-year-old survivors. Lancet 1982b; i: 1457-1460.

Kitchen WH, Yu VYH, Orgill AA, Ford G, Rickards A, Astbury J, Ryan MM, Russo W, Lissenden JV, Bajuk B. Infants born before 29 weeks gestation: survival and morbidity at 2 years of age. Br J Obstet Gynaecol 1982c; 89: 887-891.

Kitchen WH, Ryan MM, Rickards A, Astbury J, Ford G, Lissenden JV, Keith CG, Keir EH. Changing Outcome Over 13 Years of Very Low Birthweight Infants. Semin Perinatol 1982d; 6: 373-389.

Kitchen WH, Yu VYH, Orgill AA, Ford G, Rickards A, Astbury J, Lissenden JV, Bajuk B. Collaborative Study of Very-Low-Birthweight Infants. Am J Dis Child 1983; 137: 555-559.

Kitchen W, Ford GW, Doyle LW, Rickards AL, Lissenden JV, Pepperell RJ, Duke JE. Cesarean Section or Vaginal Delivery at 24 to 28 Weeks'Gestation: Comparison of Survival and Neonatal and Two-Year Morbidity. Obstet Gynecol 1985; 66: 149-157.

Klein N, Hack M, Gallagher J, Fanaroff AA. Preschool Performance of Children with Normal Intelligence Who Were Very Low-Birth-Weight Infants. Pediatrics 1985; 75: 531-537.

Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic Research. London: Lifetime Learning Publications, 1982.

Kloosterman GJ. Over Intra-uteriene groei en de intra-uteriene groeicurve. Mdschr. v. Kindergnk 1969; 37: 209-225.

Kloosterman GJ. On intrauterine growth. Int J Gynaecol Obstet 1970; 8: 895-912.

Kloosterman GJ. De voortplanting van de mens. Haarlem: Uitgeversmaatschappij Centen, 1977.

Knobloch H, Malone A, Ellison PH, Stevens F, Zdeb M. Considerations in Evaluating Changes in Outcome for Infants Weighing Less Than 1,501 Grams. Pediatrics 1982; 69: 285-295.

Koenig H. What Happens to Prematures. Am J Public Health 1950; 40: 803-807.

Kollée LAA, Eskes TKAB, Koppes JFP. Geregionaliseerde perinatale zorg voor de kleine vroeggeborene. Medisch Contact 1984; 35: 1115-1117.

Konstantinou D, Tsitsikas H, Giouroukos S. Ringas A, Saroglou I, Papagaroufalis K, Papathanasiou P, Petmezaki S. Outcome of very low birth-weight infants (<1500 g) delivered in a private maternity Hospital. Presented at the IXth European Congress of Perinatal Medicine, Dublin 1984.

Koops BL, Morgan LJ, Battaglia FC. Neonatal mortality risk in relation to birth weight and gestational age: Update. J Pediatr 1982; 101: 969-977.

Kopelman AE. The Smallest Preterm Infants. Reasons for Optimism and New Dilemmas. Am J Dis Child 1978; 132: 461-462.

Koppe JG, Treffers PE. Intensive care and the very low birthweight infant. Lancet 1981; ii: 527-528.

Koppe JG. Evaluating intensive care and the very immature infant. Lancet 1983; ii: 49-50.

Koppe JG, Peters GJM, Dubois EFL. Twintig jaar na-onderzoek van vroeggeborenen van 25-31 weken. Ned Tijdschr Geneeskd 1984; 128: 1364-1369.

Koppe JG, Leeuw R de, Verloove-Vanhorick P, Ruys JH, Bennebroek Gravenhorst J, Verwey RA, Treffers PE, Brand R. Antepartum corticosteroids. Presented at the Xth European Congress of Perinatal Medicine, Leipzig, August 11, 1986.

Kraybill EN, Kennedy CA, Teplin SW, Campbell SK. Infants With Birth Weights Less Than 1,001 g. Survival, Growth, and Development. AJDC 1984; 138: 837-842.

Kristoffersen K, Kern Hansen M. The condition of the foetus and infant in cases treated with Ritodrine R. Dan Med Bull 1979; 26: 121-122.

Kubli F. Proceedings of the Study Group on Pre-term Labour. In: Anderson A, Beard R, Brudenell MJM and Dunn PM, eds. London: Royal College of Obstetricians and Gynaecologists, 1977: 218-220.

Kuliev A, Modell B, Galjaard H. eds. Report of a WHO/Sereno Symposium held in Geneva, Switzerland, May 2-4 1984. Rome, Ares Serono Symposia, 1985.

Kulkarni P, Hall RT. Rhodes PG, Sheehan MB. Postneonatal Infant Mortality in Infants Admitted to a Neonatal Intensive Care Unit. Pediatrics 1978; 62: 178-183.

Kumar SP, Anday EK, Sacks LM, Ting RY, Delivoria-Papadopoulos M. Follow-up Studies of Very Low Birth Weight Infants (1,250 Grams or Less) Born and Treated Within a Perinatal Center. Pediatrics 1980; 66: 438-444.

La Gamma EF, Drusin LM, Mackles AW, Machalek S, Auld PAM. Neonatal Infections. An Important Determinant of Late NICU Mortality in Infants Less Than 1,000 g at Birth. Am J Dis Child 1983; 137: 838-841.

Lam C. Prognosis of infants of very low birth weight (<1,500 gm) at Alexandra Hospital, Singapore. J Singapore Paediatr Soc 1978; 20: 214-221.

Lamont RF, Dunlop PDM, Crowley P, Elder MG. Spontaneous preterm labour and delivery at under 34 weeks'gestation. Br Med J 1983; 286: 454-457.

Lamont RF. Factors influencing the Route of Delivery. In: Beard RW and Sharp F, eds. Pre-term Labour and its consequences. Proceedings of the 13th Study Group of the Royal College of Obstetricians and Gynaecologists. London, RCOG, 1985: 263-272.

Lancaster PA. Obstetric outcome. Clin Obstet Gynecol 1985; 12: 847-864.

Laurini RN. Aspects of developmental pathology. Thesis, Rijksuniversiteit Groningen, 1986. 164 pp.

Lee KS, Paneth N, Gartner LM, Pearlman M. The very low-birth-weight rate: Principal predictor of neonatal mortality in industrialized populations. J Pediatr 1980a; 97: 759-764.

Lee KS, Paneth N, Gartner LM, Pearlman MA, Gruss L. Neonatal Mortality: An Analysis of the Recent Improvement in the United States. Am J Public Health 1980b; 70: 15-21.

Levene MI, Fawer CL, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the preterm neonate. Arch Dis Child 1982; 57: 410-417.

Leveno KJ, Guzick DS, Hankins GDV, Klein VR, Young DC, Williams ML. Single-centre randomised trial of ritrodrine hydrochloride for preterm labour. Lancet 1986; i: 1293-1295.

Liggings GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50: 515-525.

Liggings GC, Kitterman JA. Maturation of the fetal lung. Dan Med Bull 1979; 26: 129-135.

Lin CC, Lindheimer MD, River P, Moarwad AM. Fetal outcome in hypertensive disorders of pregnancy. Am J Obstet Gynecol 1982; 142: 255-260.

Liu DTY, Melville HAH, Martin T. Subsequent gestational morbidity after various types of abortion. Lancet 1972; ii: 431.

Lloyd BW. Outcome of very-low-birthweight babies from Wolverhampton. Lancet 1984; ii: 739-741.

Looft C. Importance de la naissance avant terme dans l'étiologie des troubles de l'intelligence et du système nerveux chez l'enfant. Acta Paediatr 1928; VII: 15-59.

Low JA, Galbraith RS, Sauerbrei EE, Muir DW, Killen HL, Pater EA, Karchmar EJ. Maternal, fetal, and newborn complications associated with newborn intracranial hemorrhage. Am J Obstet Gynecol 1986; 154: 345-351.

Lowe CR. Effects of mothers' smoking habits on birthweight of their children. Br Med J 1959; 2: 673-676.

Lubchenco LO, Searls DT, Brazie JV. Neonatal mortality rate: Relationship to birthweight and gestational age. J Pediatr 1972; 81: 841-822.

Macfarlane A. Low Birthweight Revised. Lancet 1980; i: 930-931.

Macfarlane A. The derivation and uses of perinatal and neonatal mortality rates. J Pediatr 1981; 98: 61-62.

MacGillivray I. Preeclampsia. The Hypertensive Disease of Pregnancy. London, Philadelphia, Toronto: W.B. Saunders, 1983.

MacGillivray I, Davey DA. The influence of fetal sex on rupture of the membranes and preterm labor. Am J Obstet Gynecol 1985; 153: 814-815.

Marihuana and Health: Sixth Annual Report to the US Congress From the Secretary of HEW, 1976.

Marshall RE, Kasman C. Burnout in the Neonatal Intensive Care Unit. Pediatrics 1980; 65: 1161-1165.

McCarton-Daum C. Are prospects improving for normal neurobehavioral development among very low birthweight infants? Pediatr Res 1983; 17: 326A.

McCormick MC, Shapiro S, Starfield B. The Regionalization of Perinatal Services. Summary of the Evaluation of a National Demonstration Program. JAMA 1985a; 253: 799-804.

McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985b; 312: 82-90.

McDonald AD. Survival and handicap in infants of very low birthweight. Lancet 1981; ii: 194.

Mead PB. Management of the patient with premature rupture of the membranes. Clin Perinatol 1980; 7: 243-255.

Melchior J, Bernard N. Possibilités actuelles de prévention et de traitement des menaces d'accouchement prématuré: aspect clinique, résultats, conséquences générales. In: Bompiani A, Cosmi EV, Fischetti B, Gasparri R, Romanini C, eds. Recent Advances on Beta-mimetic drugs in Obstetrics. Roma, Societa Editrice Universo, 1977: 41-60.

Mercer HP, Lancaster PAL, Weiner T, Gupta JM. Very low birthweight infants: a follow-up study. Med J Aust 1978; 2: 581-584.

Michelsson K, Noronen M. Neurological, psychological and articulatory impairment in five-year-old children with a birthweight of 2000 g or less. Eur J Pediatr 1983; 141: 96-100.

Michelsson K, Lindahl E, Parre M, Helenius M. Nine-year Follow-up of Infants Weighing 1500 g or Less at Birth. Acta Paediatr Scand 1984; 73: 835-841.

Miller H, Hassanein K, Handsleigh P. Maternal factors in the incidence of low birthweight infants among black and white mothers. Pediatr Res 1978; 12: 1016-1019.

Miller HC. A Model for Studying the Pathogenesis and Incidence of Low-Birth-Weight Infants. Am J Dis Child 1983; 137: 325-327.

Miller HC, Jekel JF. Associations between unfavorable outcomes in successive pregnancies. Am J Obstet Gynecol 1985; 153: 20-24.

Milligan JE, Shennan AT. Perinatal management and outcome in the infant weighing 1,000 to 2,000 grams. Am J Obstet Gynecol 1980; 136: 269-272.

Milligan JE, Shennan AT, Hoskins EM. Perinatal intensive care: Where and how to draw the line. Am J Obstet Gynecol 1984; 148: 499-503.

Minkowski A, Relier JP, Cukier-Hemeury F, Moriette G. Limitation of perinatal intensive care according to viability and CNS outcome. Eur J Obstet Gynaecol Reprod Biol 1983; 15: 311-314.

Mitchell RG. Objectives and Outcome of Perinatal Care. Lancet 1985; ii: 931-934.

Mohr GJ, Bartelme P. Mental and Physical Development of Children Prematurely Born. Am J Dis Child 1930; 40: 1000-1015.

Morales WJ, Diebel ND, Lazar AJ, Zadrozny D. The effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome in preterm gestations with premature rupture of membranes. Am J Obstet Gynecol 1986; 154: 591-595.

Moriette G, De Gamarra E, Cukier-Hemeury F, Murat I, Bordarier C, Relier JP. Nouveau-nés de très faible poids de naissance. Résultats. Perspectives d'avenir. Arch Fr Pediatr 1982; 39: 587-593.

Murphy TF, Nichter CA, Liden CB. Developmental Outcome of the High-Risk Infant: A Review of Methodological Issues. Semin Perinatol 1982; 6: 353-364.

Mutch LMM, Brown NJ, Speidel BD, Dunn PM. Perinatal Mortality and neonatal survival in Avon: 1976-9. Br Med J 1981; 282: 119-122.

Myrianthopoulos NC. Malformations in Children from One to Seven Years; a report from the Collaborative Perinatal Project. New York: Alan R. Liss, Inc, 1985.

Nars PW. Die Fruehgeburt unter 1000 g. Schweiz Med Wschr 1976; 106: 945-953.

National Center for Health Statistics. Advance Report of Final Natality Statistics, 1983.

National Center for Health Statistics. Monthly vital statistics report. 1985. Vol. 34,no. 6, supplement.

Naeye RL, Burt LS, Wright DL, Blanc WA, Tatter D. Neonatal mortality, the male disadvantage. Pediatrics 1971; 48: 902-906.

Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics 1981; 68: 36-44.

Nelson KB, Ellenberg JH. Predictors of Low and Very Low Birthweight and the relation of these to Cerebral Palsy. JAMA 1985; 254; 1473-1479.

Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of Risk. N Engl J Med 1986; 315: 81-86.

Nelson RM, Resnick MB, Eitzman DV. Intensive care and the very-low-birthweight infant. Lancet 1979; ii: 737.

Nelson R, Resnick M, Nelson L, Rossley K, Dickman H, Eitzman D. Differential outcomes: Mortality and morbidity for extremely premature infants. Pediatr Res 1980; 14: 437A.

Newton ER, Haering WA, Kennedy jr JL, Herschel M, Cetrulo CL, Feingold M. Effect of Mode of Delivery on Morbidity and Mortality of Infants at Early Gestational Age. Obstet Gynecol 1986; 67: 507-511.

Nickel RE, Bennett FC, Lamson FN. School Performance of Children With Birth Weights of 1,000 g or Less. Am J Dis Child 1982; 136: 105-110.

Noble-Jamieson CM, Lukeman D, Silverman M, Davies PA. Low Birth Weight Children at School Age: Neurological, Psychological, and Pulmonary Function. Sem Perinatol 1982; 6: 266-273.

Office of Population Censuses and Surveys. OPCS-Monitor 1984; 84/5: 5.

Office of Population Censuses and Surveys. Infant and Perinatal mortality 1983: birthweight. OPCS-Monitor 1985; DH3 85/1.

Oosterbaan HP, Swaab DF. Glucocorticoïden in de zwangerschap: effecten op de foetus en de pasgeborene. Ned Tijdschr Geneeskd 1987; 131: 170-171.

Orgill AA, Astbury J, Bajuk B, Yu VYH. Early neurodevelopmental outcome of very low birthweight infants. Austr Paediatr J 1982a; 18: 193-196.

Orgill AA, Astbury J, Bajuk B, Yu VYH. Early development of infants 1000 g or less at birth. Arch Dis Child 1982b; 57: 823-827.

Orgill AA, Astbury J, Bajuk B, Yu VYH. Outcome of infants less than 29 weeks gestation. Pediatr Res 1984; 18: 338A.

Ouden AL den, Cats BP, Hermanns J. Behandelingsresultaten van kinderen met een zeer laag geboortegewicht (<1500 gram). Tijd Kindergeneeskd 1984; 52: 53-58.

Ounsted M, Moar VA, Scott A. Factors Affecting Development: Similarities and Differences among Children Who Were Small, Average, and Large for Gestational Age at Birth. Acta Paediatr Scand 1986; 75: 261-266.

Paludetto R, Orzalesi M, Corchia C, Curtis M De, Maltese E, Taurisano M, Cipollone I, Scarcella A, Mastropasqua S, Luca T De. Prognosi immediata e a distanza nei neonati con peso alla nascita < 1500 g. Ital J Ped 1979; 5: 583-591.

Paneth N, Wallenstein S, Kiely JL, Susser M. Social Class Indicators and Mortality in Low Birth Weight Infants. Am J Epidemiol 1982a; 116: 364-375.

Paneth N, Kiely JL, Wallenstein S, Marcus M, Pakter J, Susser M. Newborn intensive care and neonatal mortality in low-birth-weight infants. A population Study. N Engl J Med 1982b; 307: 149-155.

Paneth N, Kiely JL, Susser M. Age at Death Used to Assess the Effect of Interhospital Transfer of Newborns. Pediatrics, 1984; 73: 854-861.

Paneth N, Wallenstein S, Kiely JL, Snook CP, Susser M. Medical Care and Preterm Infants of Normal Birth Weight. Pediatrics 1986; 77: 158-166.

Paneth N, Kiely JL, Wallenstein S, Susser M. The Choice of Place of Delivery. Effect of Hospital Level on Mortality in All Singleton Births in New York City. AJDC 1987; 141: 60-64.

Papageorgiou AN, Colle E, Farri-Kostopoulos EF, Gelfand MM. Incidence of Respiratory Distress Syndrome Following Antenatal Betamethasone: Role of Sex, Type of Delivery and Prolonged Rupture of Membranes. Pediatrics 1981; 67: 614-617.

Pape KE, Buncic RJ, Ashby S, Fitzhardinge PM. The status at two years of low-birth-weight infants born in 1974 with birth weights of less than 1,001 gm. J Pediatr 1978; 92: 253-360.

Papiernik E, Bouyer J, Dreyfus J, Collin D, Winisdorffer G, Guegen S, Lecomte M, Lazar P. Prevention of Preterm Births: A Perinatal Study in Haguenau, France. Pediatrics 1985a; 76: 154-158.

Papiernik E, Bouyer J, Dreyfus J. Risk factors for preterm births and results of a prevention policy. The Haguenau Perinatal Study 1971-1982. In: Preterm Labour and its consequences. Proceedings of the 13th Study Group of the Royal College of Obstetrics and Gynaeco logists. London: Royal College of Obstetricians and Gynaecologists, 1985b: 15-24.

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: 529-534.

Paul RH, Koh KS, Monfared AH. Obstetric factors influencing outcome in infants weighing 1,001 to 1,500 grams. Am J Obstet Gynecol 1979; 133: 503-508.

Peckham CH. Statistical studies on prematurity. I. The incidence of Prematurity and the Effect of Certain Obstetric Factors. J Pediatr 1938; 13: 474-497.

Peddle LJ, Brown H, Buckley J, Dixon W, (MacDonald) Kaye J, Muise M, Rees E, Woodhams W, Young C. Voluntary regionalization and associated trends in perinatal care: The Nova Scotia Reproductive Care Program. Am J Obstet Gynecol 1983; 145: 170-176.

Perkins RP. The neonatal significance of selected perinatal events among infants of low birth weight. I. Overall results. Am J Obstet Gynecol 1981; 139: 546-561.

Perkins RP. The neonatal significance of selected perinatal events among infants of low birth weight. II. The influence of ruptured membranes. Am J Obstet Gynecol 1982; 142; 7-16.

