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MODERATELY PRETERM INFANTS

Studies on Length of Hospital Stay

and Neonatal Outcome

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To Daniel

ABSTRACT

Objective

Moderately preterm infants account for a large proportion of admissions and bed-days in neonatal units. Determinants of length of hospital stay, contemporary measures of morbidity by gestational week and risk factors predicting neonatal morbidity have been poorly studied. The overall purpose of this thesis was to fill these gaps with knowledge to make neonatal care more effective, and to improve short- and long-term outcome for moderately preterm infants.

Methods

Observational studies on length of hospital stay for moderately preterm infants in a longitudinal perspective over 20 years (Paper I) and a cross-sectional multicenter survey (Paper II) were performed. Risk factors for prolonged length of stay were determined in Paper II. Neonatal outcomes were studied in two national population-based studies. Paper III explored neonatal morbidity and interventions stratified by gestational week. In Paper IV, rates of transient tachypnea of the newborn (TTN) and respiratory distress syndrome (RDS) among moderately preterm infants were compared to corresponding rates in late preterm to term infants, and risk factors for these acute respiratory morbidities were evaluated.

Results

Paper I found that length of stay decreased by an average of 14 days from 1983 to 2002, in spite of no concomitant decrease in neonatal morbidity. Paper II showed that only 13% of the variation in length of stay in Swedish neonatal units (which differed up to two weeks) could be attributed to neonatal morbidity. In Paper III, overall rates of common neonatal morbidities were found to vary between 15 and 59% in moderately preterm infants, with a strong inverse relation to birth weight standard deviation score and gestational age at birth. Paper IV demonstrated that besides low gestational age, Cesarean section, male sex and low Apgar score are associated to significantly increased risks for TTN and RDS in moderately preterm infants.

Conclusions

Whereas neonatal morbidity has remained essentially unchanged and high, length of hospital stay has decreased significantly for moderately preterm infants during the last 20 years. Our data suggest that organizational factors of neonatal care are responsible for this development. Moderately preterm infants continue to face a considerable risk of acute respiratory morbidity, which is also predicted by low gestational age, multiparity, Cesarean section, low Apgar score and male sex.

LIST OF PUBLICATIONS

I.   Altman M, Vanpée M, Bendito A, Norman M.
      Shorter Hospital Stay for Moderately Preterm Infants
      Acta Paediatrica, 2006; 95: 1228-1233

II.   Altman M, Vanpée M, Cnattingius S, Norman M.
      Moderately Preterm Infants and Determinants of Length of Hospital Stay
      Archives of Disease in Childhood, Fetal Neonatal Ed. 2009; 94: F414-F418

III. Altman M, Vanpée M, Cnattingius S, Norman M.
      Neonatal Morbidity in Moderately Preterm Infants. A Swedish National
      Population Based Study
      Journal of Pediatrics. 2011 Feb;158(2):239-244.e1. Epub 2010 Sep 9

IV.   Altman M, Vanpée M, Cnattingius S, Norman M.
      Risk Factors for Acute Respiratory Morbidity in Very to Moderately Preterm
      Infants
      Submitted

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
BMI	Body Mass Index
BPD	Bronchopulmonary Dysplasia
CI	Confidence Interval
CS	Cesarean Section
GA	Gestational Age
ICD-10	International Classification of Disease volume 10
IQ	Intelligence Quota
IUGR	Intrauterine Growth Restriction
IVH	Intraventricular Haemorrhage
LOS	Length of Hospital Stay
MBR	Swedish Medical Birth Register
nCPAP	Nasal Continuous Positive Airway Pressure
NEC	Necrotizing Enterocolitis
NIDCAP	Neonatal Individualized Care and Assessment Program
NU	Neonatal Unit
OR	Odds Ratio
PaO2	Partial Pressure of Oxygen in Arterial Blood
PDA	Patent Ductus Arteriosus
PIE	Pulmonary Interstitial Emphysema
PMA	Postmenstrual Age
PNQ	Swedish Perinatal Quality Register
PPHN	Persistent Pulmonary Hypertension of the Newborn
PPROM	Preterm Premature Rupture of Membranes
PVL	Periventricular Leukomalacia
QALY	Quality-Adjusted Life Years
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
SD	Standard Deviation
SEK	Swedish Crown
SGA	Small for Gestational Age
TTN	Transient Tachypnea of the Newborn
USD	United States Dollar