Pharoah POD. International Comparisons of Perinatal and Infant Mortality Rates. Proc. roy. Soc. Med. 1976; 69: 335-338.

Pharoah POD, Alberman ED. Mortality of low birthweight infants in England and Wales 1953-1979. Arch Dis Child 1981; 56: 86-89.

Philip AGS. Intensive Care and the very low-birth-weight infant. Lancet 1979; ii: 255.

Philip AGS, Little GA, Polivy DR, Lucey JF. Neonatal Mortality Risk for the Eighties: The Importance of Birth Weight/Gestational Age Groups. Pediatrics 1981; 68: 122-130.

Pickering RM, Forbes JF. Risks of preterm delivery and small-for-gestational age infants following abortion: a population study. Br J Obstet Gynaecol 1985; 92: 1106-1112.

Piekkala P, Kero P, Erkkola R, Sillanpää M. Perinatal events and neonatal morbidity: an analysis of 5380 cases. Early Hum Dev 1986; 13: 249-268.

Placzek MM, Whitelaw A. Early and late neonatal septicaemia. Arch Dis Child 1983; 58: 728-731.

Prinssen JCC, Kropman JA. De Nederlandse sportvisser. Een onderzoek naar kenmerken, gedrag en wensen van de sportvissers. Nijmegen: Instituut voor Toegepaste Sociologie, 1975.

Priolisi A. Low Birthweight Revised. Lancet 1980; i: 930-931.

Raju T. An Epidemiologic Study of Very Low and Very Very Low Birth Weight Infants. In: Vidyasagar D, ed. The Tiny Baby. Clin Perinatol 1986; 13: 233-250.

Rawlings G, Stewart A, Reynolds EOR, Strang LB. Changing prognosis for infants of very low birth weight. Lancet 1971; i: 516-519.

Reynolds EOR. Neonatal intensive care and the prevention of major handicap. Ciba Found Symp, Amsterdam: Elsevier, 1978; 59: 77-106.

Reynolds EOR, Stewart AL. Intensive care and the very-low-birth-weight infant. Lancet 1979; ii: 254.

Rhodes PG, Graves GR, Campbell SB, Patel DM, LeBlanc MH. Survival in VLBW (500-1500 gm) infants with cooperative neonatal and obstetrical education and management efforts. Pediatr Res 1983; 17: 332A.

Rider RV, Harper PA, Knobloch H, Fetter SE. An evaluation of standards for the hospital care of premature infants. J Am Med Assoc 1957; 165: 1233-1236.

Riegel K, Hohenauer L, Lemburg P, Loewenich Von V. Intensiv Medizin fuer Neugeborene. Monatsschr Kinderheilkd 1979; 127: 1-13.

Roberton NRC. Intensive care and the very low birthweight infant. Lancet 1979; ii: 362.

Roede MJ, Wieringen JC van. Growth diagrams 1980. Tijdschr Soc Gez 1985; 63: suppl. 34 pp.

Rooth G. Low birthweight revised. Lancet 1980; i: 639-641.

Rosanelli K. Ueber die Wirkung von praenatal verabreichten Diazepam auf das Fruehgeborene. Geburtshilfe Frauenheilkd 1970; 30: 713-724.

Rosen MG. Factors During Labor and Delivery that Influence Brain Disorders. In: Freeman JM, ed. Prenatal and Perinatal Factors Associated With Brain Disorders. NIH-Publication, no. 85-1149, 1985.

Rosett HL, Weiner L, Lee A, Zuckerman B, Dooling E, Oppenheimer E. Patterns of alcohol consumption and fetal development. Obstet Gynecol 1983; 61: 539-546.

Ross G, Schechner S, Frayer WW, Auld PAM. Perinatal and Neurobehavioral Predictors of One-Year Outcome in Infants < 1500 Grams. Sem Perinatol 1982; 6: 317-326.

Rothberg AD, Maisels J, Bagnato S, Murphy J, Gifford K, McKinley K, Palmer EA, Vannucci RC. Outcome for survivors of mechanical ventilation weighing less than 1,250 gm at birth. J Pediat 1981; 98: 106-111.

Rothberg AD, Maisels J, Bagnato S, Murphy J, Gifford K, McKinley K. Infants Weighing 1,000 Grams or Less at Birth: Developmental Outcome for Ventilated and Nonventilated Infants. Pediatrics 1983; 71: 599-602.

Ruiz MPD, LeFever JA, Hakanson DO, Clark DA, Williams ML. Early Development of Infants of Birth Weight Less Than 1,000 Grams with Reference to Mechanical Ventilation in Newborn Period. Pediatrics 1981; 68: 330-335.

Russell MAH. Smoking habits of men and women. Br Med J 1980; 281: 17-20.

Sabel KG, Olegard R, Victorin L. Remaining Sequelae With Modern Perinatal Care. Pediatrics 1976; 57: 652-658.

Saigal S, Rosenbaum P, Stoskopf B, Milner R. Follow-up of infants 501 to 1,500 gm birth weight delivered to residents of a geographically defined region with perinatal intensive care facilities. J Pediatr 1982; 100: 606-613.

Saigal S, McCormick M, Starfield BH, Crawley B. Changes in Infant Morbidity Associated with Decreases in Neonatal Mortality. Pediatrics 1983; 72: 408-415.

Saigal S, Rosenbaum P, Stoskopf B, Sinclair JC. Outcome in infants 501 to 1000 gm birth weight delivered to residents of the McMaster Health Region. J Pediatr 1984; 105: 969-976.

Saint-Anne Dargassies S. Long-term Neurological Follow-up Study of 286 Truly Premature Infants. I: Neurological Sequelae. Dev Med Child Neurol 1977; 19: 462-478.

Salvat J, Omar B, Sele B, Nahmanovici C, Racinet C, Malinas Y. Efficacité du traitement maternel préventif de la détresse respiratoire idiopathique des prématurés par la bétaméthasone associée aux bêtamimétiques. Rev Fr Gynéc 1978; 73: 389-393.

Sameroff AJ. Early influences on development: fact or fancy? Merrill-Palmer Quarterly 1975; 21: 267-293.

SAS: SAS User's Guide: Statistics. Cary, North Carolina: SAS Institute, 1982: 257-258.

Scheer K, Nubar J. Variation of fetal presentation with gestational age. Am J Obstet Gynecol 1976; 125: 269-270.

Schutte MF. Over de behandeling van de dreigende vroeggeboorte. Thesis, Universiteit van Amsterdam, 1981. 261 pp.

Schutte MF, Treffers PE, Kloosterman GJ, Soepatmi. Management of premature rupture of membranes: the risk of vaginal examination to the infant. Am J Obstet Gynecol 1983; 146: 395-400.

Shapiro S, McCormick MC, Starfield BH, Krischer JP, Bross D. Relevance of correlates of infant deaths for significant morbidity at 1 year of age. Am J Obstet Gynecol 1980; 136: 363-373.

Shapiro S, McCormick MC, Starfield BH, Crawley B. Changes in Infant Morbidity Associated with Decreases in Neonatal Mortality. Pediatrics 1983; 72: 408-415.

Shenai JP, Johnson GE, Varney RV. Mechanical Vibration in Neonatal Transport. Pediatrics 1981; 68: 55-57.

Shennan AT, Milligan JE. The growth and development of infants weighing 1,000 to 2,000 grams at birth and delivered in a perinatal unit. Am J Obstet Gynecol 1980; 136: 273-275.

Shennan AT, Milligan JE, Hoskins EM. Perinatal factors associated with death or handicap in very preterm infants. Am J Obstet Gynecol 1985; 151: 231-238.

Shinnar S, Molteni RA, Gammon K, D'Souza BJ, Altman J, Freeman JM. Intraventricular hemorrhage in the premature infant. A Changing Outlook. N Engl J Med 1982; 306: 1464-1468.

Siegel E, Gillings D, Campbell S, Guild P. A Controlled Evaluation of Rural Regional Perinatal Care: Impact on Mortality and Morbidity. Am J Public Health 1985; 75: 246-253.

Siegel E, Gillings D, Campbell S, Guild P. Controlled Evaluation of Rural Regional Perinatal Care: Developmental and Neurologic Outcomes at 1 Year. Pediatrics 1986; 77: 187-195.

Silverman F, Suidan J, Wasserman J, Antoine C, Young BK. The Apgar Score: Is it Enough? Obstet Gynecol 1985; 66: 331-336.

Simpson GF, Harbert GM. Use of B-methasone in management of preterm gestation with premature rupture of membranes. Obstet Gynecol 1985; 60: 168-175.

Sims DG, Wynn J, Chiswick ML. Outcome for newborn babies declined admission to a regional neonatal intensive care unit. Arch Dis Child 1982; 57: 334-337.

Sinclair JC, Torrance GW, Boyle MH, Horwood SP, Saigal S, Sackett DL. Evaluation of neonatal-intensive-care programs. N Engl J Med 1981; 305: 489-494.

Sinha SK, Davies JM, Sims DG, Chiswick ML. Relation between periventricular haemorrhage and ischaemic brain lesions diagnosed by ultrasound in very pre-term infants. Lancet 1985; ii: 1154-1156.

Skoutelli HN, Dubowitz LMS, Levene MI, Miller G. Predictors for survival and normal neurodevelopmental outcome of infants weighing less than 1001 grams at birth. Dev Med Child Neurol 1985; 27: 588-595.

Slikke JW van der, Treffers PE. Influence of induced abortion on gestational duration in subsequent pregnancies. Br Med J 1978; 270-272.

Smallpeice V, Davies P. Immediate feeding of premature infants with undiluted breast-milk. Lancet 1964; ii: 1349-1352.

Smith L, Somner FF, Tetzchner S von. A Longitudinal Study of Low Birthweight Children: Reproductive, Perinatal, and Environmental Precursors of Developmental Status at Three Years of Age. Semin Perinatol 1982; 6: 294-304.

Smith MA, Baum JD. Costs of visiting babies in special care baby units. Arch Dis Child 1983; 58: 56-59.

Spinnato JA, Sibai BM, Shaver DC, Anderson GD. Inaccuracy of Dubowitz Gestational Age in Low Birth Weight Infants. Obstet Gynecol 1984; 63: 491-495.

Sporken JMJ, Hein PR, Boon JM, Bijlmer RPG. Vooruitzichten bij kinderen geboren vóór de 34e zwangerschapsweek. II. Morbiditeit. Ned Tijdschr Geneeskd 1982; 19: 862-866.

Sporken JMJ. De prognose van kinderen geboren vóór de 34e zwangerschapsweek. Thesis, Katholieke Universiteit Nijmegen, 1986. 145 pp.

Stahlman MT. Newborn intensive care: Success or failure? J Pediatr 1984; 105: 162-167.

Stanley FJ, Alberman ED. Infants of Very Low Birthweight. I. Perinatal Factors Affecting Survival. Dev Med Child Neurol 1978; 20: 300-312.

Stanley FJ, Hobbs MST. Neonatal mortality and cerebral palsy: the impact of neonatal intensive care. Aust Paediatr J 1980; 16: 35-39.

Stark A, Frantz ID. Respiratory Distress Syndrome. Pediatr Clin North Am 1986; 33: 533-544.

Stave U, Ruvalo C. Neurological development in very-low birthweight infants. Application of a standardized examination and Prechtl's optimality concept in routine evaluations. Early Hum Dev 1980; 4/3: 229-241.

Steiner ES, Sanders EM, Phillips ECK, Maddock CR. Very low birth weight children at school age: comparison of neonatal management methods. Br Med J 1980; 281: 1237-1240.

Stewart AL, Reynolds EOR. Improved Prognosis for Infants of Very Low Birthweight. Pediatrics 1974; 54: 724-735.

Stewart AL, Turcan DM, Rawlings G, Reynolds EOR. Prognosis for infants weighing 1000 g or less at birth. Arch Dis Child 1977; 52: 97-104.

Stewart A. Follow-up of preterm infants. In: Anderson A, Beard R, Bruderell JM, Dunn PM, eds. Pre-term Labour. London: Royal College of Obstetricians and Gynaecologists, 1977: 372-384.

Stewart A, Turcan D, Rawlings G, Hart S, Gregory S. Outcome for infants at high risk of major handicap. In: Elliot K, O'Connor M, eds. Major Mental Handicap: Methods and Costs of Prevention. Ciba Found Symp. Amsterdam: Elsevier, 1978; 59: 151-164.

Stewart AL, Reynolds EOR, Lipscomb AP. Outcome for infants of very low birthweight: survey of world literature. Lancet 1981; i: 1038-1041.

Strauss A, Kirz D, Modanlou HD, Freeman RK. Perinatal events and intraventricular/subependymal hemorrhage in the very low-birth weight infant. Am J Obstet Gynecol 1985; 151: 1022-1027.

Sykes GS, Johnson P, Ashworth F, Molloy PM, Gu W, Stirrat GM, Turnbull AC. Do Apgar Scores indicate asphyxia? Lancet 1982; i: 494-496.

Sykes GS, Molloy PM, Johnson P, Stirrat GM, Turnbull AC. Fetal distress and the condition of newborn infants. Br Med J 1983; 287: 943-945.

Szymonowicz, Yu VYH, Walker A, Wilson F. Reduction in periventricular haemorrhage in preterm infants. Arch Dis Child 1986; 61: 661-665.

Teberg A, Hodgman JE, Wu PYK, Spears RL. Recent Improvement in Outcome for the Small Premature Infant. Clin Pediatr 1977; 16: 307-313.

Teberg A, Hotrakitya S, Wu PYK, Yeh S. Cause of death in very low birth weight predominantly hispanic population: relationship to birth weight and gestational age. Pediatr Res 1984; 18: part 2 of 2 parts, 351A.

Tejani N, Rebold B, Tuck S, Ditroia D, Sutro W, Verma U. Obstetric factors in the Causation of Early Periventricular-Intraventricular Hemorrhage. Obstet Gynecol 1984; 64: 510-515.

Tenovuo A, Kero P, Piekkala, Sillanpää, Erkkola R. Advances in Perinatal Care and Declining Regional Neonatal Mortality in Finland, 1968-82. Acta Ped Scand 1986; 75: 362-369.

Thomassen-Brepols, LJ. Psychosociale aspecten van prenatale diagnostiek. Thesis, Erasmus Universiteit, Rotterdam, 1985. 169 pp.

Thompson MH, Khot AS. Impact of neonatal intensive care. Arch Dis Child 1985; 60: 213-214.

Thompson RE, Souma ML, Cassady G, Sumners J. Impact of Intensive Care on Neonatal Mortality in a Community Hospital. South Med J 1976; 69: 688-690.

Thomsen AC, Mørup L, Brogaard Hansen K. Antibiotic elimination of group-B streptococci in urine in prevention of preterm labour. Lancet 1987; i: 591-593.

Touwen BCL. Very Low birth weight infants. Eur J Pediatr 1986; 145: 460.

Treffers PE, Leeuw R de, Huidekoper BL, Gubler F, Leschot NJ, Verjaal M. Congenital anomalies. A survey of 39,828 infants born during 21 years. In: Huisjes HJ, ed. Aspects of perinatal morbidity. Groningen: Dep. Obst. University Hospital, 1981.

Tyson RM. A Fifteen-year study of prematurity. From the Standpoint of Incidence, Mortality, and Survival. J Pediatr 1946; 28: 648-664.

Urrutia JG, Mathew T, Brookfield E, Satish M, McQuiston S, Butterfield J, ElShafie S. Long term follow-up in <1500 gm. birthweight (VLBW). Pediatr Res 1984; 18: 352A.

Usher RH, Allen AC, McLean FH. Risk of respiratory distress syndrome related to gestational age, route of delivery and maternal diabetes. Am J Obstet Gynecol 1971; iii: 826-832.

Usher R. Changing Mortality Rates With Perinatal Intensive Care and Regionalization. Semin Perinatol 1977; 1: 309-319.

Vapaavuori EK,Räihä NCR. Intensive Care of Small Premature Infants. I. Clinical findings and results of treatment. Acta Paediatr Scand 1970; 59: 353-362.

Vasa R, Vidyasagar, Winegar A, Peterson P, Spellacy WN. Perinatal Factors Influencing the Outcome of 501-to 1000-gm Newborns. In: Vidyasagar D, ed. "The Tiny Baby". Clin Perinatol 1986; 13: 267-284.

Velde JW van der. Smoking in pregnancy, a clinical and histological exploration. Thesis, Universiteit van Amsterdam, 1985. 71 pp.

Verloove-Vanhorick SP, Ruys JH. Ernstige praematuritas. Resultaten van intensieve behandeling van zuigelingen, geboren na een zeer korte zwangerschap. Tijd Kindergeneeskd 1982; 50: 144-153.

Verloove-Vanhorick SP, Verwey RA, Keirse MJNC. Neonatal mortality in very low birth weight and very preterm infants. Am J Obstet Gynecol 1985; 153: 929-930.

Verloove-Vanhorick SP, Verwey RA, Brand R, Bennebroek Gravenhorst J, Keirse MJNC. Neonatal mortality risk in relation to gestational age and birthweight. Lancet 1986a; i: 55-57.

Verloove-Vanhorick SP, Ruys JH. Postneonatal mortality. J Pediatr 1986b; 108: 161.

Versluys C. Loont "neonatale intensive care" de moeite? Tijd Kindergeneeskd 1977; 45: 149-163.

Verwey RA, Verloove-Vanhorick SP, Brand R, Bennebroek Gravenhorst J, Ruys JH. Overlevingskansen van kinderen geboren na een zeer korte zwangerschapsduur en/of met een zeer laag geboortegewicht: een tabel voor de praktijk. Medisch Contact 1986; 40: 1287-1288.

Vidyasagar D, ed. The Tiny Baby. Clin Perinat 1986; 13.

Vierhout ME, Out JJ. De electieve inleiding van de baring, een prospectief obstetrisch en psychologisch onderzoek. Thesis, Erasmus Universiteit, Rotterdam, 1983. 257 pp.

Visser GHA. Het inleiden van de baring. Thesis, Rijksuniversiteit Groningen, 1978. 267 pp.

Visser GHA. Antenatal cardiotocography in the evaluation of fetal well-being. Aust NZ J Obstet Gynaecol 1984; 24: 80.

Visser GHA. Heart Rate and Movement Patterns in the Preterm Fetus. In: Beard RW and Sharp F, eds. Pre-term Labour and its consequences. London: Royal College of Obstetricians and Gynaecologists, 1985: 281-289.

Vlaanderen W. De spontane abortus. Thesis, Universiteit van Amsterdam, 1983. 149 pp.

Vohr BR, Oh W, Rosenfield AG, Cowett RM. The preterm small for-gestational age infant: A two-year follow-up study. Am J Obstet Gynecol 1979; 133: 425-431.

Vries M de, Zwertbroek W, Becker AE. De obductie: zin of onzin. Ned Tijdschr Geneeskd 1986; 130: 1273-1276.

Walker DJB, Feldman A, Vohr BR, Oh W. Cost-Benefit Analysis of Neonatal Intensive Care for Infants Weighing Less Than 1,000 Grams at Birth. Pediatrics 1984; 74: 20-25.

Wall M. Ueber die Weiterentwicklung fruehgeborener Kinder mit besonderer Beruecksichtigung spaeterer nervoeser, psychischer und intellektueller Stoerungen. Monatsschrift fuer Geburtshuelfe und Gynaekologie 1913; XXXVII: 456-486.

Wallace HM, Goldstein H. The status of infant mortality in Sweden and the United States. J Pediatr 1975; 87: 995-1000.

Wallich V, Fruhinsholz A. Avenir Eloigné du prématuré. Ann de Gyn 1911; LXVIII: 625-655.

Wals Ph de, Weatherall JAC, Lechat MF, eds. Registration of congenital anomalies in Eurocat-centres 1979-1983, an EEC concerted action project. Louvain-la-Neuve: Cabay, 1985.

Weatherall J. International infant mortality comparisons. Some difficulties in interpretation. J Mat Child Health 1977; 278-284.

Wellen I. The infant mortality in specific hypertensive disease of pregnancy and in essential hypertension. Am J Obstet Gynecol 1953; 66: 36-45

Westerlaak JM van, Kropman JA, Collaris JWM. Beroepenklapper. Instituut voor Toegepaste Sociologie, Nijmegen 1975.

Westgren M, Ingemarsson I, Ahlström H, Lindroth M, Svennigsen NW. Delivery and long-term outcome of very low birth weight infants. Acta Obstet Gynecol Scand 1982; 61: 25-30.

Whitelaw A. Death as an option in neonatal intensive care. Lancet 1986; ii: 328-331.

WHO: Expert committee on Prematurity: Final Report. Geneva, Switzerland: WHO Technical Report Series. No. 27, 1950.

WHO: Expert Committee on Maternal and Child Health: Public Health Aspect of Low Birthweight. Geneva, Switzerland: WHO Technical Report Series. No. 217, 1961.

WHO: Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Acta Obstet Gynecol Scand 1977; 56: 247-253.

Wigglesworth JS. Monitoring Perinatal Mortality. A Pathophysiological Approach. Lancet 1980; ii: 684-686.

Wilson JC, Levy DL, Wilds PL. Premature rupture of membranes prior to term: consequences of nonintervention. Obstet Gynecol 1982; 60: 601-606.

Working Party to discuss nomenclature based on Gestational age and Birthweight. Arch Dis Child 1970; 45: 730.

Wright CSW, Campbell S, Beazley J. Second-trimester abortion after vaginal termination of pregnancy. Lancet 1972; i: 1278-1279.

Wright FH, Blough RR, Chamberlin A, Ernest T, Halstead WC, Meier P, Moore RY, Naunton RF, Newell FW. A Controlled Follow-up Study of Small Prematures Born from 1952 through 1956. Am J Dis Child 1972; 124:

Yerushalmy J. Mothers' cigarette smoking and survival of infant. Am J Obstet Gynecol 1964; 88: 505-518.

Yerushalmy J. Relation of birth weight, gestational age, and the rate of intrauterine growth to perinatal mortality. Clin Obst Gynecol 1970; 13: 107-129.

Ylppö A. Pathologisch-anatomische Studien bei Fruehgeborenen. Makroskopische und mikroskopische Untersuchungen mit Hinweisen auf die Klinik und mit besonderer Beruecksichtigung der Haemorrhagien. Zeitschr Kinderheilkd 1919; 20: 213-381.

Yu VYH, Wood C. Perinatal asphyxia and outcome of very low birthweight infants. Med J Aust 1978; 2: 578-581.

Yu VYH, Hollingsworth E. Respiratory Failure in Infants Weighing 1000 g or Less at Birth. Aust Pediatr J 1979a; 15: 152-159.

Yu VYH, Hollingsworth E. Improving prognosis for infants weighing 1000 g or less at birth. Arch Dis Child 1979b; 55: 422-426.

Yu VYH, Bajuk B, Hollingsworth E. Neonatal intensive care for extremely low birthweight infants - a dilemma in perinatal medicine. Aust Pediatr J 1981; 17: 262-264.

Yu VYH, Zhao SM, Bajuk B. Results of intensive care for 375 very low birthweight infants. Aust Pediatr J 1982; 18: 188-192.

Yu VYH, Orgill AA, Astbury J, Bajuk B. Neonatal and 2-Year Outcome of Infants Born at 24-28 Weeks Gestation. Presented at the IXth Congress of Perinatal Medicine, Dublin, 1984a.

Yu VYH, Watkins A, Bajuk B. Neonatal and postneonatal mortality in very low birthweight infants. Arch Dis Child 1984b; 59: 987-999.

Yu VYH, Wong PY, Bajuk B, Orgill AA, Astbury J. Outcome of extremely-low-birthweight infants. Br J Obstet Gynaecol 1986a; 93: 162-170.

Yu VYH, Downe L, Astbury J, Bajuk B. Perinatal factors and adverse outcome in extremely low birthweight infants. Arch Dis Child 1986b; 61: 554-558.

Yu VYH, Loke HL, Bajuk B, Szymonowicz W, Orgill AA, Astbury J. Prognosis for infants born at 23 to 28 weeks' gestation. Br Med J 1986c; 293: 1200-1203.

Samenvatting, conclusies en aanbevelingen

In hoofdstuk 1 worden de begrippen (zeer) laag geboortegewicht (VLBW), (ernstige) vroeggeboorte en intensieve zorg besproken.

De WHO (Wereldgezondheidsorganisatie) en de FIGO (Internationale Federatie van Obstetrie en Gynaecologie) adviseren, pasgeborenen in te delen in bepaalde categorieën geboortegewicht en zwangerschapsduur. Desondanks is het, getuige recent gepubliceerde artikelen, nog steeds gebruikelijk, de onderzochte groep kinderen alléén te definiëren op grond van het geboortegewicht, vaak in ongelijksoortige categorieën. Derhalve is vergelijking van verschillende onderzoeken zeer onnauwkeurig. Bij het bespreken van de uitkomsten wordt veelal geen onderscheid gemaakt tussen groepen die een verschillende etiologie hebben, zoals intra-uteriene groeivertraging of ernstige vroeggeboorte.

Het is aan te bevelen, in toekomstig onderzoek de categorieën te gebruiken zoals geadviseerd door de WHO en de FIGO, en onderzoekspopulaties nauwkeurig te omschrijven, zowel wat betreft zwangerschapsduur als geboortegewicht.

In Nederland vormt het gebrek aan gegevens betreffende zwangerschapsduur en geboortegewicht van alle geboorten en alle gevallen van zuigelingensterfte een ernstige belemmering voor het uitvoeren van wetenschappelijk onderzoek op het gebied van de perinatale epidemiologie. Ten einde sterftepercentages in specifieke categorieën van geboortegewicht of zwangerschapsduur te kunnen berekenen, zijn gegevens noodzakelijk van alle gevallen van zuigelingensterfte (teller), maar ook van alle doodgeborenen en levendgeborenen (noemer). Tot op heden worden geboortegewicht en zwangerschapsduur alléén opgegeven aan het Centraal Bureau voor de Statistiek, indien een pasgeborene overlijdt binnen 1 week na de geboorte.

In de eerste plaats dient er een verplichte registratie te komen van alle geboorten (zowel doodgeborenen als levendgeborenen) welke plaatsvinden na een zwangerschapsduur van 22 weken of meer. Daarbij moet van elk geboren kind tenminste de zwangerschapsduur en het geboortegewicht vastgelegd worden. In de tweede plaats is het aan te bevelen, dat opgave wordt gedaan van zwangerschapsduur en geboortegewicht van alle zuigelingen, die in het eerste levensjaar overlijden. Hiertoe is slechts een kleine wijziging nodig van de "doodsoorzaak-verklaring" (het gele B-formulier).

In hoofdstuk 2 wordt een overzicht gegeven van de literatuur betreffende zeer preterme kinderen met een zeer laag geboortegewicht. Hoe onnauwkeurig de vergelijkingen tussen de besproken onderzoeken ook mogen zijn, er kunnen toch een aantal conclusies uit getrokken worden:

-in alle categorieën geboortegewicht, ook die van de kinderen met een extreem laag geboortegewicht (<1000 g), is de sterfte aanzienlijk

gedaald in de laatste decennia. Het percentage kinderen met een ernstige handicap bleef daarbij vrijwel gelijk. Dientengevolge is het percentage kinderen dat zonder ernstige handicap overleeft, bijna verdrievoudigd.

-trials, bij voorkeur gerandomiseerde, dubbelblinde trials, zijn een bij uitstek geschikte methode om de effectiviteit van bepaalde behandelingsmethoden te onderzoeken. Elke nieuwe behandeling behoort op deze wijze beoordeeld te zijn, alvorens te worden ingevoerd in de dagelijkse praktijk. Sommige procedures zijn echter moeilijk te randomiseren en het is vaak onmogelijk een dergelijk onderzoek "blind" uit te voeren. Derhalve blijven observationele studies nodig bij de evaluatie van vele aspecten van de perinatale zorg.

-regionaal opgezette studies, waarin alle gevallen opgenomen worden, die binnen een nauwkeurig afgegrensd gebied voorkomen, kunnen bruikbare epidemiologische gegevens opleveren, zonder vertekening ten gevolge van bestaande verwijzingspatronen tussen ziekenhuizen. Binnen dergelijke gebieden heeft stimulering van regionalisatie en centralisatie van de perinatale zorg een gunstig effect. Het concentreren van bevallingen, waarbij sprake is van een verhoogde sterftekans voor het kind, in gespecialiseerde centra leidt tot betere overlevingskansen.

In hoofdstuk 3 wordt het doel van het hier beschreven onderzoek uiteengezet. Allereerst werden incidenties en percentages van sterfte en morbiditeit vastgesteld. Daarnaast werd het verband bestudeerd tussen enerzijds sterfte en het optreden van bepaalde afwijkingen en anderzijds een aantal perinatale factoren, voor zover het de zwangerschap, bevalling, geboorte en ziekenhuisopname van het kind na de geboorte betrof.

Hoofdstuk 4 beschrijft de onderzoeksopzet. Het onderzoek werd prospectief, beschrijvend, longitudinaal uitgevoerd in een samenwerkingsverband van Nederlandse kinderartsen. Gegevens betreffende kinderen, die levend geboren werden in het jaar 1983, na een zwangerschap van minder dan 32 weken en (of) met een geboortegewicht van minder dan 1500 g werden (anoniem) vastgelegd. Na ontslag uit het ziekenhuis werd naonderzoek verricht op de leeftijd van 3, 6, 12 en 24 maanden (gecorrigeerd voor de mate van vroeggeboorte, dat wil zeggen na de à terme datum).

In de eerste plaats werden de verzamelde gegevens (voor dit proefschrift beperkt tot de perinatale periode) beschrijvend geanalyseerd. In de tweede plaats werd multivariate analyse toegepast, waardoor het mogelijk werd te onderzoeken, of er verband bestond tussen bepaalde perinatale factoren en bepaalde opgetreden afwijkingen, daarbij rekening houdend met de invloed van vele andere factoren.

De onderzoeksgroep bestaat uit 1338 kinderen, geboren uit 1214 moeders en omvat 94% van al dergelijke kinderen, die in Nederland in 1983 levend geboren zijn. Hiervan waren 48% meisjes en 52% jongens.

In hoofdstuk 5 zijn de belangrijkste aspecten van de 1214 moeders van de onderzochte kinderen vermeld.

De overgrote meerderheid van de moeders waren, vóór de beschreven zwangerschap, gezonde vrouwen.

Leeftijd van de moeder, zowel erg jong als ouder was geassocieerd met een hogere incidentie van zeer preterme of VLBW geboorten.

Burgelijke staat en pariteit zijn bij de POPS-moeders vergelijkbaar met die bij moeders in de totale bevolking. Wel had bijna een derde van de POPS-moeders één of meer vroeggeboorten in de anamnese.

In dit eerste gedeelte van het POPS-onderzoek ontbrak een deel van de gegevens die nodig zijn voor het vaststellen van de socio-economische klasse. Hierdoor kon de invloed van deze factor binnen de studiepopulatie niet goed onderzocht worden. Gezien het reeds vaak beschreven verband tussen socio-economische klasse en vroeggeboorte, laag geboortegewicht en uiteindelijk resultaat van de (intensieve) zorg, bevelen wij aan, dergelijke gegevens volledig te registreren bij toekomstig onderzoek in Nederland, niettegenstaande de hedendaagse terughoudendheid bij het stellen van deze vragen.

In hoofdstuk 6 zijn obstetrische gegevens over de onderzochte zwangerschappen en bevallingen beschreven.

Hypertensie tijdens de zwangerschap trad op bij de moeders van 22.8% van de POPS-kinderen, met name bij moeders van kinderen die geboren werden na een zwangerschapsduur van 32 weken of meer, maar met een geboortegewicht onder 1500 g (49%). Talrijke externe factoren met een mogelijk negatieve invloed tijdens de zwangerschap kwamen voor: roken 29%, alcohol 0.5%, soft drugs 0.4%, hard drugs 0.3%, geneesmiddelengebruik tijdens de zwangerschap 59% en tijdens de bevalling 65%. Bij 39% van de kinderen waren de vliezen voortijdig gebroken; bijna de helft daarvan had een latente periode tussen het breken van de vliezen en het begin van de bevalling van meer dan 24 uur. De frequentie van chorioamnionitis nam toe naarmate de latente periode langer was.

Weeënremming gedurende meer dan 24 uur werd bij de moeders van 44% van de POPS-kinderen toegepast. Eén derde van hen kreeg ook glucocorticosteroïden toegediend ter bevordering van de foetale longrijping.

Stuitligging kwam voor bij 329 kinderen (25%); meer dan de helft daarvan werd spontaan vaginaal geboren. Electieve sectio caesarea werd verricht in 23%. Nog eens 20% van de kinderen werd geboren na een spoed-sectio caesarea, waardoor het totale sectio percentage bij de POPS-kinderen 42% was.

Hoofdstuk 7 geeft een beschrijving van de voornaamste kenmerken van de 1338 onderzochte kinderen.

Met uitzondering van drie gevallen was zwangerschapsduur van alle kinderen geregistreerd. Deze varieerde van 22 tot 40 weken: mediane zwangerschapsduur 30 weken en 2 dagen. Van de 1338 kinderen hadden er 1010 een zwangerschapsduur van minder dan 32 complete weken. Bovendien werden er in 1983, in niet-deelnemende ziekenhuizen, nog 58 van dergelijke kinderen geboren, welke niet in het onderzoek betrokken werden. Derhalve bedroeg de incidentie van ernstige vroeggeboorte (<32 weken) in Nederland: 0.63%.

Het geboortegewicht was van alle kinderen geregistreerd. Dit varieerde van 420 tot 2780 g: mediaan 1250 g. Bovendien werden er in 1983, in niet-deelnemende ziekenhuizen, nog 67 van dergelijke kinderen geboren, welke niet in het onderzoek betrokken werden. Derhalve bedroeg de incidentie van zeer laag geboortegewicht (<1500 g) in Nederland: 0.68%.

Volgens de Amsterdamse groeicurves had 17% van de onderzochte kinderen met een zwangerschapsduur van minder dan 32 weken een te laag geboortegewicht voor de duur van de zwangerschap (SGA). Dit is duidelijk meer dan de verwachte 10%. Ofwel deze maatstaven zijn niet langer van toepassing, ofwel in onze onderzoeksgroep komen veel meer gevallen van groeivertraging voor dan vroeger. Nadere analyse van onze gegevens is daarom nodig, ten einde criteria voor intra-uteriene groeivertraging bij korte zwangerschapsduur vast te stellen.

In ons onderzoek bleek de Apgar score de enige maat te zijn, waarover voldoende gegevens bekend waren om gebruikt te kunnen worden als parameter voor de toestand van het kind direct na de geboorte. In 19% van de gevallen was de Apgar score 6 of lager.

Bij 188 moeders was er sprake van een meerlingzwangerschap waaruit in totaal 312 kinderen (23%) geboren werden, als tweeling, drieling of vierling.

In hoofdstuk 8 zijn de deelnemende ziekenhuizen beschreven. De ziekenhuizen werden geklassificeerd in 3 niveaus van zorgverlening:

level 1. ziekenhuizen met beperkte of geen faciliteiten voor de behandeling van zeer vroeggeborenen en (of) kinderen met een zeer laag geboortegewicht (n=106)
level 2. ziekenhuizen met faciliteiten voor obstetrische en neonatale bijzondere zorg, maar slechts voor intensieve zorg van korte duur (n=19)
level 3. centra voor perinatale intensieve zorg (n=8)

Door centralisatie werd 36% van de kinderen in de onderzoeksgroep geboren in een centrum voor perinatale intensieve zorg (level 3). Deze

centralisatie is grotendeels het gevolg van antenataal transport (n=240) met name van kinderen met een zwangerschapsduur van minder dan 32 weken.

Daarnaast waren nog een groot aantal overplaatsingen van pasgeborenen nodig (neonataal intensive care transport, n=427). Dit geeft aan, dat de vele POPS-kinderen intensieve zorg behoefden, welke niet beschikbaar was in het ziekenhuis van geboorte. Tengevolge van plaatsgebrek in het meest nabije neonatologische centrum was in 78 gevallen vervoer over grote afstand nodig naar een centrum in een andere regio.

In hoofdstuk 9 wordt de uitkomst beschreven van een enquête welke gehouden werd onder de kinderartsen van ziekenhuizen, die niet deelnamen aan het POPS-onderzoek. Hieruit blijkt, dat het POPS-cohort 94% omvat van alle kinderen, die in 1983 levend geboren zijn met een zwangerschapsduur van minder dan 32 weken en (of) met een geboortegewicht van minder dan 1500 g.

Vergelijking met andere beschikbare bronnen (Landelijke Verloskunde Registratie, Eurocat, Centraal Bureau voor de Statistiek) bevestigde dat het cohort inderdaad vrijwel volledig is. Discrepanties werden alleen gevonden in de categorieën kinderen met extreem korte zwangerschapsduur ($\leq$24 weken).

Wij herhalen de aanbeveling, dat een verplichte registratie moet worden ingevoerd van alle geboorten met een zwangerschapsduur van 22 weken of meer (zowel doodgeborenen als levendgeborenen). Dit is des te urgenter, omdat Nederland één van de zeer weinige West-Europese landen is waar een dergelijk registratiesysteem ontbreekt.

In hoofdstuk 10 wordt de sterfte in de onderzochte groep kinderen besproken. De belangrijkste sterftepercentages zijn:

-eerste dag sterfte (24 uur):	11.0%
-vroeg-neonatale sterfte (7 dagen):	19.9%
-neonatale sterfte:	23.3%
-sterfte tijdens opname:	25.4%
-zuigelingen sterfte:	27.2%

Vergelijking van de gebruikelijke categorieën op grond van een geboortegewichtsindeling toonde aan, dat de sterfte bij kinderen met een zeer laag geboortegewicht (<1500 g) in Nederland relatief laag is.