1 INTRODUCTION

A rapidly increasing number of infants are surviving preterm birth since the introduction of modern neonatal care three to four decades ago. Today in Europe, an estimated 9 million children and adolescents have been born preterm. Of all preterm infants, more than two thirds are born moderately preterm which approximates 6-7 million European citizens under the age of 18. In Sweden, 4.4-4.7% of all newborns or 4,500-5,000 in absolute numbers every year are born moderately preterm. A large proportion of these infants are admitted to neonatal care units, some for observation and others for active medical treatment. Due to their large numbers, the moderately preterm infants consume a considerable part of neonatal resources and bed-days.

Although extremely preterm births are associated with the highest risks for adverse outcomes, the much larger group of moderately preterm infants may imply a greater attributable health problem, not only in the neonatal period but also in later life. Moderately preterm infants have been identified as a low risk group by both parents and professionals for decades - contributing to the fact that their peri- and neonatal exposures and morbidities are poorly described - however, recent studies show increased risks for adverse long-term outcomes such as hypertension, diabetes, disability, psychiatric disease and low income.[1-4]

The primary aim of this thesis was to highlight the group of infants born at 30-34 gestational weeks and to provide up-dated information regarding their length of hospital stay and neonatal morbidity. Length of hospital stay was analysed both in the past and in the present, and different factors that may contribute to the length of stay were determined. Rates of neonatal morbidity and use of neonatal interventions in infants born at 30-34 weeks were described in detail and possible risk factors for adverse neonatal outcome were explored.

2 BACKGROUND

2.1 VITAL STATISTICS IN SWEDEN

2.1.1 Population and birth numbers

The Swedish population is currently 9.4 million (31 december 2010). The country is sparsely populated with 21 inhabitants per square kilometer and a majority of the population is located in the southern part of the country. About 85% of the Swedish citizens live in urban areas. In 2010, 14.7% of all inhabitants in Sweden were born outside the country.[5]

In the recent years, birth rates in Sweden have been approximately 110,000 per year. In 2009, perinatal mortality was 5.6/1,000 and neonatal mortality, defined as deaths of live births within the first 28 days of life, has varied between 1.4 and 2.5/1,000 live born infants in the last decade (Figure 1). Pregnancy care is free of charge and virtually all pregnant women adhere to a standardized antenatal care program starting in early pregnancy;[6] 97% of all pregnant women have a routine ultrasound examination at 16 to 18 postmenstrual weeks to determine gestational age (GA). In 1973, 91% of primiparas were younger than 30 years whereas in 2009, the corresponding figure was 59%.[7] Between 2004 and 2008 (i.e., the main study period of this thesis), 22% of the mothers had been born outside the Nordic countries (i.e., Sweden, Denmark, Finland, Iceland, and Norway), 25% were overweight (body mass index (BMI) ≥ 25 kg/m^2) in early pregnancy, daily smoking in early pregnancy decreased from 8.8 to 6.9%, and 47% had higher (college or university) education.[8] The Cesarean section rate was 17% and approximately 10% of all newborn infants were admitted to the neonatal unit.

2.1.2 Preterm births

Of all live born infants in Sweden, approximately 5.6% are preterm, i.e., born before 37 completed gestational weeks and approximately 1.2% are very preterm, i.e. born before 33 completed gestational weeks. As opposed to many other countries, the rates of preterm birth in Sweden have been rather stable since the beginning of the 1970:s.[8] In the US, 10.5% of pregnancies were shorter than 37 weeks in 1990 and this number increased by 21% to 12.7% in 2006.[9]