De meeste gevallen van sterfte deden zich voor in de eerste levensweek (73% van het totaal aantal overleden POPS-kinderen). Een aanzienlijk aantal kinderen overleed echter pas na de 28e levensdag (8%).

Het is daarom aan te bevelen, sterfte bij pasgeborenen niet alleen te rapporteren in de vorm van perinatale of neonatale sterfte, maar ook als postneonatale sterfte, zowel tijdens de eerste aaneengesloten periode van ziekenhuisopname (sterfte tijdens opname) als na ontslag naar huis.

In 1983 vond in Nederland 37% van de totale eerste-week-sterfte plaats in de onderzoeksgroep (266 van 723 kinderen). Van de sterfte gedurende de eerste 28 levensdagen (neonatale sterfte) was dit 34% (312/904), van de sterfte in het eerste levensjaar 25% (364/1432). Teneinde een verdere daling te bereiken van de perinatale sterfte en de zuigelingensterfte in Nederland, moet derhalve de zorgverlening aan deze groep kinderen die een hoge sterftekans hebben, nog verder verbeterd worden.

Hoofdstuk 11 geeft een overzicht van de doodsoorzaken bij de 340 kinderen die overleden tijdens de ziekenhuisopname na de geboorte.

Het idiopatisch respiratoir distress syndroom vormde nog steeds de belangrijkste doodsoorzaak (n=122), vaak in combinatie met een intracraniële bloeding (n=116). In vergelijking met à terme kinderen spelen aangeboren afwijkingen een ondergeschikte rol als doodsoorzaak (n=36). De "diagnose" immaturiteit werd frequent (n=55) opgegeven als doodsoorzaak. Het is aan te bevelen, deze term niet meer te gebruiken, aangezien deze niet bijdraagt tot het begrip van de etiologie en pathofysiologie van de stoornissen die in de neonatale periode optreden en die tot de dood kunnen leiden.

Pathologisch anatomisch onderzoek werd in een groot aantal gevallen verricht (63%). Uit onze studie bleek echter, dat 15% van de obducties gegevens opleverde, waardoor de opgegeven doodsoorzaak veranderde of de klinische diagnose uitgebreid werd met informatie die essentieel was voor het behandelende team. Wij bevelen dan ook aan, bij alle overleden kinderen in deze categorie obductie te verrichten, bij voorkeur volgens een (perinataal) protocol.

In hoofdstuk 12 worden de belangrijkste afwijkingen besproken die zich in de neonatale periode bij de onderzochte kinderen hebben voorgedaan.

De incidentie zowel van IRDS (klinisch beeld 46%, bevestigd door middel van laboratoriumonderzoek 33%) als van ICH (klinisch 25%, bevestigd 20%) is laag in vergelijking met de literatuur. Het percentage kinderen dat overlijdt ten gevolge van de aandoening, met name IRDS, is aanzienlijk gedaald dank zij de hedendaagse methoden voor intensieve behandeling. Toch is er eigenlijk nog geen effectieve geneeswijze voor deze aandoeningen.

Het is aan te bevelen, dat het effect van veelbelovende behandelingsmethoden zoals het toedienen van surfactant, Vitamine E of fenobarbital, eerst naar behoren wordt onderzocht in een prospectief, gerandomiseerd onderzoek, alvorens deze behandelingen worden ingevoerd in de dagelijkse praktijk.

De incidentie van aangeboren afwijkingen (totaal 10.9%, waarvan ernstige aangeboren afwijkingen 9.3%) is hoog, vooral in de subpopulatie kinderen met een geboortegewicht dat te laag is voor de zwangerschaps-

duur (SGA). Het effect van de preventieve maatregelen, zoals die heden ten dage worden toegepast, is onbekend.

Het is aanbevelenswaardig, een continue registratie van aangeboren afwijkingen te doen plaatsvinden op landelijke schaal, ten einde trends in het vóórkomen van aangeboren afwijkingen te kunnen opmerken. Een dergelijke registratie kan ofwel opgenomen worden in een continue registratie van neonatale morbiditeit ("Landelijke Neonatale Registratie") ofwel in een apart systeem.

In hoofdstuk 13 wordt ingegaan op de methodologie van de toegepaste statistische techniek (logistische regressie analyse). Door het gebruik van een multivariate analyse techniek kan de invloed worden berekend van één bepaalde perinatale factor (exposure), terwijl gecorrigeerd wordt voor vele andere factoren die op zichzelf ook invloed op de uitkomst hebben. Dit is noodzakelijk, omdat deze factoren ongelijk verdeeld zijn over de onderzochte populatie.

In hoofdstuk 14 is het verband onderzocht tussen sterfte enerzijds en een aantal perinatale risicofactoren anderzijds. Hiertoe is gebruik gemaakt van de in hoofdstuk 13 beschreven methode: logistische regressie analyse.

Perinatale factoren, die geassocieerd waren met een lagere sterftekans, waren: belaste obstetrische anamnese, hypertensie van de moeder, langdurig gebroken vliezen, antenataal transport en toediening van glucocorticosteroiden.

Perinatale factoren, die niet geassocieerd waren met de sterftekans (na correctie voor de andere perinatale factoren) waren: pariteit, ziekenhuisopname tijdens de zwangerschap, weeënremming, choriamnionitis, electieve geboorte, geboortemechanisme en geslacht van het kind.

Perinatale factoren, die geassocieerd bleken te zijn met een hogere sterftekans, waren: reeds bestaande ziekte van de moeder, aangeboren afwijkingen van het kind, meerlingzwangerschap, stuit-of dwarsligging, geboorte buiten een centrum voor perinatale intensieve zorg, lage Apgar score, SGA, IRDS, ICH en convulsies.

Deze bevindingen zijn gedeeltelijk in tegenspraak met algemeen aanvaarde inzichten. Tot onze verrassing was hypertensie van de moeder geassocieerd met een significant lagere sterftekans. Het hieraan ten grondslag liggende pathofysiologische mechanisme is nog niet opgehelderd. Wij veronderstellen dat hypertensie van de moeder een verandering teweeg brengt in de foeto-placentaire circulatie, waardoor het adaptatieproces na de geboorte gemakkelijker verloopt. Deze hypothese dient nader onderzocht te worden.

Kinderen die geboren worden na behandeling van de moeder met glucocorticosteroiden, hebben een lagere gecorrigeerde sterftekans. Deze bevinding bevestigt eerder gepubliceerde resultaten van gerandomiseerde

trials. Aangezien toediening van glucocorticosteroiden in Nederland slechts op beperkte schaal gebeurt, dient herwaardering van deze behandeling plaats te vinden.

In tegenstelling tot vele andere studies werd in ons onderzoek geen verschil gevonden in gecorrigeerde sterftekans tussen jongens en meisjes. Wij schrijven het vroeger aangetoonde hogere sterfterisico voor jongens toe aan de kortere zwangerschapsduur, die jongens hebben wanneer een dergelijke vergelijking gemaakt wordt in geboortegewichtsgroepen.

Electieve baring en sectio caesarea vinden plaats op zorgvuldige indicatie, waardoor dergelijke ingrepen alleen voorkomen in gevallen met een verhoogd risico. In ons onderzoek konden wij geen associatie aantonen tussen deze beide factoren enerzijds en de gecorrigeerde sterftekans anderzijds. Stuitligging was geassocieerd met een significant verhoogde sterftekans. Klaarblijkelijk is het feit dat een kind zich vóór de geboorte in stuitligging presenteert, op zichzelf belangrijk voor de prognose. Kindsligging bepaalt echter in sterke mate het geboortemechanisme. Daarom hebben wij de gecorrigeerde sterftekans van de factor stuitligging versus hoofdligging apart berekend voor kinderen die per sectio caesarea geboren werden en voor kinderen die vaginaal geboren werden. In de groep die per sectio caesarea geboren werd, was de sterftekans van stuitligging vrijwel gelijk aan die van hoofdligging: odds ratio 0.80 (95% betrouwbaarheidsinterval 0.40-1.94). Echter, in de groep kinderen die vaginaal geboren werd, was stuitligging geassocieerd met een significant verhoogde sterftekans: odds ratio 2.48 (95% betrouwbaarheidsinterval 1.54-3.99). Aangezien andere overwegingen, welke niet in ons onderzoek betrokken zijn, een rol gespeeld kunnen hebben bij de bepaling van het geboortemechanisme, dienen deze resultaten met enige voorzichtigheid geïnterpreteerd te worden. De vraag wat het optimale geboortemechanisme is voor zeer preterme kinderen in stuitligging kan alleen beantwoord worden met een prospectief, gerandomiseerd onderzoek.

Verschillen in overlevingskansen voor zeer preterme kinderen met een zeer laag geboortegewicht werden gevonden bij de drie niveaus van zorg in het ziekenhuis van geboorte en de daarmee samenhangende factoren antenataal en neonataal transport. Hoewel uit een onderzoek als dit geen causaal verband mag worden afgeleid, is het aannemelijk dat de gevonden verschillen in (gecorrigeerde) overlevingskans verkleind kunnen worden door verbetering van het systeem van perinatale zorgverlening voor deze ernstig zieke kinderen. Het is daarom aan te bevelen zeer preterme geboorten en geboorten van kinderen met een zeer laag gewicht te centraliseren in ziekenhuizen die perinatale intensieve zorg verlenen. De beperkende factor bij een dergelijke centralisatie is het voortdurende tekort aan capaciteit. Dit veroorzaakt overbezetting van de bestaande centra en vaak kunnen antenatale of neonatale overplaatsingen niet geaccepteerd worden. Het "Concept Planningsbesluit inzake de intensieve

zorg voor pasgeborenen", van het Ministerie van WVC, waarin wordt voorgesteld het aantal couveuseplaatsen voor "intensive care" uit te breiden van 60 tot 100 en voor "high care" van 72 tot 140, dient met zo groot mogelijke spoed uitgevoerd te worden.

In hoofdstuk 15 is eveneens met behulp van logistische regressie analyse het verband onderzocht tussen neonatale morbiditeit enerzijds en een aantal perinatale risicofactoren anderzijds.

Geassocieerd met een lagere kans op IRDS waren: ziekenhuisopname tijdens de zwangerschap, antenataal transport en toediening van glucocorticosteroiden voor de bevalling.

De lagere kans op IRDS na ziekenhuisopname van de moeder tijdens de zwangerschap en na antenataal transport, wijst op het belang van een goed voorbereide bevalling en van adequate zorg voor het kind meteen na de geboorte. Dit legt nogmaals de nadruk op de noodzaak het systeem van perinatale zorgverlening voor deze kinderen verder te verbeteren.

De bevinding dat het kind minder kans op IRDS heeft indien de moeder voor de bevalling behandeld is met glucocorticosteroiden, bevestigt de resultaten vermeld in hoofdstuk 14 en noopt tot herwaardering van deze behandelingsmethode.

De volgende perinatale factoren waren geassocieerd met een hogere kans op IRDS: manlijk geslacht van het kind, meerlingzwangerschap, weeënremming, sectio caesarea, lage Apgar score en ICH.

De associatie tussen manlijk geslacht en een verhoogde kans op IRDS is in overeenstemming met de resultaten van eerdere onderzoeken. Het blijkt evenwel dat deze associatie niet hoeft te leiden tot een verhoogde sterftekans. Ook de associaties tussen IRDS en sectio caesarea of lage Apgar score zijn eerder beschreven. Bij meerlingzwangerschap en weeënremming daarentegen, is dit een onverwachte bevinding. Onderzoek naar de hieraan ten grondslag liggende pathofysiologie is noodzakelijk.

De factor hypertensie tijdens de zwangerschap was geassocieerd met een lagere kans op ICH. Dit suggereert dat verhoogde bloeddruk tijdens de zwangerschap invloed heeft op de (circulatoire) aanpassing van het kind aan het extrauterien bestaan, met name waar het de hersenbloedstroom betreft. Nader onderzoek is gewenst.

De volgende perinatale factoren waren geassocieerd met een verhoogde kans op ICH: lage Apgar score, IRDS, sepsis en convulsies. Dit is in overeenstemming met algemeen aanvaarde inzichten.

Slechts enkele factoren toonden een verband met de kans op sepsis. Geboorte in een level 2 ziekenhuis bleek geassocieerd met een lagere kans op sepsis. Dit zou het gevolg kunnen zijn van het minder vaak toepassen van invasieve behandelings- en bewakingsmethoden.

De factor langdurig gebroken vliezen was geassocieerd met een verhoogde kans op sepsis. Het verband tussen deze twee factoren is bekend, hoewel oorzaak en gevolg nog niet duidelijk zijn.

De associaties tussen IRDS, ICH en sepsis die ook in onze onderzoeksgroep gevonden werden, bevestigen het feit dat deze aandoeningen vaak achtereenvolgens voorkomen bij vele van deze kinderen.

Samenvattend zijn de volgende aanbevelingen te doen:

Toekomstig perinatologisch onderzoek in Nederland

- -sterfte bij pasgeborenen behoort tenminste gerapporteerd te worden zowel in termen van neonatale sterfte als post-neonatale sterfte.
- -voor zeer preterme kinderen dienen de Amsterdamse "groeicurves" herberekend te worden.
- -voor het vaststellen van het optimale geboortemechanisme voor preterme kinderen in stuitligging is een gerandomiseerde trial nodig.
- -nader onderzoek is noodzakelijk naar de pathofysiologische mechanismen die een rol spelen bij hypertensie van de moeder tijdens de zwangerschap (geassocieerd met een lagere gecorrigeerde sterftekans en een lagere gecorrigeerde kans op ICH), meerlingzwangerschap (geassocieerd met een hogere gecorrigeerde sterftekans en een hogere gecorrigeerde kans op IRDS) en weeënremming (geassocieerd met een hogere gecorrigeerde kans op IRDS).
- -gegevens betreffende de socio-economische klasse dienen volledig vastgelegd te worden.

Perinatale zorgverlening in Nederland

- -uitbreiding van de beschikbare faciliteiten voor neonatale intensieve zorg dient met de grootst mogelijke spoed door de overheid verwezenlijkt te worden.
- -alle geboorten dienen geregistreerd te worden vanaf een zwangerschapsduur van 22 weken zowel van doodgeboren als van levendgeboren kinderen. Hierbij dienen zwangerschapsduur en geboortegewicht vastgelegd te worden.
- -alle gevallen van zuigelingensterfte dienen geregistreerd te worden met vermelding van zwangerschapsduur en geboortegewicht.
- -de toediening van glucocorticosteroiden tijdens de zwangerschap in zorgvuldig geselecteerde gevallen, als behandelingsmethode ter bevordering van de longrijping van het kind, verdient nadere overweging.

Ter evaluatie van de perinatale gezondheidszorg en ter stimulering aan perinatologisch epidemiologisch onderzoek dient in Nederland spoedig een nationaal perinatologisch bureau opgericht te worden.

Dankwoord

Het Project Onderzoek Prematuritas en Small for gestational age werd uitgevoerd in een landelijk samenwerkingsverband van kinderartsen (appendix H), op initiatief van de Sectie Perinatologie van de Nederlandse Vereniging voor Kindergeneeskunde. Vele vrouwenartsen stelden eveneens gegevens beschikbaar.

Aan het onderzoek hebben verder meegewerkt:

De afdeling Medische Statistiek van de Rijksuniversiteit Leiden, in het bijzonder Theo Stijnen; Marij C.A. Ebeling, arts; Thea M. van Zeben-van der Aa, kinderarts; Janet Tonus-Dietz, Corrie van der Geer-van der Vlugt, Alwine Maat-Cohen en Ina Kloosterboer-Boerrigter (projectsecretariaat).

Aan de totstandkoming van dit proefschrift hebben meegewerkt:
Lou Hermans en medewerkers (illustraties), Peter van Eck van der Sluijs (omslagfoto), Claar Verwey en Oliver Gebhardt (Engelse tekst), en Alwine Maat-Cohen (tekstverwerking).

Curricula vitae

S. Pauline Verloove-Vanhorick werd geboren op 7 januari 1946 te Amsterdam. In 1964 behaalde zij aldaar het diploma gymnasium beta. Zij studeerde geneeskunde aan de Rijksuniversiteit Leiden, waar in 1972 het artsexamen werd afgelegd.

Van 1972 tot 1976 werd zij opgeleid tot kinderarts in de afdeling Kindergeneeskunde van het Academisch Ziekenhuis Leiden (Prof. dr. G.M.H. Veeneklaas). Sindsdien is zij als staflid verbonden aan het Neonatologisch Centrum (Prof. dr. J.H. Ruys) van de afdeling Kindergeneeskunde (Prof. dr. L.J. Dooren) aldaar.

Van 1976 tot 1982 was zij vooral klinisch werkzaam, mede in het kader van de subspecialisatie Neonatologie. Vanaf 1982 is zij belast met de leiding van het "Project Onderzoek Prematuritas en Small for gestational age", waarvoor het Neonatologisch Centrum een subsidie ontvangt van het Praeventiefonds.

Robert A. Verwey werd geboren op 8 mei 1946 te Amsterdam. In 1964 behaalde hij te Rotterdam het diploma HBS-b. Hij studeerde geneeskunde aan de Rijksuniversiteit Leiden, waar in 1972 het artsexamen werd afgelegd. Na een tropenopleiding was hij van 1974 tot 1977 werkzaam in Tanzania.

Daarna werd hij opgeleid tot vrouwenarts in de afdeling Gynaecologie en Verloskunde van het Academisch Ziekenhuis Leiden (Prof. dr. E.V. van Hall en Prof. dr. J. Bennebroek Gravenhorst), en in het Diaconessenhuis Leiden (Dr. C.D. van der Does). Van 1982 tot 1987 was hij als chef de clinique verbonden aan de afdeling Verloskunde van het Academisch Ziekenhuis Leiden. Sinds april 1987 is hij werkzaam in de Diakonessenin-richting "Bronovo" te 's-Gravenhage in associatie met P.H. Kolkman en M.R. Mackenzie.

a-formulier

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

identificatie

a1

formulier nummer POPS : _____

universitaire neonat. int. care unit : _____

registratienummer aldaar : _____

andere couveuse afdeling(en) : _____

registratienummer aldaar : _____

kaart nr. 1 101 [0 1]

01 **registratienummer POPS** 103 [ ] 104 [ ] 107 [ ] niet invullen

gegevens moeder

02 **geboortedatum** (dg / mnd / jr) 111 [ ]

03 **meisjesnaam** (eerste 3 letters) 117 [ ]

04 **postcode** (woonplaats) 120 [ ]

05 **socio-economische groep:** **moeder:** beroep _____ **vader:** beroep _____ 126 [ ] niet invullen
opleiding _____ opleiding _____
wijze van **ziektekostenverzekering:** verplicht / vrijwillig / particulier

06 **bevolkingsgroep:**
beide ouders **kaukasisch** (blank) nee 0 ja 1 127 [ ]
een van beide of beide ouders **mediterraan** nee 0 ja 1 128 [ ]
negroïd nee 0 ja 1 129 [ ]
aziatisch nee 0 ja 1 130 [ ]
anders nee 0 ja 1 131 [ ]

07 **burgelijke staat moeder:** gehuwd 0 niet (meer) gehuwd, wel in gezinsverband levend met partner of ouders 1 132 [ ]
niet (meer) gehuwd, alleen 2 andere 3

obstetrische gegevens

08 **datum laatste menstruatie** (dg / mnd / jr) 133 [ ]

09 **aantal zwangerschappen vóór deze** 139 [ ]

10 **aantal abortussen vóór deze** (0 t/m 15+[5] weken = 0 t/m 111 dg) 140 [ ]

11 **aantal partus immaturus en/of prematurus vóór deze** (16 t/m 36+[6] weken = 112 t/m 258 dg) 141 [ ]

12 **aantal levende kinderen** (8 = 8 of meer) 142 [ ]

13 **ziekten vóór de zwangerschap:** **hartaandoening** nee 0 ja 1 143 [ ]
epilepsie nee 0 ja 1 144 [ ]
diab. mellitus nee 0 ja 1 145 [ ]
nierziekte nee 0 ja 1 146 [ ]
hypertensie nee 0 ja 1 147 [ ]
(diastolische bloeddruk ≥ 90 mm Hg)

14 **ziekten tijdens zwangerschap:** **diab. mell. grav.** nee 0 dieet 1 insuline 2 148 [ ]
actief bloedgroepantagonisme nee 0 ja 1 149 [ ]
(Rh, Duffy, Kell, ABO), (positieve antistoffiter, plasmaferese, intrauteriene bloedtransfusies of vervroegde geboorte)
hypertensie nee 0 2 x ≥ 90 mm Hg diast. 1 150 [ ]
pre- eclampsie 2 eclampsie 3

15 **intoxicaties tijdens de zwangerschap:**
roken nee 0 ja 0-10 sig/dag 1 151 [ ]
ja meer dan 10 sig/dag 2

formulier nummer POPS : _____

	alkoholverslaving	nee 0	ja 1	152
	soft drugs	nee 0	ja 1	153
	hard drugs	nee 0	ja 1	154
	methadon	nee 0	ja 1	155
16 **ziekenhuisopname**	tijdens en verbandhoudende met zwangerschap; herhaalde opnames bij elkaar tellen			
	nee 0 ja minder dan 1 week 1		ja 1 week of langer 2	156
17 **CTG-afwijkingen**	tijdens zwangerschap vóór partus	nee 0	ja 1 niet verricht 8	157
	Ja, indien Fischer-score < 8 of oordeel van obstetricus aanhouden, gebaseerd op b.v. type II-dips = late deceleraties, aantal 0-doorgangen, sinusoid patroon e.d.)			
18 **medicijngebruik**	tijdens de zwangerschap (geen ijzer, vitamine, fluor vermelden)			
	diuretica	nee 0	ja 1	158
	antihypertensiva	nee 0	ja 1	159
	tranquillizers	nee 0	ja 1	160
	anti-epileptica	nee 0	ja 1	161
	antibiotica	nee 0	ja 1	162
	gestagenen	nee 0	ja 1	163
	asthma ther.	nee 0	ja 1	164
	andere	nee 0	ja 1	165
	namelijk _____			

kaart nr. 2 201 0 2

geboorte

19 **geboortedatum**	(dg / mnd / jr)	203
20 **geboortetijdstip**	(uur / min.)	209
21 **zwangerschapsduur**	(wk + dg) zoals opgegeven door obstetricus (op grond van amenorrhoe duur en/of echografie en/of zwangerschapstesten)	213 +
22 **betrouwbaarheid termijn**	zeker 0 dubieus 1 onbetrouwbaar 2	216
23 **geslacht**	vrouw 1 man 2 onduidelijk 3	217
24 **ligging**	van het kind bij de geboorte (ook invullen bij sectio caesarea)	
	achterhoofd 0 andere hoofd 1 stuit 2 dwars 3 overige 4	218
25 **gebruik van weeënremmende middelen,** langer dan 24 uur.		
β-mimetica (prepar, partusisten, Th 1165A, duvadilan)	nee 0	ja 1 219
prostaglandine synthetase remmers (b.v. indomethacine)	nee 0	ja 1 220
andere	nee 0	ja 1 221
in combinatie met corticosteroiden	nee 0	ja 1 222
26 **gebruik van weeën stimulerende middelen**		
	nee 0 ja oxytocine 1 ja prostaglandine 2 andere 3	223
27 **inleiding van de baring**	d.m.v. amniotomie en/of weeënstimulerende middelen nee 0	ja 1 224
28 **wijze van geboorte**		
vaginaal	**hoofdligging, spontaan**	ja 0 met expressie 1 nee 2 225
	vacuumextractie	nee 0 ja 1 226
	forcipale extractie	nee 0 ja 1 227
	stuitgeboorte (ilrscht)	nee 0 ja 1 228
	stuitextractie	nee 0 ja 1 229
	versie en extractie	nee 0 ja 1 230

formulier nummer POPS : _____

sectio caesarea nee 0 ja, bij staande vliezen zonder weeënactiviteit 1 ja, bij gebroken vliezen zonder weeënactiviteit 2 ja, bij staande vliezen met weeënactiviteit 3 ja, bij gebroken vliezen met weeënactiviteit 4 — 231

andere wijze van geboorte nee 0 ja 1 — 232

namelijk _____

29 **CTG tijdens de partus** (zie ook vraag 17) normaal 0 afwijkend 1 niet verricht 8 — 233

30 **sedativa en / of analgetica** tijdens de partus

pethidine nee 0 ja 1 — 234

valium nee 0 ja 1 — 235

andere nee 0 ja 1 — 236

31 **anaesthesie** tijdens de partus epi / peridurasl nee 0 ja 1 — 237

totaal nee 0 ja 1 — 238

locaal nee 0 ja 1 — 239

32 **gebroken vliezen** bij het begin van de partus

nee 0 minder dan 12 uur 1 12-24 uur 2 1-7 dg 3 langer dan 7 dg 4 — 240

33 **elnolte infectie** met koorts en/of leucocytose van de moeder tijdens de partus nee 0 ja 1 — 241

34 **vruchtwateraspect** helder 0 meconiumhoudend 1 stinkend foetide 2 met bloed 3 — 242

kind

25 **geboortegewicht** (grammen) — 243

36 **geboortelengte** (cm) — 247

37 **schedelomtrek** (cm), (gemeten na minstens 24 uur en binnen 7 dagen) — 249

38 **rijpingsscore** (wk + dg) (bijv. volgens Dubowitz, Ballard, Finnstrøm, Mitchel-Farr of Parkin, a.v.p. onderstrepen welke methode gevolgd is) — 251 +

39 **apgar score**

	0	1	2	
hartfreq.	afw.	< 100	> 100	na 1 minuut (niet verricht 88) — 254
ademhaling	afw.	traag irreg	goed	na 3 minuten (niet verricht 88) — 256
tonus	slap	matig	goed	na 5 minuten (niet verricht 88) — 258
prikkelbaarh.	afw.	matig	goed	na 10 minuten (niet verricht 88) — 260
kleur	blauw-bleek	extrem. blauw	roze (extremiteiten nog blauw)	

40 **pH arteriael navelstreng** (2 decimalen) niet verricht 888 — 262 ,

pCO_2 arteriael navelstreng (kPa 1 decimaal; 1 kPa = 7,5 mm Hg) niet verricht 888 — 265 ,

41 **pH veneus navelstreng** (2 decimalen) niet verricht 888 — 268 ,

pCO_2 veneus navelstreng (kPa, 1 decimaal; 1 kPa = 7,5 mm Hg) niet verricht 888 — 271 ,

42 **pH capillair** binnen 30 min. na de geboorte (2 decimalen) niet verricht 888 — 274 ,

pCO_2 capillair binnen 30 min. na de geboorte (kPa, 1 decimaal; 1 kPa = 7,5 mm Hg) niet verricht 888 — 277 ,

43 **meerling** enkelvoud 0 tweeling 1e kind 1 tweeling 2e kind 2 drieling 1e kind 3 drieling volgende kind 4 vierling 1e kind 5 vierling volgende kind 6 vijf- of zesling 1e kind 7 vijf- of zesling volgende kind 8 — 280

kaart nr. 3 — 301 [0 | 3]

44 **plaats van geboorte** universitaire afd. verloskunde, met neonatologisch intensive-care-centrum 0 — 309

algemeen ziekenh. met neonatologische high-care en medium-care; enige intensive-care faciliteiten 1

algemeen ziekenh. met kinderarts, „opvang-couveuse" 2

ziekenhuis of kraamkliniek zonder kinderarts 3

elders 4

formulier nummer POPS : _____

45 **transport**	geen transport **0** intra-uterien, mevrouw niet in partu **1** intra-uterien, mevrouw wel in partu **2** zo snel mogelijk post partum, team uit centrum binnen 1 uur aanwezig **3** zo snel mogelijk post partum, tijdsverloop tot team uit centrum aanwezig > 1 uur **4** „secundair" transport na optreden pathologie **5** „secundair" transport na aanvankelijk dreigend overlijden **6**	304
46 **wijze van transport**	geen **0** intensive care-transport (babylance) door: Amsterdam VU **1** Amsterdam WG **2** Groningen **3** t aiden **4** Nijmegen **5** Rotterdam **6** Utrecht **7** ander transport **8** Haastricht **9**	305
47 **hypothermie**	(op 1e levensdag < 35,5° C) nee **0** ja **1**	306
48 **longafwijkingen**	**I.R.D.S.** nee **0** klinisch (> 24 uur 0_2-behoefte, kreunen e.d.) **1** röntgenologisch (> 24 uur granulair beeld, luchtbronchogram) **2**	307
	wet-lung nee **0** klinisch **1** röntgenologisch (interlobaire vochtlijn) **2**	308
	(cong.) pneumonie nee **0** ja **1**	309
	atelectase nee **0** ja **1**	310
	pneumothorax of pneu elders nee **0** ja **1**	311
	interstitieel emfyseem nee **0** ja **1**	312
	meconium aspiratie nee **0** ja **1**	313
	voedingsaspiratie nee **0** ja **1**	314
	bronchopulmonaire dysplasie nee **0** ja **1**	315
	Mikity Wilson nee **0** ja **1**	316
49 **persisterende foetale circulatie**	nee **0** ja **1** tolazoline **2**	317
50 **open Ductus Botalli**	(van haemodynamisch belang) nee **0** waarschijnlijk **1** ja (bewezen bij echo, hartcatheterisatie of operatie) **2**	318
therapie daarvoor	**conservatief** (vochtbeperking, diurstica) nee **0** ja **1**	319
	medicamenteus (Indomethacine) nee **0** ja **1**	320
	operatief nee **0** ja **1**	321
51 **apnoe-aanvallen**	(minstens 15 sec. of met bradycardie <100/min) nee **0** ja **1**	322
therapie:	**prikkelen** nee **0** ja **1**	323
	medicamenteus (coffeïne, theofylline etc.) nee **0** ja **1**	324
	CPAP nee **0** ja **1**	325
	IPPV nee **0** ja **1**	326
52 **bradycardieën**	(<100/min., zonder apnoe) nee **0** ja **1**	327
53 **continuous positive airway pressure (CPAP)** (aantal dagen, b.v. 004)		328
54 **intermittent positive airway pressure (IPPV)** (aantal dagen, b.v. 008)		331
55 **congenitale infecties** (positieve bloedkweek, sputumkweek e.d.; contaminatie huid e.d. niet als infectie opgeven)		
	cong. β-haem. strept. gr. B nee **0** ja **1** geen kweek verricht **8**	334
	hepatitis (hepatitis B virus) nee **0** ja **1** geen onderzoek verricht **8**	335
	herpes nee **0** ja **1** geen onderzoek verricht **8**	336
	cytomegalie nee **0** ja **1** geen onderzoek verricht **8**	337
	listeria nee **0** ja **1** geen onderzoek verricht **8**	338
	rubella nee **0** ja **1** geen onderzoek verricht **8**	339
	toxoplasmose nee **0** ja **1** geen onderzoek verricht **8**	340
	lues nee **0** ja **1** geen onderzoek verricht **8**	341

formulier nummer POPS : _____

56 **sepsis**	**klinisch beeld** sterk verdacht	nee 0 ja 1	342
	bloedbeeld typisch voor sepsis	nee 0 ja 1	343
	positieve bloedkweek	nee 0 ja 1	344
57 **sepsis verwekker**	**β-haemol. strept. gr. B**	nee 0 ja 1	345
	E-coli	nee 0 ja 1	346
	staphyl. aureus	nee 0 ja 1	347
	staphyl. epid. = albus	nee 0 ja 1	348
	andere	nee 0 ja 1	349
58 **meningitis**	**klinisch beeld** sterk verdacht	nee 0 ja 1	350
	positieve liquor kweek	nee 0 ja 1	351
59 **serum bilirubine**	hoogste waarde (capillair, in µmol/l)		352
60 **dag waarop deze waarde bereikt werd**			355
61 **fototherapie**	(aantal dagen)		357
62 **wisseltransfusies**	(aantal; uitgezonderd partiële wisseltransfusie wegens hyperviscositeit)		359
63 **indicatie voor wisseltransfusie**	**hyperbilirubinaemie**	nee 0 ja 1	360
	sepsis	nee 0 ja 1	361
	metabole stoornis	nee 0 ja 1	362
	intoxicatie	nee 0 ja 1	363
64 **totale parenterale voeding**	(mengsel van glucose, aminozuren en/of vet)	niet of < 24 uur 0 1 t/m 7 dg 1 8 t/m 28 dg 2 > 28 dg 3	364
65 **transpylorische voeding**	(oro-duodenaal, nasoduodenaal enz.)	niet of < 24 uur 0 1 t/m 7 dg 1 7 t/m 28 dg 2 > 28 dg 3	365
66 **necrotiserende enterocolitis**	nee 0 klinisch zeer verdacht 1 röntgenologisch duidelijk 2 operatief behandeld 3		366
67 **intracraniële bloeding**	(klinisch)	nee 0 verdacht 1 duidelijk 2	367
68 **diagnose intracraniële bloeding vastgesteld m.b.v.**			
	lumbaalpunctie	nee 0 verdacht 1 bewezen 2	368
	echografie	nee 0 verdacht 1 bewezen 2	369
	CT-scan	nee 0 verdacht 1 bewezen 2	370
	pulsatie-index Doppler	nee 0 verdacht 1 bewezen 2	371
	PA	nee 0 bewezen 2	372
69 **localisatie intracraniële bloeding**			
	subependymaal	nee 0 ja 1	373
	parenchymaal	nee 0 ja 1	374
	suberachnoïdaal	nee 0 ja 1	375
	intraventriculair	nee 0 ja 1	376
	cerebellair	nee 0 ja 1	377
	subduraal	nee 0 ja 1	378
70 **convulsies**	geen 0 op 1e levensdag 1 2e t/m 4e levensdag 2 5e dag of later 3		379
kaart nr. 4			401 9 ; 4
71 **hydrocefalie**	**te snelle toename ventrikelgrootte**	nee 0 ja 1	403
	te snelle toename schedelomtrek	nee 0 ja 1	404
	frequente liquorpuncties	nee 0 ja 1	405
	ventrikulo-peritoneale of andere drainage	nee 0 ja 1	406

formulier nummer POPS : _____

72 afwijkingen centr. zenuwstelsel (tonus, motoriek, (neonatale) reflexen) normaal **0** dubieus **1** afwijkend **2** 407

73 afwijkingen perifere zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d. nee **0** ja **1** 408

74 retroiëntale fibroplasie nee **0** mogelijk **1** ja **2** geen fundoscopie verricht **8** 409
(mogelijk = verdacht, misschien in lichte mate; ja = bij fundoscopie duidelijk vastgestelde vaatproliferatie en/of ingroei, in beginfase of ernstiger)

75 medicamenteuze behandeling (uitgezonderd vitamines, ijzer e.d.)

antibiotica	nee **0** ja **1**	410
diuretica	nee **0** ja **1**	411
digoxine	nee **0** ja **1**	412
corticosteroiden	nee **0** ja **1**	413
anti-convulsiva (luminal wga. hyperbilirubinaemie als „andere" coderen)	nee **0** ja **1**	414
andere	nee **0** ja **1**	415

76 aangeboren afwijkingen geen **0** wel met leven verenigbaar **1** niet met leven verenigbaar **2** 416

77 soort aangeboren afwijking (maximaal 6, zie lijst achterzijde) 417 419 421 423 425 427

78 overleden aan

aangeboren afwijking (zie vraag 76)	nee **0** ja **1** n.v.t. **8**	429
IRDS	nee **0** ja **1** n.v.t. **8**	430
intracraniële bloeding	nee **0** ja **1** n.v.t. **8**	431
congenitale infectie	nee **0** ja **1** n.v.t. **8**	432
sepsis	nee **0** ja **1** n.v.t. **8**	433
necrotiserende enterocolitis	nee **0** ja **1** n.v.t. **8**	434
andere, nl. _____	nee **0** ja **1** n.v.t. **8**	435

79 datum van overlijden (dg / mnd / jr) niet van toepassing **88 88 88** 436

80 tijdstip van overlijden (uren / min.) niet van toepassing **88 88** 442

81 wijze van overlijden spontaan **1** niet (verder) behandelbaar geacht **2** fout en/of accident **3** n.v.t. **8** 446

82 datum ontslag uit universitaire intensive care unit (dg / mnd / jr) (niet van toepassing **88 88 88**) 447

83 datum ontslag naar huis (of gezinsvervangend tehuis) (niet van toepassing **88 88 88**) 453
(beide data kunnen dus hetzelfde zijn)

84 toestand kind bij ontslag naar huis goed **0** dubieus **1** afwijkend **2** 459
(b.v. neurologische stoornis, longproblemen, voedingsproblemen enz.) n.v.t. **8**

85 gewicht bij ontslag naar huis (in grammen) niet van toepassing **88 88** 460

86 ontwikkeling kind bij ontslag naar huis, m.n. contact e.d. passend bij gecorr. leeftijd **0** 464
dubieus **1** achter **2** n.v.t. **8**

eigen coderingen inzender 455 470

nacontroles zullen verricht worden door

kinderarts _____

ziekenhuis _____
(deze krijgt b-c-d-e formulieren toegestuurd)

uitval op later tijdstip 475 niet invullen

2e centrum 476

2e andere afdeling 477

LIJST AANGEBOREN AFWIJKINGEN (zie vraag 77)