Figure 1. Neonatal mortality, preterm delivery and multiple births in Sweden 1973-2008. Source:www.socialstyrelsen.se[8]
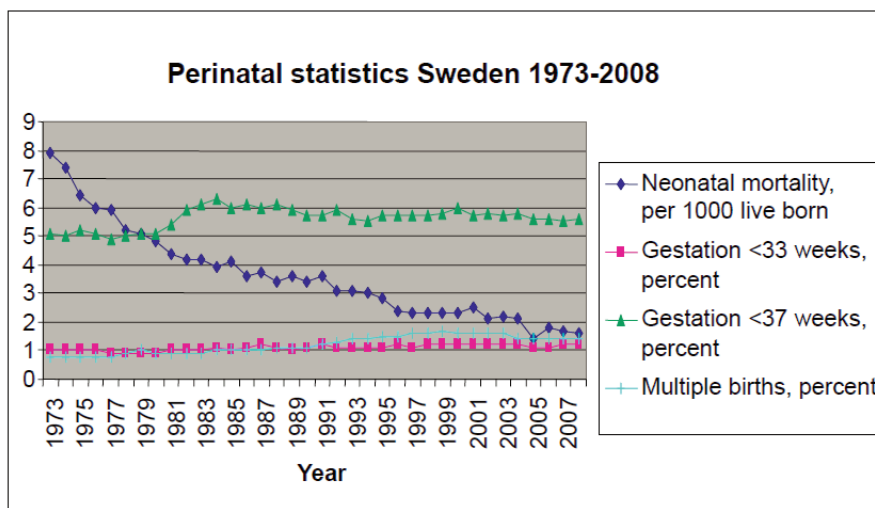
2.2 ORGANIZATION OF NEONATAL CARE IN SWEDEN

2.2.1 The Swedish health care system

Health care in Sweden is a universal public system where all citizens have equal access to health care services. The system is mainly financed by taxes and although the government has the overall responsibility for national health affairs, financing and the task of providing health care is decentralized to 21 political and geographical county councils. In addition to the universal health care system, there are also private medical care alternatives. Some of these are connected to the tax-paid public system and others are financed by private insurances or paid directly by the patient. Hospitals are subdivided into regional (university) hospitals with highly specialized care, county hospitals with specialized care, smaller hospitals with basic care and out-patient primary care units.

2.2.2 Neonatal care

Neonatal care is provided by 39 neonatal units located in an equal number of hospitals responsible for births in pre-defined geographic areas. Highly specialized intensive care and care for extremely preterm or critically ill infants are centralized to seven regional hospitals, each of which corresponds to a larger health region of the country (Figure 2). These university hospitals have neonatal units of level III according to Stark[10] and are situated in the following cities: Umeå (Northern Region), Uppsala (Uppsala-Örebro region), Örebro (Uppsala-Örebro region), Stockholm (Stockholm region), Göteborg (Western region), Linköping (South Eastern region) and Lund (Southern region).

Figure 2: A map of health care regions and municipalities of Sweden.
Picture by: Lokal_profil. CC-BY-SA-2.5.

Northern Region	
Uppsala-Örebro Region	
Stockholm Region	
South Eastern Region	
Western Region	
Southern Region	
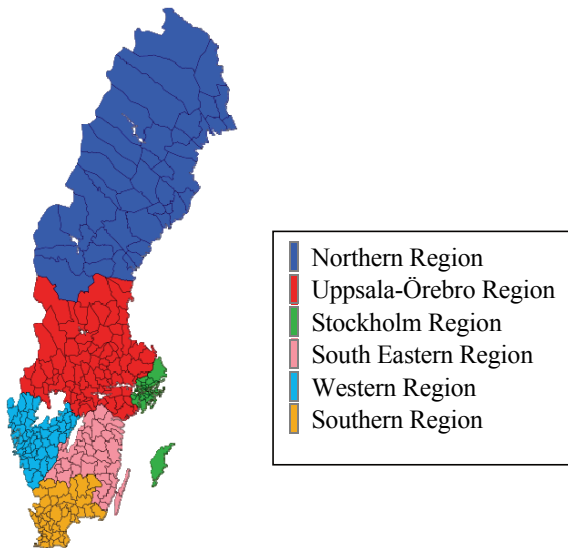
2.2.3 Neonatal unit levels

There is evidence that risks for neonatal mortality and morbidity in extremely preterm or low-birth weight infants are higher in infants born at hospitals providing basic or specialty care as compared to infants born at hospitals with subspecialty neonatal care.[11,12] Transfer between units has also been associated with a higher risk of mortality in very preterm infants.[13] In a Swedish setting, level of neonatal care influenced risk of mortality in preterm infants at gestational ages below 28 weeks.[14,15]

The US Committee on Fetus and Newborn 2003-2004 has proposed that neonatal units should be classified in three levels according to the functional capability and resources of neonatal care.[10] In this classification, Level I (basic) units provide hospital-based neonatal care including resuscitation, evaluation and postnatal care of healthy newborn infants and stabilization of ill or immature infants until transfer to a higher level of care. Level II (specialty) units care for infants born at more than 32 weeks' gestation with physiologic immaturity or who are moderately ill. The units have access to nasal continuous positive airway pressure (nCPAP) treatment and mechanical ventilation can be provided for a short duration of time. Level III (subspecialty) units provide continuous life-support and care for high-risk infants and those with extreme immaturity or critical illness. The committee suggests that regionalized perinatal care systems are created to ensure that each newborn infant is delivered and cared for in an appropriate facility. Furthermore, the committee recommends uniform national standards on training of personnel, equipment and organization of services at each level of neonatal care. Finally, the importance of proper evaluation at each level of neonatal

care by collection of population-based data on short- and long-term outcomes is stressed.

Swedish neonatal units have been divided into a three-level subclassification similar to the American recommendations. According to the classification in the Swedish Perinatal Quality Register (PNQ), eight neonatal units provide neonatal care corresponding to level I, 23 are level II and eight provide highly specialized care and are classified as level III. In addition to these, there are several smaller hospitals without an organized in-patient neonatal unit that can perform resuscitation, care for and evaluate healthy newborn infants, and stabilize ill or immature infants until they can be transferred to the proper level of care.

2.2.4 Recent organizational changes in neonatal care

In the last decade, neonatal care has improved not only in the field of new medical treatments and interventions such as antenatal steroids, surfactant replacement therapy and improved mechanical ventilation devices, but also as a result of an increasing interest in organization of care and care practice. It has been reported that the environment in the neonatal care unit and family involvement may be of importance for the outcome of the newborn infant and the length of hospital stay.[16-20]

Family centered care

The newborn infant's need for a quiet and individually adapted environment includes proximity to the parents and in particular to the mother.[21] In the design of modern neonatal units in Sweden today, much thought is usually given on how to care for the mother and the ill infant as close to each other as possible. In several modern neonatal units, infants that are physiologically stable but still need specialized care, can stay in so-called "family-rooms" together with one or both parents. A randomized controlled trial of family care (from birth) versus standard care in a level II neonatal unit in Stockholm showed a reduction of length of hospital stay by 5 days in the family care (intervention) group.[16] The results suggested that family care had a stronger impact on length of hospital stay in the more preterm infants. There were no differences in neonatal morbidity between the two groups except for a small decrease in moderate bronchopulmonary dysplasia (BPD) in the intervention group.

NIDCAP

Neonatal Individualized Developmental Care and Assessment Program (NIDCAP) is an early intervention care developed by Als et al. to help create a more agreeable environment and care that is customized to the developmental stage of the individual infant.[22] This program has been reported to decrease neonatal morbidity,[23,24] to have positive effects on later neurobehavioural development[24] in very preterm infants and has been implemented in many Swedish neonatal units.