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. centraal zenuwstelsel

zintuigen

10 microphthalmie
11 andere cong. afw. ogen
12 cong. afw. oren

hartvaatstelsel

20 vitium cordis
21 ontbreken van een navelarterie
29 andere cong. vaatanomalieën

ademhalingswegen

30 choanaal atresie
39 overige cong. afw. tractus respiratorius

spijsverteringsstelsel

40 gehemeltespleet
41 lipspleet
42 oesofago-tracheale fistel
43 oesofagus atresie
44 overige darmatresie incl. van de anus
45 hernia diafragmatica
49 andere cong. afw. tractus digestivus

urogenitaal systeem

50 hypospadie en epispadie
59 andere cong. afw. tractus urogenitalis

huid

60 naevus pigmentosus
61 haemangioma cavernosum
69 andere cong. huidafwijkingen

bewegingsstelsel

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 (inclusief spierstelsel)

overige congenitale afwijkingen

80 struma congenita
81 syndroom van Down
82 andere chromosoomafwijkingen
83 situs inversus
84 multipele congenitale afwijkingen
89 overige congenitale afwijkingen (niet nader omschreven)
90 inborn error of metabolism
91 syndroom van Potter

verzending van formulieren liefst m.b.v. voorgeadresseerde plaketiketten,of adresseren aan:

POPS, Academisch Ziekenhuis,
Gebouw 33,
Rijnsburgerweg 10
2333 AA LEIDEN

APPENDIX B

b-formulier

b_1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **3 maanden**

geboortedatum : _____

datum ontslag naar huis : _____

streefdatum controle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 5 501 [0 | 5]

01 registratienummer POPS 503 [| | | | | | | |]

02 streefdatum controle (dg / mnd / jr) 511 [| | | | | |]

03 controle datum (dg / mnd / jr) 517 [| | | | | |]

04 niet voor nacontrôle beschikbaar wegens: 523 [ ]
wel beschikbaar **0** overleden tussen ontslag en controle **1** (datum ___/___/___
diagnose _____)
verhuisd **2** (nl. naar: _____
controle aldaar door: _____)
verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**
verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 lengte (cm) b.v. 63 cm : 063 524 [| |]

06 gewicht (kg, 1 decimaal) b.v. 5780 g : 05,7 527 [| | ,]

07 schedelomtrek (cm) 530 [| |]

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

1 maand:

08 ogen fixeren ja **0** nee **1** 532 [ ]

09 reageert op toespreken (m) ja **0** nee **1** 533 [ ]

10 beweegt armen evenveel ja **0** nee **1** 534 [ ]

11 beweegt benen evenveel ja **0** nee **1** 535 [ ]

12 heft kin even van onderlaag ja **0** nee **1** 536 [ ]

2 maanden:

13 lacht terug (m) ja **0** nee **1** 537 [ ]

14 volgt met ogen en hoofd ja **0** nee **1** 538 [ ]

3 maanden:

15 handen af en toe open ja **0** nee **1** 539 [ ]

16 kijkt naar eigen handen (m) ja **0** nee **1** 540 [ ]

17 maakt geluiden terug (m) ja **0** nee **1** 541 [ ]

18 blijft hangen bij optillen onder de oksels ja **0** nee **1** 542 [ ]

19 heft in buiklligging hoofd tot 45° ja **0** nee **1** 543 [ ]

6 maanden:

22 speelt met handen midden voor ja **0** nee **1** 546 [ ]

23 pakt in rugligging voorwerp binnen bereik ja **0** nee **1** 547 [ ]

24 neemt hoofd mee bij optrekken tot zit ja **0** nee **1** 548 [ ]

25 draait hoofd naar geluid ja **0** nee **1** 549 [ ]

26 bij vertikaal optillen, benen gebogen of trappelen ja **0** nee **1** 550 [ ]

27 kijkt rond met 90° geheven hoofd ja **0** nee **1** 551 [ ]

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)
nee **0** suspect **1** duidelijk afwijkend **2** 553 [ ]
indien suspect, a.v.p. toelichten _____

formulier nummer POPS : _____

30 afwijkingen perifeer zenuwstelsel	(Erbse parese, facialis parese, abducens parese e.d.)			nee 0	ja 1	554
31 convulsies	nee 0	ja zonder EEG-afwijkingen 1		ja met EEG-afwijkingen 2		555
32 fysiotherapie	nee 0		alleen periodiek adviezen aan ouders 1			556
	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Vojta, enz.) 2					
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie			nee 0	ja 1	557
	Mikity Wilson			nee 0	ja 1	558
	andere chron. luchtwegafwijkingen			nee 0	ja 1	559
	recidiv. bovenste luchtweginfecties			nee 0	ja 1	560
	recidiv. (broncho) pneumonie			nee 0	ja 1	561
	andere infectieuze aandoeningen			nee 0	ja 1	562
34 afwijkingen tractus digestivus	voedingsproblemen (organisch)			nee 0	ja 1	563
	dyspepsie			nee 0	ja 1	564
	andere			nee 0	ja 1	565
35 hernia's	inguinalis		nee 0	ja 1	dubbelzijdig 2	566
	umbilicalis			nee 0	ja 1	567
	geopereerd			nee 0	ja 1	568
36 gehoorsafwijking	twijfel ouders en/of arts			nee 0	ja 1	569
	afwijkend audiologisch onderzoek			nee 0	ja 1	570
37 oogafwijkingen	**retrolentale fibroplasie**			nee 0	licht 1 ernstig 2	571
	(licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)					
	strabisme			nee 0	ja 1	572
	andere afwijking, nl. _____			nee 0	ja 1	573
38 ziekenhuisopname	tussen ontslag en deze contrôle			nee 0	ja 1	574
	indicatie _____					601 0 ; 6
kaart nr. 6						
39 geconsult. overige specialisten	**oogarts**	nee 0	routine contrôle 1		op indicatie 2	603
	KNO-arts	nee 0	routine contrôle 1		op indicatie 2	604
	(kinder)neuroloog	nee 0	routine contrôle 1		op indicatie 2	605
	orthoped. chir.	nee 0	routine contrôle 1		op indicatie 2	606
	revalidatiearts	nee 0	routine contrôle 1		op indicatie 2	607
	kindercardioloog	nee 0	routine contrôle 1		op indicatie 2	608
	andere nl. _____	nee 0	routine contrôle 1		op indicatie 2	609

(als "routine-contrôle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen	**veel huilen**			nee 0	ja 1	610
	slaapstoornis			nee 0	ja 1	611
	onrust			nee 0	ja 1	612
	voedingsmoeilijkheden			nee 0	ja 1	613
	dreigende mishandeling			nee 0	ja 1	614
	mishandeling			nee 0	ja 1	615
	andere, nl _____			nee 0	ja 1	616
41 lengte moeder	(cm)					617
42 lengte vader	(cm)					620
eigen coderingen inzender						623
						629

APPENDIX C

c-formulier

c1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **6 maanden**

geboortedatum : _____

streefdatum contrôle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 7 701 [0 | 7]

01 registratienummer POPS 703 [| | | | | |]

02 streefdatum contrôle (dg / mnd / jr)* 711 [| | | | |]

03 contrôle datum (dg / mnd / jr) 717 [| | | | |]

04 niet voor nacontrôle beschikbaar wegens: 723 [ ]

wel beschikbaar **0** overleden tussen ontslag en contrôle **1** (datum ____/____/____,

diagnose _____)

verhuisd **2** (nl. naar: _____

contrôle aldaar door: _____)

verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**

verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 lengte (cm) b.v. 63 cm : 063 724 [| |]

06 gewicht (kg, 1 decimaal) b.v. 7780 g : 07,7 727 [| | , |]

07 schedelomtrek (cm) 730 [| |]

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

3 maanden:

08 handen af en toe open ja **0** nee **1** 732 [ ]

09 kijkt naar eigen handen (m) ja **0** nee **1** 733 [ ]

10 maakt geluiden terug (m) ja **0** nee **1** 734 [ ]

11 blijft hangen bij optillen onder de oksels ja **0** nee **1** 735 [ ]

12 heft in buikligging hoofd tot 45° ja **0** nee **1** 736 [ ]

6 maanden:

15 speelt met handen midden voor ja **0** nee **1** 739 [ ]

16 pakt in rugligging voorwerp binnen bereik ja **0** nee **1** 740 [ ]

17 neemt hoofd mee bij optrekken tot zit ja **0** nee **1** 741 [ ]

18 draait hoofd naar geluid ja **0** nee **1** 742 [ ]

19 bij vertikaal optillen, benen gebogen of trappelen ja **0** nee **1** 743 [ ]

20 kijkt rond met 90° geheven hoofd ja **0** nee **1** 744 [ ]

9 maanden:

22 pakt voorwerp over ja **0** nee **1** 746 [ ]

23 houdt voorwerp vast, pakt nog een voorwerp in andere hand ja **0** nee **1** 747 [ ]

24 speelt met beide voeten (m) ja **0** nee **1** 748 [ ]

25 rolt zich om van rug naar buik en omgekeerd (m) ja **0** nee **1** 749 [ ]

26 kan hoofd goed ophouden in zit ja **0** nee **1** 750 [ ]

27 zit op billen, ook met gestrekte benen ja **0** nee **1** 751 [ ]

28 zegt dada - baba of gaga (m) ja **0** nee **1** 752 [ ]

formulier nummer POPS : _____

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)	nee 0 suspect 1 duidelijk afwijkend 2		753
	indien suspect, a.v.p. toelichten _____		
30 afwijkingen perifeer zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d.)	nee 0 ja 1		754
31 convulsies	nee 0 ja zonder EEG-afwijkingen 1 ja met EEG-afwijkingen 2		755
32 fysiotherapie	nee 0 alleen periodiek adviezen aan ouders 1		756
	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2		
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie nee 0 ja 1		757
	Mikity Wilson nee 0 ja 1		758
	andere chron. luchtwegafwijkingen nee 0 ja 1		759
	recidiv. bovenste luchtweginfecties nee 0 ja 1		760
	recidiv. (broncho) pneumonie nee 0 ja 1		761
	andere infectieuze aandoeningen nee 0 ja 1		762
34 afwijkingen tractus digestivus	voedingsproblemen (organisch) nee 0 ja 1		763
	dyspepsie nee 0 ja 1		764
	andere nee 0 ja 1		765
35 hernia's	inguinalis nee 0 ja 1 dubbelzijdig 2		766
	umbilicalis nee 0 ja 1		767
	geopereerd nee 0 ja 1		768
36 gehoorsafwijking	twijfel ouders en/of arts nee 0 ja 1		769
	afwijkend audiologisch onderzoek nee 0 ja 1		770
37 oogafwijkingen	retrolentale fibroplasie nee 0 licht 1 ernstig 2		771
	(licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)		
	strabisme nee 0 ja 1		772
	andere afwijking, nl. _____ nee 0 ja 1		773
38 ziekenhuisopname	tussen vorige POPS-contrôle en deze nee 0 ja 1		774
	indicatie _____		
kaart nr. 8			801 0 : 8
39 geconsult. overige specialisten	**oogarts** nee 0 routine contrôle 1 op indicatie 2		803
	KNO-arts nee 0 routine contrôle 1 op indicatie 2		804
	(kinder)neuroloog nee 0 routine contrôle 1 op indicatie 2		805
	orthoped. chir. nee 0 routine contrôle 1 op indicatie 2		806
	revalidatiearts nee 0 routine contrôle 1 op indicatie 2		807
	kindercardioloog nee 0 routine contrôle 1 op indicatie 2		808
	andere nl. _____ nee 0 routine contrôle 1 op indicatie 2		809
(als "routine-contrôle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie. als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).			
40 psychosociale problemen	**veel huilen** nee 0 ja 1		810
	slaapstoornis nee 0 ja 1		811
	onrust nee 0 ja 1		812
	voedingsmoeilijkheden nee 0 ja 1		813
	dreigende mishandeling nee 0 ja 1		814
	mishandeling nee 0 ja 1		815
	andere, nl _____ nee 0 ja 1		816
eigen coderingen inzender			823
			826

APPENDIX D

d-formulier

d_1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **12 maanden**

geboortedatum : _____

streefdatum contrôle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 9 901 [9 | 9]

01 **registratienummer POPS** 903 [_____]

02 **streefdatum contrôle** (dg / mnd / jr) 911 [__|__|__]

03 **contrôle datum** (dg / mnd / jr) 917 [__|__|__]

04 **niet voor nacontrôle beschikbaar wegens:** 923 [_]

wel beschikbaar **0** overleden tussen ontslag en contrôle **1** (datum ____/____/____,
diagnose _____)

verhuisd **2** (nl. naar: _____

contrôle aldaar door: _____)

verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**

verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 **lengte** (cm) b.v. 73 cm : 073 924 [___]

06 **gewicht** (kg, 1 decimaal) b.v. 9780 g : 09.7 927 [___,_]

07 **schedelomtrek** (cm) 930 [___]

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

9 maanden:

08 **pakt voorwerp over** ja **0** nee **1** 932 [_]

09 **houdt voorwerp vast, pakt nog een voorwerp in andere hand** ja **0** nee **1** 933 [_]

10 **speelt met beide voeten** (m) ja **0** nee **1** 934 [_]

11 **rolt zich om van rug naar buik en omgekeerd** (m) ja **0** nee **1** 935 [_]

12 **kan hoofd goed ophouden in zit** ja **0** nee **1** 936 [_]

13 **zit op billen, ook met gestrekte benen** ja **0** nee **1** 937 [_]

14 **zegt dada - babe of gaga** (m) ja **0** nee **1** 938 [_]

12 maanden:

15 **blijft los zitten** ja **0** nee **1** 939 [_]

16 **pakt propje met duim en wijsvinger** ja **0** nee **1** 940 [_]

17 **kruipt vooruit, buik op grond** (m) ja **0** nee **1** 941 [_]

18 **trekt zich op tot staan** (m) ja **0** nee **1** 942 [_]

19 **zwaait "dag, dag"** (m) ja **0** nee **1** 943 [_]

20 **brabbelt bij zijn spel** (m) ja **0** nee **1** 944 [_]

15 maanden:

22 **doet blokje in/uit doos** ja **0** nee **1** 946 [_]

23 **speelt "geven en nemen"** (m) ja **0** nee **1** 947 [_]

24 **kruipt, buik vrij van de grond** (m) ja **0** nee **1** 948 [_]

25 **loopt langs** (m) ja **0** nee **1** 949 [_]

26 **begrijpt enkele dagelijks gebruikte woorden** (m) ja **0** nee **1** 950 [_]

27 **gebruikt 2 woorden met begrip** (m) ja **0** nee **1** 951 [_]

formulier nummer POPS : _____

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)
nee 0 suspect 1 duidelijk afwijkend 2 953

indien suspect, s.v.p. toelichten _____

30 afwijkingen perifeer zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d.) nee 0 ja 1 954

31 convulsies nee 0 ja zonder EEG-afwijkingen 1 ja met EEG-afwijkingen 2 955

32 fysiotherapie nee 0 alleen periodiek adviezen aan ouders 1 956
gerogelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2

33 afwijkingen tractus respiratorius

bronchopulmonale dysplasie	nee 0	ja 1	957
Mikity Wilson	nee 0	ja 1	958
andere chron. luchtwegafwijkingen	nee 0	ja 1	959
recidiv. bovenste luchtweginfecties	nee 0	ja 1	960
recidiv. (broncho) pneumonie	nee 0	ja 1	961
andere infectieuze aandoeningen	nee 0	ja 1	962

34 afwijkingen tractus digestivus

voedingsproblemen (organisch)	nee 0	ja 1	963
dyspepsie	nee 0	ja 1	964
andere	nee 0	ja 1	965

35 hernia's

inguinalis	nee 0	ja 1	dubbelzijdig 2	966
umbilicalis	nee 0	ja 1		967
geopereerd	nee 0	ja 1		968

36 gehoorsafwijking

twijfel ouders en/of arts	nee 0	ja 1	969
afwijkend audiologisch onderzoek	nee 0	ja 1	970

37 oogafwijkingen

retrolentale fibroplasie (licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)	nee 0	licht 1	ernstig 2	971
strabisme	nee 0	ja 1		972
andere afwijking, nl. _____	nee 0	ja 1		973

38 ziekenhuisopname tussen vorige POPS-controle en deze nee 0 ja 1 974

indicatie _____
kaart nr. 10 1001 1 0

39 geconsult. overige specialisten

oogarts	nee 0	routine controle 1	op indicatie 2	1003
KNO-arts	nee 0	routine controle 1	op indicatie 2	1004
(kinder)neuroloog	nee 0	routine controle 1	op indicatie 2	1005
orthoped. chir.	nee 0	routine controle 1	op indicatie 2	1006
revalidatiearts	nee 0	routine controle 1	op indicatie 2	1007
kindercardioloog	nee 0	routine controle 1	op indicatie 2	1008
andere nl. _____	nee 0	routine controle 1	op indicatie 2	1009

(als "routine-controle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen

veel huilen	nee 0	ja 1	1010
slaapstoornis	nee 0	ja 1	1011
onrust	nee 0	ja 1	1012
voedingsmoeilijkheden	nee 0	ja 1	1013
dreigende mishandeling	nee 0	ja 1	1014
mishandeling	nee 0	ja 1	1015
andere, nl _____	nee 0	ja 1	1016

eigen coderingen inzender 1023

1026

e-formulier

*1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

poliklinische nacontrôle gecorrigeerde leeftijd **24 maanden**

geboortedatum : _____

streefdatum contrôle : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 11 1101 1 1

01 registratienummer POPS 1103

02 streefdatum contrôle (dg / mnd / jr) 1111

03 contrôle datum (dg / mnd / jr) 1117

04 niet voor nacontrôle beschikbaar wegens: 1123
wel beschikbaar **0** overleden tussen ontslag en contrôle **1** (datum ___/___/___,
diagnose _____)
verhuisd **2** (nl. naar: _____
contrôle aldaar door: _____)
verdere medewerking door ouders geweigerd i.v.m. goede toestand kind **3**
verdere medewerking door ouders geweigerd i.v.m. slechte toestand kind **4**

05 lengte (cm) b.v. 88 cm : 088 1124

06 gewicht (kg, 1 decimaal) b.v. 13,1 kg : 13 1 1127 ,

07 schedelomtrek (cm) 1130

psychomotoriek

(zie ook bijgevoegde handleiding onderzoekschema volgens Dr. H. J. van Wiechen)