Organized Home Care

In 1998 an early discharge program was tested in two Swedish hospitals as an attempt to shorten length of stay (LOS) in uncomplicated cases.[25] A randomized control trial included physiologically stable preterm infants, allocated either to an early discharge

group with organized home care, or to a control group receiving standard care. In the early discharge program, parents were educated to gavage feed and resuscitate and they had access to domiciliary support from specialized nurses by telephone or home visits. Apnea monitors for home use were used until gavage feeding was ended. The study showed that length of stay could be shortened by an average of nine days in the early discharge group. Quality control of the early discharge program showed no increase in readmissions, no increase in infant morbidity and no mortality after discharge,[25] a continuously large proportion of breastfed infants and a high satisfaction rate among parents.[26]

2.3 PRETERM BIRTH
2.3.1 Definitions of preterm birth

Preterm birth has been defined as birth before 37 weeks (or before 259 days) after the onset of the mother's last menstrual period. Term birth is accordingly defined as birth at 37-41 weeks (or 259-293 days) gestation and post term are births at 42 weeks or more (≥294 days) (Figure 3). This definition is recognized by the World Health Organization, whereas the subdivision of preterm birth is more arbitrary and varies between different settings. The most common terminology uses *extremely preterm birth* (<28 weeks GA), *very preterm birth* (<32 weeks GA), *moderately preterm birth* (32-36 weeks GA) and *late preterm birth* (34-36 weeks GA).[27] However, the interval between 32 and 36 gestational weeks has been subject to a variety of different terminologies, including "late preterm," "near term," "marginally preterm," "moderately preterm," "minimally preterm," and "mildly preterm", terms which all can be found in the literature.[28] The terminology "completed weeks" may also be confusing. To clarify, a combination of gestational weeks and days is commonly used. For example, 34 completed weeks includes pregnancies with a gestational age of 34 weeks + 0 days to 34 weeks and 6 days.

In this thesis entitled "Moderately Preterm Infants", the study group was defined as infants born at 30+0 to 34+6 gestational weeks (Figure 3). We are aware of the inconsistency with the most commonly used definition of "moderately preterm" in the recent literature,[27] but we have chosen to keep our original gestational age limits throughout the work to be able to compare outcomes and results between the included studies. In addition, preterm infants born at 35-36 weeks of gestation are routinely cared for in the maternity unit, whereas preterm infants born at or below 34 weeks of gestation are admitted to neonatal units in Sweden, generating data in our neonatal unit register ("PNQ").

Figure 3. Common classifications of preterm birth and the definition used in our study group.
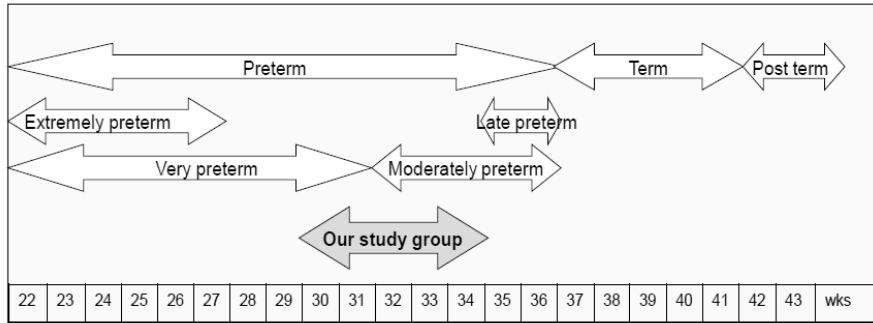
2.3.2 Determination of pregnancy length

Ultrasound measurement of the fetal size was introduced in 1973 in Sweden and has been the routine method of dating pregnancy length in the country since at least 1996.[6] Although first trimester or early second trimester ultrasound for pregnancy dating is considered more accurate than last menstrual date, it can sometimes cause systematic underestimation of pregnancy length, for example in early fetal growth restriction and in female fetuses.[29] Repeated routine fetal ultrasonography assessments have not been implemented in Sweden.

Compared to ultrasound dating, determination of pregnancy length according to last menstrual date is considered to systematically assign pregnancies as 2-3 days longer and to overestimate the number of post term births. This phenomenon may be partially caused by delayed ovulation and/or early growth restriction[30,31] and must be remembered when comparing studies on preterm birth that originate from different methods of pregnancy dating.

2.3.3 Etiology and mechanisms of preterm birth

There are three major obstetric events leading to preterm birth (Figure 4), all of them associated to separate causal chains. The distribution of these obstetric precursors for preterm birth depends on gestational age. Spontaneous preterm labor with intact membranes are either preterm early idiopathic activation of the complex endocrine system involved in the onset of labor or a result of a pathological chain of events starting with infection/inflammation or trauma.[27] Preterm premature rupture of membranes (PPROM) is thought to result from an asymptomatic intrauterine infection leading to inflammation of the amnion and degradation of the fetal membranes.[32] Most of the pregnancies with PPROM end with spontaneous onset of labor within a week. A well-known complication to PPROM is intrauterine and fetal infection. Deliveries on maternal or fetal indications can result in an induced vaginal delivery or a Cesarean section.

Figure 4. Obstetric precursors of preterm birth. From Goldenberg et al.[27]
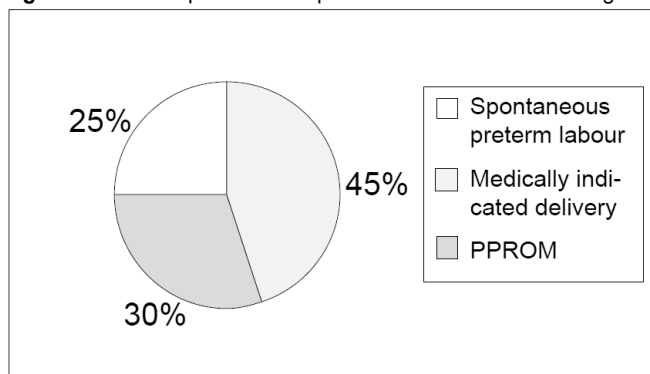
Risk factors for preterm birth

Preterm birth can be seen as a syndrome caused by several interacting mechanisms. Of the currently identified risk factors, four major groups can be seen: maternal characteristics, pregnancy risk factors, risk factors mediated by inflammation and genetic factors. One isolated risk factor is commonly not enough to cause preterm birth.[33] However, if one or several of the identified risk factors can be prevented, the rate of preterm birth in a population could perhaps be reduced, resulting in large positive health effects.[34]

Among maternal characteristics, it is well known that certain ethnic groups have increased risks for preterm birth. In African-American women, preterm birth is as common as 16-18% whereas the Caucasian population have an incidence of 5-9%. The causes for this difference are unknown.[35] A low pre-pregnancy BMI is associated with an increased risk of preterm birth whereas a high pre-pregnancy BMI is associated with increased risks for some congenital anomalies, preeclampsia and diabetes mellitus which are factors that also increase the risk of preterm birth. After a first preterm birth, the risk of another preterm birth is increased 2.5-fold.[27] The risk of repeating very preterm birth is higher than the risk of repeating moderately preterm birth.[36] After a pregnancy complicated by preeclampsia, the next pregnancy is at a doubled risk of preterm birth, despite the absence of preeclampsia in that second pregnancy.[37]

Second, some pregnancy characteristics are known to influence gestational length. An inter pregnancy interval of less than six months results in a doubled risk of preterm birth, presumably because the uterus takes more time to recover from the first pregnancy. Multiple pregnancy is a strong risk factor for preterm birth. Nearly 60% of all twins are born preterm, the majority from spontaneous labor or PPROM. The suggested cause for these preterm births is overdistension of the uterus.[33] Vaginal bleeding, polyhydramniosis, oligohydramniosis are all associated to increased risks for preterm birth.[27]

Third, inflammation has been suggested to be an important cause of preterm birth. The mechanism is thought to be a chemical degradation of the fetal membranes from

inflammatory mediators such as cytokines and prostaglandins which may lead to a premature disruption of the membranes, and stimulation of uterus contractility and cervix maturation, which may initiate preterm labor.[38] Systemic and/or local inflammation responses have been reported or suggested in maternal abdominal surgery, high levels of psychological stress, smoking,[39] use of smokeless tobacco (snuff),[40] intrauterine infection, bacterial vaginosis and other infections such as pyelonephritis, pneumonia, appendicitis and periodontal disease.[27,33] Quantitative genetic analyses show that around 25% of the variation in preterm birth is explained by maternal genetic factors, whereas fetal genetic factors (inherited from both the mother and father) only marginally influence the liability in preterm birth.[41] Intrauterine infections are often chronic, sometimes asymptomatic and are overrepresented in preterm births before gestational week 34 but not thereafter.[38]