18 maanden:				
08 stapelt 2 blokjes	ja **0**	nee **1**	1132	
09 gaat op onderzoek uit (m)	ja **0**	nee **1**	1133	
10 zegt 3 "woorden" (m)	ja **0**	nee **1**	1134	
11 wijzen/pakken van 2 genoemde voorwerpen	ja **0**	nee **1**	1135	
12 loopt los	ja **0**	nee **1**	1136	
13 gooit bal zonder om te vallen	ja **0**	nee **1**	1137	
24 maanden:				
15 stapelt 3 blokjes	ja **0**	nee **1**	1139	
16 doet anderen na (m)	ja **0**	nee **1**	1140	
17 drinkt zelf uit beker (m)	ja **0**	nee **1**	1141	
18 zegt "zinnen" van 2 woorden (m)	ja **0**	nee **1**	1142	
19 doet op verzoek bal in doos	ja **0**	nee **1**	1143	
20 raapt vanuit hurkzit iets op	ja **0**	nee **1**	1144	
21 loopt goed los	ja **0**	nee **1**	1145	
30 maanden:				
22 stapelt 6 blokjes	ja **0**	nee **1**	1146	
23 plaatst ronde vorm in stoof	ja **0**	nee **1**	1147	
24 trekt kledingstuk uit (m)	ja **0**	nee **1**	1148	
25 eet zelf met lepel (m)	ja **0**	nee **1**	1149	
26 noemt zichzelf bij eigen naam of "ik" (m)	ja **0**	nee **1**	1150	
27 wijst 5 voorwerpen aan in boek	ja **0**	nee **1**	1151	
28 schopt bal weg	ja **0**	nee **1**	1152	

formulier nummer POPS : _____

29 afwijkingen centraal zenuwstelsel (m.n. tonus, motoriek, reflexen)	nee 0 suspect 1 duidelijk afwijkend 2		1153
	indien suspect, a.v.p. toelichten _____		
30 afwijkingen perifeer zenuwstelsel (Erbse parese, facialis parese, abducens parese e.d.)	nee 0 ja 1		1154
31 convulsies	nee 0 ja zonder EEG-afwijkingen 1 ja met EEG-afwijkingen 2		1155
32 fysiotherapie	nee 0 alleen periodiek adviezen aan ouders 1		1156
	geregelde behandeling door fysiotherapeut (N.D.T. = Bobath; Voyta, enz.) 2		
33 afwijkingen tractus respiratorius	bronchopulmonale dysplasie nee 0 ja 1		1157
	Mikity Wilson nee 0 ja 1		1158
	andere chron. luchtwegafwijkingen nee 0 ja 1		1159
	recidiv. bovenste luchtweginfecties nee 0 ja 1		1160
	recidiv. (broncho) pneumonie nee 0 ja 1		1161
	andere infectieuze aandoeningen nee 0 ja 1		1162
34 afwijkingen tractus digestivus	voedingsproblemen (organisch) nee 0 ja 1		1163
	dyspepsie nee 0 ja 1		1164
	andere nee 0 ja 1		1165
35 hernia's	inguinalis nee 0 ja 1 dubbelzijdig 2		1166
	umbilicalis nee 0 ja 1		1167
	geopereerd nee 0 ja 1		1168
36 gehoorsafwijking	twijfel ouders en/of arts nee 0 ja 1		1169
	afwijkend audiologisch onderzoek nee 0 ja 1		1170
37 oogafwijkingen	**retrolentale fibroplasie** nee 0 licht 1 ernstig 2		1171
	(licht = nog redelijke visus, ernstig = vrijwel blind aan één of beide ogen)		
	strabisme nee 0 ja 1		1172
	andere afwijking, nl. _____ nee 0 ja 1		1173
38 ziekenhuisopname	tussen vorige POPS-contrôle en deze nee 0 ja 1		1174
	indicatie _____		
kaart nr. 12			1201 1 2
39 geconsult. overige specialisten	**oogarts** nee 0 routine contrôle 1 op indicatie 2		1203
	KNO-arts nee 0 routine contrôle 1 op indicatie 2		1204
	(kinder)neuroloog nee 0 routine contrôle 1 op indicatie 2		1205
	orthoped. chir. nee 0 routine contrôle 1 op indicatie 2		1206
	revalidatiearts nee 0 routine contrôle 1 op indicatie 2		1207
	kindercardioloog nee 0 routine contrôle 1 op indicatie 2		1208
	andere nl. _____ nee 0 routine contrôle 1 op indicatie 2		1209

(als "routine-contrôle" aangeven wanneer ± alle nagecontroleerde kinderen door de betreffende specialist worden gezien, b.v. consult oogarts als routine wanneer u alle ex-prematuren poliklinisch laat nazien op retrolentale fibroplasie.
als „op indicatie" aangeven, wanneer het consult plaatsvindt omdat er waarschijnlijk afwijkingen op dat terrein zijn, b.v. wanneer u het kind verwijst omdat de moeder denkt dat het kind niet goed ziet).

40 psychosociale problemen	**veel huilen** nee 0 ja 1		1210
	slaapstoornis nee 0 ja 1		1211
	onrust nee 0 ja 1		1212
	voedingsmoeilijkheden nee 0 ja 1		1213
	dreigende mishandeling nee 0 ja 1		1214
	mishandeling nee 0 ja 1		1215
	andere, nl. _____ nee 0 ja 1		1216
eigen coderingen inzender			1223
			1228

formulier nummer POPS : _____

41 socio-economische groep: **moeder:** beroep _____ **vader:** beroep _____ 1233 [ ] niet invullen
opleiding _____ opleiding _____

wijze van **ziektekostenverzekering:** verplicht/vrijwillig/particulier

42 geboortedatum moeder (dg / mnd / jr) 1234 [ ][ ][ ][ ][ ][ ]

43 lengte moeder (cm) 1240 [ ][ ][ ]

44 lengte vader (cm) 1243 [ ][ ][ ]

45 verdere bijzonderheden, die u tot nu toe niet hebt kunnen coderen, bijvoorbeeld:

later vastgestelde congenitale afwijking (cor vitum, cong.heupdysplasie e.d.)

nee **0** ja **1** onbekend **9** 1246 [ ]

indien deze vraag met ja beantwoord is, gaarne toelichten

_____

ziekte of aandoening, die (waarschijnlijk) geen verband houdt met de vroegere pre- of dysmaturiteit

nee **0** ja **1** onbekend **9** 1247 [ ]

indien deze vraag met ja beantwoord is, gaarne toelichten

_____

Indien vraag 29 (CZS-afwijkingen) met suspect (1) of duidelijk afwijkend (2) beantwoord is, a.v.p. nader definiëren:

46 conclusie na 2 jaar nacontrole: normaal **0** lichte handicap **1** ernstige handicap **2** 1248 [ ]

toelichting:

lichte handicap: afwijking, ondanks welke het kind (waarschijnlijk) een gewone school zal kunnen bezoeken, en normaal in de maatschappij zal kunnen functioneren.

(bv. visus- of gehoorstoornis die met hulpmiddelen redelijk te corrigeren is, lichte afwijking CZS, lichte mentale retardatie d.w.z. DQ 80-90 of 3-4 maanden ontwikkelingsachterstand)

ernstige handicap: afwijking, waardoor het kind (waarschijnlijk) geen gewone school zal kunnen bezoeken, en die ernstig zal ingrijpen in het normale leven.

(bv. ernstige visus- of gehoorstoornis, ernstige afwijking CZS, ernstige retardatie d.w.z. DQ <80 of 5 of meer maanden ontwikkelingsachterstand)

47 registratienummer POPS _____

f-formulier

f_1

project onderzoek prematuritas en SGA in nederland (POPS)

praeventiefonds subsidie nr. 28-766

formulier nummer POPS : _____

geboortedatum : _____

datum van overlijden : _____

codeerinstructie:
als een (deel van een) gegeven onbekend is, coderen met 999.
indien niet van toepassing 888.

kaart nr. 13 1301 [1 | 3]

01 **registratienummer POPS** 1303 [ ]
1304 [| |]
1307 [| | |]

02 **is obductie verricht?** ja 0 nee 1 1311 [ ]

09 **heeft de obductie nieuwe diagnose(n) opgeleverd?** nee 0 ja 1 1312 [ ]

zo ja, welke? _____

APPENDIX G

PSYCHO - MOTORISCHE ONTWIKKELING 0 - 15 MND.

naam: | geb.datum: | zwangerschapsduur weken | Leeftijd in weken of maanden | reg.nr.

		R L	R L	R L	R L	R L	R L	R L	R L	R L	R L	R L	R L	opmerkingen
4 wkn 1 mnd	1. Ogen fixeren													
	2. Reageert op toespreken (M)													
	3. Beweegt armen evenveel													
	4. Beweegt benen evenveel													
	5. Heft kin even van onderlaag													
8 wkn 2 mnd	6. Lacht terug (M)													
	7. Volgt met ogen én hoofd													
13 wkn 3 mnd	8. Handen af en toe open													
	9. Kijkt naar eigen handen (M)													
	10. Maakt geluiden terug (M)													
	11. Blijft hangen bij optillen onder de oksels													
	12. Heft in buikligging hoofd tot 45°													
26 wkn 6 mnd	13. Speelt met handen middenvoor													
	14. Pakt in rugligging voorwerp binnen bereik													
	15. Neemt hoofd mee bij optrekken tot zit													
	16. Draait hoofd naar geluid													
	17. Bij vertikaal optillen, benen gebogen of trappelen													
	18. Kijkt rond met 90° geheven hoofd													
39 wkn 9 mnd	19. Pakt voorwerp over													
	20. Houdt voorwerp vast, pakt nog een voorwerp in andere hand													
	21. Speelt met beide voeten (M)													
	22. Rolt zich om van rug naar buik en omgekeerd (M)													
	23. Kan hoofd goed ophouden in zit													
	24. Zit op billen, ook met gestrekte benen													
	25. Zegt dada - baba of gaga (M)													
52 wkn 12 mnd	26. Blijft los zitten													
	27. Pakt propje met duim en wijsvinger													
	28. Kruipt vooruit, buik op grond (M)													
	29. Trekt zich op tot staan (M)													
	30. Zwaait "dag,dag" (M)													
	31. Brabbelt bij zijn spel (M)													
65 wkn 15 mnd	32. Doet blokje in/uit doos													
	33. Speelt "geven en nemen" (M)													
	34. Kruipt, buik vrij van de grond (M)													
	35. Loopt langs (M)													
	36. Begrijpt enkele dagelijks gebruikte woorden (M)													
	37. Gebruikt twee woorden met begrip (M)													

samenvatting:

Onderzoeksschema volgens Dr.H.J.van Wiechen.

(gewijzigde uitgave 1981)

Op de aanbevolen onderzoekleeftijden toonde tenminste 90% van een groep Nederlandse kinderen de betreffende ontwikkelingskenmerken ("leeftijdsspreiding ontwikkelingskenmerken zuigelingen periode" N.I.P.G./T.N.O. 1979)

Andere gewaadpleegde bronnen, Touwen 1973, Cools & Hermanns 1975.

PSYCHO - MOTORISCHE ONTWIKKELING 18 - 54 MND.

naam: | Leeftijd in jaren en maanden | req.nr.

geb.datum:

		R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	opmerkingen
18 mnd	38. Stapelt 2 blokjes																					
	39. Gaat op onderzoek uit (M)																					
	40. Zegt 3 'woorden' (M)																					
	41. Wijzen/pakken van 2 genoemde voorwerpen																					
	42. Loopt los																					
	43. Gooit bal zonder om te vallen																					
2 jr	44. Stapelt 3 blokjes																					
	45. Doet anderen na (M)																					
	46. Drinkt zelf uit beker (M)																					
	47. Zegt 'zinnen' van 2 woorden (M)																					
	48. Doet op verzoek bal in doos																					
	49. Raapt vanuit hurkzit iets op																					
	50. Loopt goed los																					
2 jr 6 mnd	51. Stapelt 6 blokjes																					
	52. Plaatst ronde vorm in stoof																					
	53. Trekt kledingstuk uit (M)																					
	54. Eet zelf met lepel (M)																					
	55. Noemt zichzelf bij eigen naam of "ik" (M)																					
	56. Wijst 5 voorwerpen aan in boek																					
	57. Schopt bal weg																					
3 jr	58. Bouwt trein met schoorsteen na																					
	59. Tekent vertikale lijn na																					
	60. Plaatst 3 vormen in stoof																					
	61. Zegt 'zinnen' van 3 of meer woorden (M)																					
	62. Wijst 4 lichaamsdelen aan																					
	63. Fietst op driewieler (M)																					
3 jr 9 mnd	64. Bouwt brug na																					
	65. Houdt potlood met vingers vast																					
	66. Plaatst 4 vormen in stoof																					
	67. Trekt eigen kledingstuk aan (M)																					
	68. Praat tijdens het spel (M)																					
	69. Vraagt waarom (M)																					
	70. Springt met beide voeten tegelijk																					
4 jr 6 mnd	71. Tekent kruis na																					
	72. Wast, droogt handen (M)																					
	73. Is goed verstaanbaar voor anderen																					
	74. Vertelt wat thuis of elders gebeurd is (M)																					
	75. Legt op verzoek blokje op/onder/voor/achter/naast stoel																					
	76. Kan minstens 5 tellen op één voet staan																					

samenvatting:

Onderzoekschema volgens Dr. H.J. van Wiechen (gewijzigde uitgave 1981).

De meeste ontwikkelingskenmerken worden op de aanbevolen onderzoeksmomenten getoond door tenminste 90% van een groep Nederlandse kinderen (Schlesinger-Was, 1981).
Andere geraadpleegde bronnen: Cools en Hermanns, 1977; Schaerlaekens, 1977.

APPENDIX H

Deelnemerslijst Kinderartsen POPS 1983
(Project onderzoek Prematuritas en Small for Gestational age)

1. AMSTERDAM	Academisch Ziekenhuis der Vrije Universiteit	Prof.Dr.C.Versluys Mw.J.Derksen-Samsom Mw.D.H.van der Vorm
2. AMSTERDAM	Academisch Medisch Centrum	Mw.Dr.J.G.Koppe M.J.K.de Kleine Mw.J.H.Kok Dr.R.de Leeuw Mw.A.Marinkovic-Ilsen Mw.H.Smolders-de Haas
3. GRONINGEN	Academisch Ziekenhuis	Dr.A.Okken S.Bambang Oetomo
4. LEIDEN	Academisch Ziekenhuis	Prof.Dr.J.H.Ruys Mw.M.van de Bor Mw.A.den Ouden Mw.D.van Zoeren-Grobben
9. MAASTRICHT	Ziekenhuis St.Annadal	Prof.Dr.L.H.J.Ramaekers Dr.C.E.Blanco W.J.Maertzdorf Dr.F.J.Walther
5. NIJMEGEN	St.Radboud Ziekenhuis	Dr.J.M.Boon Dr.L.A.A.Kollée C.H.Schröder T.S.Thé
6. ROTTERDAM	Sophia Kinderziekenhuis	Prof.Dr.J.W.Mettau W.Baerts Dr.W.P.F.Fetter Dr.P.J.J.Sauer
7. UTRECHT	Wilhelmina Kinder-Ziekenhuis	R.Ch.Senders B.P.Cats Mw.I.van Ertbruggen L.J.Gerards Mw.T.G.Krediet
005. ALKMAAR	Medisch Centrum Alkmaar	J.F.van der Blij
006. ALMELO	Stichting Streek-ziekenhuis Almelo	R.P.Beekman N.Hofstee F.J.A.M.Holtus
007. ALPHEN A/D RIJN	Ziekenhuis Rijnoord	D.K.Nanlohy
008. AMERSFOORT	Stichting Prot.-Chr. Ziekenhuis "De Lichtenberg"	Mw.H.J.Dijkhuis A.van Rhijn Dr.H.G.Scholten

010. AMSTERDAM	Andreas Ziekenhuis	Dr.J.W.C.de Groot
		Mw.M.J.van Houten
011. AMSTERDAM	Sint Lucas Ziekenhuis	Mw.M.K.Sanders
013. APELDOORN	Juliana Ziekenhuis	R.F.Oosterkamp
		Dr.H.G.Sie
012. APELDOORN	Lukas Ziekenhuis	A.J.W.Leenders
014. ARNHEM	Gemeenteziekenhuis	R.J.de Boer
		W.Brussel
		Mw.B.M.Lankester-Knape
		J.Verhage
		J.H.Wilton
015. ARNHEM	St.Elisabeth's Gasthuis	R.J.de Boer
		W.Brussel
		Mw.B.M.Lankester-Knape
		J.Verhage
		J.H.Wilton
073. ARNHEM	Hervormd Diaconessen-	Mw.R.H.M.Dijkman-Neerinckx
	huis	K.T.Kwik
016. ASSEN	Wilhelmina Ziekenhuis	G.F.Nelck
		Mw.M.L.Vos-Bender
		H.Wierenga
017. BERGEN OP ZOOM	Stichting Ziekenhuis	H.W.van Kerkwijk
	"Lievensberg"	L.G.M.Wilberts
099. BLARICUM	Streekziekenhuis Gooi-	Mw.G.Engel
	Noord: Diakonessenhuis,	C.E.van Marle
	Naarden; Majella	E.F.J. Notermans
	Ziekenhuis,Bussum	
	Ziekenhuis	
	St.Jan-Hoog-Laren	
074. BOXTEL	St.Liduina Stichting	B.E.M.van den Boezem
		G.J.van de Vlist
020. BREDA	St.Ignatius Ziekenhuis	Th.J.I.M.van Heijst
		H.J.Werre
046. BRUNSSUM	St.Gregorius Ziekenhuis	M.Soewarso
036. COEVORDEN	Sticht.Streekziekenhuis	C.Blok
	Coevorden/Hardenberg	Mw.I.Dominicus
021. DELFT	Reinier de Graaf	Mw.A.L.T.Overbeek-van Gils
	Stichting/St.Hippolytus	P.J.C.v.d.Straaten
	Ziekenhuis	L.Vlasveld
022. DEN HELDER	Stichting Gemini	Dr.N.Beganovic
	Ziekenhuis	J.A.M.v.d.Ham
		A.M.P.Koolen
023. DEVENTER	Stichting St.Jozef	Mw.A.H.Cromme-Dijkhuis
	Ziekenhuis/St. Geer-	Dr. H. Holl
	truiden Ziekenhuis	Dr.J.J.van der Vlugt

024. DOETINCHEM	St.Jozef Ziekenhuis	J.Blijleven R.H.H.Wilms
075. DOKKUM	Prot.-Chr. Ziekenhuis "De Sionsberg"	P.A.van der Bijl K.Went
025. DORDRECHT	Gemeente Ziekenhuis	R.Schornagel C.E.Vos
027. DORDRECHT	Diaconessenhuis "Refaja"	N.Ceelie Mw.C.M.E.Smit
026. DORDRECHT	R.K.Ziekenhuis	J.Hagendoorn Mw.I.C.van Kesteren
028. EINDHOVEN	Stichting "Catharina- Ziekenhuis"	L.T.F. Janssen A.G.W.M.Tielens Dr.J.J.J.Waelkens
097. EINDHOVEN	Diaconessenhuis	B.I.Agoston J.Toorman
029. EINDHOVEN	Stichting St.Josephziekenhuis	Mw.D.Lambooy-van Laar Dr.E.J.P.Lommen Dr.C.de Monchy
030. EMMELOORD	Dr.J.H.Jansenziekenhuis	Mw.G.Nijessen
091. ENSCHEDE	Ziekenhuis van de Vereniging "Ziekenzorg"	J.H.W.Boeve H.de Nijs Bik
077. GELEEN	Medisch Centrum Geleen	F.A.Rive
031. GOES	Stichting Oosterschelde Ziekenhuizen: "De Bevelanden", Goes Zweedse Rode Kruis Ziekenhuis, Zierikzee	Dr.P.W.de Haas H. Verwey
100. GORINCHEM	Het Streekziekenhuis Prinses Beatrix	P.Zwart Dr.W.A.R.Huybers
032. GOUDA	Bleuland Ziekenhuis	E.J.C.Schipper C.V.Tjon Pian Gi
033. GOUDA	St.Jozef Ziekenhuis	Mw.A.F.F.Manusama Mw.F.Thijssen-Bos
002. 's-GRAVENHAGE	Juliana Kinder- ziekenhuis	G.F.Drejer F.H.M.Jansen G.M.de Jong J.M.Kouwenberg Mw.M.M.Wagenvoort
094. GRONINGEN	R.K.Ziekenverpleging onder de titel van "Onze Lieve Vrouwe Behoudenis der Kranken"	H.D.Hamming N.Sorgedrager H.A.Woltil
101. HARLINGEN	Streekziekenhuis "Oranjeoord"	M.Moens

037.	HEEMSKERK	Sint Jozef Ziekenhuis	P.Harmsen J.W.L.H.Meertens
038.	HEEMSTEDE	Diaconessenhuis	Mw.E.C.van Meeuwen Mw.H.H.Kiezebrink-Lindenhovius
039.	HEERENVEEN	De Tjongerschans	C.J.P.Weyer Tj.Wiersma
040.	HEERLEN	"De Wever" Ziekenhuis	C.H.N.Brackel Mw.Dr.M.L.M.Houben P.M.V.M.Theunissen J.M.J.Sijstermans
041.	HELMOND	St.Lambertus Ziekenhuis/St.Willebrordus Ziekenhuis, Deurne	R.P.Droog J.P.de Jager Dr.P.J.H.Wijers
078.	's-HERTOGENBOSCH	Carolus Ziekenhuis	R.J.G.S.Heydendael G.J.van der Vlist
042.	's-HERTOGENBOSCH	Groot Ziekengasthuis	J.H.Hoekstra F.A.E.Nabben A.H.F.van Olphen
098.	's-HERTOGENBOSCH	Protestants Ziekenhuis "Willem Alexander"	B.E.M.van den Boezem Dr.W.van Lookeren Campagne
079.	HILVERSUM	Diaconessenhuis	Mw.W.A.Kingma
081.	HOOGEVEEN	Ziekenhuis "Bethesda"	J.H.M.Bollen J.F.Janssen
043.	HOORN	Algemeen Streekziekenhuis "West-Friesland	Dr.B.Baldewsing P.C.Overberg
044.	HOORN	St.Jans Gasthuis	J.G.Drewes L.J.van Oudheusden
045.	KAMPEN	Ziekenhuizen N.W.Overijssel/Stadsziekenhuis	Mw.M.van Ruth
046.	KERKRADE	St.Jozef Ziekenhuis St. Elisabethkliniek, Heerlen	A.J.da Costa
047.	LEEUWARDEN	Medisch Centrum Leeuwarden	P.A.van der Bijl Mw.H.L.E.Kamann K.Went
003.	LEIDEN	Diaconessenhuis	Mw.A.Talma Mw.G.M.A.Swart
001.	LEIDERDORP	St.Elisabeth-Ziekenhuis	Dr.S.E.Bos Mw.A.R.Smit
004.	LEIDSCHENDAM	Sint Antoniushove	Th.A.Nijenhuis Mw.M.H.Ens-Dokkum
102.	LELYSTAD	Zuiderzeeziekenhuis	H.J.J.Jacobs Mw.A.S.G.Kossakowski

049. MEPPEL	Hervormd Diaconessen-huis	Dr.I.M.Baldew A.C.M.van Kessel
082. MIDDELBURG	Het Gasthuis	H.Doorn
050. NIJMEGEN	Canisius-Wilhelmina Ziekenhuis	F.J.L.M. Hoevenaars Dr.P.M.V.van Wieringen Mw.C.L.M.van der Zee
051. OSS	St.Anna Ziekenhuis	H.L.P.Smeets
052. PURMEREND	St. Liduina Ziekenhuis	J.L.Ket J.B.Wibawa
105. ROOSENDAAL	Ziekenhuis "St.Franciscus"	Dr.F.A.M.Meersschaert A.R.M.Mourmans
083. ROTTERDAM	Sint Clara Ziekenhuis	B.C.van Pelt R.Rodrigues Pereira
057. ROTTERDAM	Stichting Van Dam-Bethesda Ziekenhuis	J.H.G.Zwijnenberg
054. ROTTERDAM	Ziekenhuis "Eudokia"	P.A.LeMaire H.Oving
084. ROTTERDAM	Ikazia Ziekenhuis	W.J. den Ouden
055. ROTTERDAM	St.Franciscus Gasthuis	Mw.J.C.M.B.Versteeg Mw.C.J.A.van de List-Nuver Mw.J.C.M.Stigter
056. ROTTERDAM	Zuiderziekenhuis	Mw.A.M.Oudesluys-Murphy
058. SCHIEDAM	Schieland Ziekenhuis	Mw.A.E.C.Crone-Venneman B.A.Leliveld
059. SITTARD	Ziekenhuis"De Goddelijke Voorzienigheid"	J.J.M.Peters E.J.M.Raven Dr.S.P.M.van der Zee
060. SNEEK	St.Antonius Ziekenhuis	R.van Eijk R.J.Bakker
103. STADSKANAAL	Prot.-Chr.Ziekenhuis "Refaja"	Mw.Y.C.Bastiaans A.M.Voorhoeve
085. TILBURG	St.Elisabeth-Ziekenhuis	R.A.Holl Dr.W.H.Puyn J.A.Rammeloo
061. TILBURG	Maria-Ziekenhuis	J.R.Marcar H.M.J.Klinkers A.S.Tibosch
093. UTRECHT	Ziekenhuis Overvecht	Dr.T.W.J.Schulpen
096. VEENENDAAL	"Juliana Ziekenhuis"	B.S.Voorbrood
062. VEGHEL	Stichting St.Joseph Ziekenhuis	Mw.W.van de Broek-Hotke

063. VELP	Het Ziekenhuis	R.J.de Boer W.Brussel Mw.B.M.Lankester-Knape J.Verhage J.H.Wilton
064. VENLO	Stichting Ziekenhuis Venlo-Tegelen	Mw.A.W.M.Gierlings
066. VLISSINGEN	Stichting Bethesda-St.Josephziekenhuis	Mw.E.G.Jansen
086. WAGENINGEN	Stichting Pieter Pauw	H.Th.Spit
104. WARNSVELD	Het Nieuwe Spittaal	L.H.A.Hinkofer F.E.L.M.Sutorius
087. WINSCHOTEN	St.Lucas-ziekenhuis	R.A.Elias H.C.van Weert
088. WINTERSWIJK	Stichting Ziekenhuis-voorzieningen Oost-Achterhoek	W.G.Bliek
092. WOERDEN	Hofpoort Ziekenhuis	Mw.G.W.D.Bloem Mw.M.C.van Doornik P.A.W.A.Renardel de Lavalette
067. IJMUIDEN-OOST	Zeeweg Ziekenhuis	A.G.Ketel Mw.N.A.L.Biervliet-Dahlberg
089. IJSSELSTEIN	Interconfessioneel Streekziekenhuis "Isselwaerde"	P.A.W.A.Renardel de Lavalette
068. ZEVENAAR	Streekziekenhuis Zevenaar	A.J.Manders F.B.M.Verheij
069. ZWOLLE	Stichting Sophia Ziekenhuis	Mw.Dr.J.J.M.van Collenburg J.F.van Gils Dr.J.G.v.Lookeren Campagne
070. ZWOLLE	Ziekenhuis "De Weezenlanden"	Mw.Dr.J.J.M.van Collenburg F.van der Logt Mw.Dr.K.G.N.Tjoa

APPENDIX I

ENQUETE-FORMULIER
Project Onderzoek Prematuritas en SGA in Nederland (POPS)
Praeventiefonds subsidie nr. 28-766

ziekenhuis:
arts :
datum :

---

registratienummer kliniek
eigen classificatie (a-formulier vraag 44): 0 1 2

Gegevens kliniek neonatologie:
totaal aantal couveuzes: >8=0 6-8=1 4-6=2 <4=3
mogelijkheid voor CPAP>24 u ja=0 nee=1
mogelijkheid voor IPPV>24 u ja=0 nee=1
bijzondere aandacht/interesse voor i.c.: ja=0 nee=1
kinderartsen (full-time):
minstens 1 met subspecialisme neonatologie ja=0
algemene kinderartsen >2=1 2=2 1.5-2=3 1=4
assistenten: in opleiding ja=0 vakantie =1 geen=2
aparte verpleegkundigen voor i.c. ged. 24 uur: ja=0 discontinu=1
met kind. aantekening: >helft=0 <helft=1
met i.c. neonatologie: >helft=0 <helft=1

Gegevens opvang
overleg over "intra-uteriene" probleemkinderen ja 0 nee 1
incidenteel overleg verloskunde ja 0 onv.1 nee 2
wekelijks overleg verloskunde ja 0 nee 1
mede-bepaling beleid verloskunde ja 0 onv.1 nee 2

Gegevens kliniek verloskunde
assistenten in opleiding ja 0 nee 1
nabijheid van kinderarts c.q. assistent kindergeneeskunde:
aanwezig in kliniek: 24 uur ja 0 nee 1
overdag ja 0 nee 1
aanwezig bij partus:
routinematig bij alle pathologie 0
zo mogelijk, op indicatie durante partu 1
soms niet 2
indien kinderarts niet routinematig aanwezig:
tijdsverloop oproep - aanwezigheid
<5 min.=0 5-10 min.=1 >10 min =2
is, bij afwezigheid kinderarts, i.c. in reanimatieruimte door derden geregeld (gynaecoloog, verloskunde assistent, anaesthesist)
geruime mate 0 beperkt 1 afwezig 2

APPENDIX J

Prediction of risks; prediction sets

Based on the logistic regression analysis, the risk for a certain outcome variable (e.g. mortality) can be estimated for each possible combination of risk factors under consideration. The regression equation used for the calculation of the OR provides us with an estimate of the risk conditional on the choice of a value for all factors considered (including the exposure which plays the same roll as the other risk factors in this case). For all dichotomous factors this means a choice out of 2 possibilities.

There are however some severe drawbacks to this method.

-to obtain an estimate, one must provide a choice for each factor in the logistic regression equation (which in our case contains up to some 25 risk factors). Publication is virtually impossible.

-if the values of some factors are unknown, all possible combinations of these factors should be considered in order to obtain some insight in the way the estimated risk varies with (depends on) these unknown factors.

-the logistic model could give erroneous (or at least unapplicable) results for those combinations of categories that do not occur (frequently) in the actual population.

However, starting with the original equation containing all risk factors, one can perform (just as in the case of assessing interaction) a stepwise backward analysis which "stops" when deleting another risk factor would result in a significant loss of fit for the equation. The risk factors still in the equation constitute a "minimal prediction set", containing as few variables as possible. In the same way, a "significant" prediction set can be constructed, in which all factors are retained that are themselves significantly associated with the outcome. Although prediction might be better if we use the complete set of predictors, in the daily routine it may be worthwhile to use a minimal prediction set; that way, fewer risk factors have to be specified in order to obtain the estimated risks.

Most categories formed by a combination of specific values of these predictors, will contain a substantial number of infants on which the equation is based.

In case the value of a risk factor is unknown, one can estimate the risk for both possible values of that factor in order to elucidate the variation in risks. The number of estimates one has to compute doubles with each unknown factor. Clearly, a small set of predictors minimizes the "chance" of having to deal with a large number of unknown predictors.

Only some of the significant prediction sets for the outcome measures under consideration will be presented here (figures J 1-4). However, based on the "minimal" and "significant" prediction sets we developed a simple computer program that allows the clinician to choose the values of a few risk factors interactively, and that automatically presents the risks for all outcome variables considered in this thesis. These risks give the clinician an estimate of the risk conditional on the knowledge available in a particular case, based only on the knowledge about the risk factors specified in the model. Thus, the risk provided by the logistic regression equation in this program could give the clinician valuable background information, but no more than that. It will certainly not provide an accurate estimate of the chances for a particular infant.

For interested perinatologists these prediction sets are available in the form of an MS-DOS compatible microcomputer program (minimum requirements 512 Kb RAM, 1 floppy disk drive). The authors will be happy to provide a copy, if a preformatted 5 1/4 inch floppy disk is sent to the POPS-secretarial office, Department of Paediatrics, University Hospital, 2333 AA Leiden, the Netherlands.

Figure J 1-2 Example of the estimated neonatal mortality risk, depending on specific values of the predictors. In this case, the neonatal mortality risk for singleton infants is presented versus that for infants from multiple births.

PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE INFANTS (POPS)

estimates of NEONATAL MORTALITY (within 28 days)

PERCENTAGE Gestational age (completed weeks)

Birthweight	24	25	26	27	28	29	30	31	32	33	34	35
2000								11%	7%			
1750							13%	8%	5%			
1500					26%	18%	12%	8%	5%	3%	2%	1%
1250			53%	41%	30%	21%	14%	10%	6%	4%	3%	2%
1000		74%	64%	53%	41%	30%	21%	14%	10%	6%	4%	2%
750	91%	86%	79%	70%	59%	47%	36%	26%	18%			
500	96%											

auto (all sign.predictors) 10 pred.,all shown

F1 = help

when knowledge does not extend beyond PREGNANCY

PMD	no	2
DIN	no	6
HDP	no	7
CGM	no	8
MPR	single	10
CCR	no	13
FEPX	known	16
FEPY	vertex	17
GEA	>table	30
BWG	>table	31

Multiple pregnancy

Estimate: 14.5%
95%ci:[10.9% ,19.0%]

PROJECT ON PRETERM AND SMALL FOR GESTATIONAL AGE INFANTS (POPS)

estimates of NEONATAL MORTALITY (within 28 days)

PERCENTAGE Gestational age (completed weeks)

Birthweight	24	25	26	27	28	29	30	31	32	33	34	35
2000								16%	11%			
1750							18%	12%	8%			
1500					35%	25%	17%	12%	8%	5%	3%	2%
1250			63%	51%	40%	29%	20%	14%	9%	6%	4%	2%
1000		81%	73%	63%	51%	40%	29%	20%	14%	9%	6%	4%
750	94%	90%	85%	78%	69%	58%	46%	35%	25%			
500	98%											

auto (all sign.predictors) 10 pred.,all shown

F1 = help

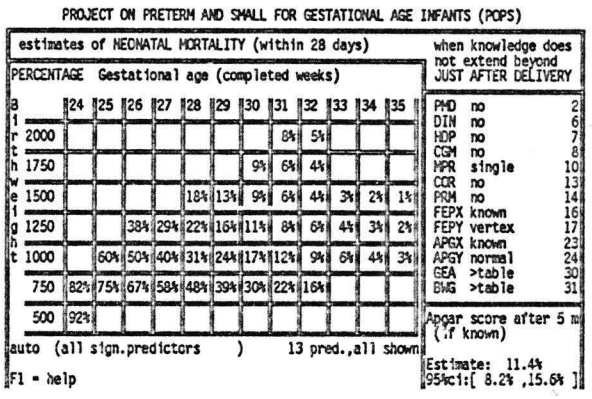
when knowledge does not extend beyond PREGNANCY

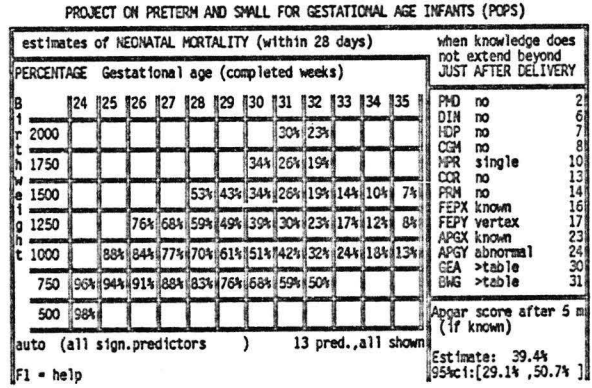
PMD	no	2
DIN	no	6
HDP	no	7
CGM	no	8
MPR	multiple	10
CCR	no	13
FEPX	known	16
FEPY	vertex	17
GEA	>table	30
BWG	>table	31

Multiple pregnancy

Estimate: 20.4%
95%ci:[14.7% ,27.6%]

Figure J 3-4 Example of the estimated neonatal mortality risk, depending on specific values of the predictors. In this case, the neonatal mortality risk for infants with a high Apgar score is presented versus that for infants with a low Apgar score.





OVERLEVINGSKANS (%) POPS 1983

GG \ ZD	23-23^6	24-24^6	25-25^6	26-26^6	27-27^6	28-28^6	29-29^6	30-30^6	31-31^6
2200-2299									80
2100-2199									84
2000-2099								83	87
1900-1999								86	89
1800-1899							83	88	91
1700-1799							84	89	91
1600-1699						78	85	89	92
1500-1599						78	85	89	92
1400-1499						77	84	88	91
1300-1399				53	66	76	83	87	91
1200-1299				50	63	73	81	86	89
1100-1199			32	46	59	70	78	84	88
1000-1099			28	41	54	66	75	81	86
900-999			24	36	49	61	70	78	83
800-899	6	11	19	30	43	55	65	73	79
700-799	4	9	15	25	36	48	59	67	74
600-699	3	7	12	20	30	41	51	61	68
500-599	2	5							
400-499	2								

Overlevingskans van levend geboren kinderen met zwangerschapsduur < 32 weken en/of geboortegewicht <1500 g, als percentage kinderen dat in aansluiting aan de neonatale periode levend naar huis wordt ontslagen. Modelbenadering verkregen uit logistische regressie analyse.

GG \ ZD	32-32^6	33-33^6	34-34^6	35-35^6	36-36^6	37-37^6	38-38^6
1500-1599	92						
1400-1499	93	94	95	95	96	95	95
1300-1399	92	94	95	95	95	95	
1200-1299	92	93	94	94	95	94	
1100-1199	90	92	93	93	94		
1000-1099	88	90	92	92			
900-999	86	88					
800-899	83	85					
700-799	78	82					
600-699	73						
500-599							
400-499							

POPS: Project Onderzoek Prematuritas en Small for gestational age

ZD : Zwangerschapsduur

GG : Geboortegewicht