Finally, genetic factors seem to contribute or modulate risk of preterm birth. Sisters to women who have undergone preterm birth have an 80% increased risk of preterm birth.[41] Grandparents of women having a preterm birth are more likely to have been born preterm themselves. Certain single-nucleotide polymorphisms have been associated to preterm labor and PPROM.[27]

Obstetric management of a threatening preterm delivery must be a balanced decision between the risk of a continued pregnancy for both mother and infant and the risk of preterm birth for the infant. This decision itself must take into account the cause for preterm labour or iatrogenic delivery versus the estimated risk of neonatal complications, in relation to gestational age and other risk factors that may alter the infant's outcome.

2.3.4 Evaluating outcomes of preterm birth

Information from studies on short- and long term morbidity for preterm survivors of neonatal intensive care is crucial to four groups of people; those who are born preterm, parents that face preterm birth, physicians and other staff members that care for preterm infants and researchers that interpret, compare and communicate results of scientific works to others.[42] To be able to compare results from different study populations, one must use defined and uniform criteria for inclusion, exclusion and outcome measures. The disparities in registration of perinatal death, especially around the border of viability in extremely preterm infants, exemplify this problem.[43] Another example is the suspected selective bias in prospective studies comparing socioeconomic status on risk of preterm birth, where mothers who consented to participate in a study that "requires time, effort and psychological investment" may have a lower risk of preterm birth.[44] There are also the differences in gestational age estimation to take into account (section 2.3.2).

2.4 MORBIDITY IN NEWBORN INFANTS
2.4.1 General morbidity

The panorama of morbidity in newborn infants is dominated by the transition from intrauterine to extra uterine life. Some of the neonatal diagnoses can almost be

considered physiologic changes, while others are life threatening pathologic processes. The most common group of diseases (except hyperbilirubinemia) is disorders of the respiratory system. The spectrum of severity ranges between self-limiting mild symptomatic disorders and fulminant respiratory distress demanding intensive care. Another common morbidity is infections, due to the immature immune system and vulnerability to pathogenic organisms in both term and preterm infants.

2.4.2 Specific morbidity in preterm infants

Transient tachypnea of the Newborn (TTN)

TTN or wet lung disease is a common disorder characterized by a delay in absorption of fetal lung fluid. TTN affects both preterm and term infants, and presents immediately after birth. Chest X-ray films show prominent perihilar vascular marking, patches of infiltration and an increased amount of interstitial fluid. The lungs may be hyperinflated and the diaphragm depressed. TTN often resolves spontaneously within 1-2 days, but some infants may need oxygen therapy and nCPAP. TTN has not been associated with any long-term complications.[45-47]

Respiratory distress syndrome (RDS)

RDS is a common complication from preterm birth and incidence is inversely related to gestational age at birth. RDS is mainly caused by surfactant deficiency. Without surfactant, surface tension in the alveoli is high and lung compliance low. As a result, hyaline membranes are formed followed by alveolar inflammation. Onset of RDS is rapid, usually within a few hours after birth. Typical signs are tachypnea, grunting, and intercostal retractions. Need for oxygen and respiratory efforts increase the first 24-36 hours. The x-ray film shows diffuse atelectasis, air bronchogram and "ground glass" pattern. Treatment for RDS includes supplemental oxygen, nCPAP, mechanical ventilation and administration of exogenous surfactant. Typically, RDS improves after 2-3 days but death from progressive hypoxia and respiratory failure can occur. Severe RDS may also be a precursor of chronic lung disease or BPD. Surfactant therapy increases survival and decreases risk of pneumothorax and BPD. After the introduction of antenatal prophylactic steroid treatment, many cases of RDS have been prevented.[48] Antenatal steroid treatment induces production of surfactant and is currently recommended in Sweden when delivery is expected before 32+6 gestational weeks.[45,47-51]

Pneumothorax/Pulmonary Interstitial Emphysema (PIE)

Leakage of gas from the airways into the pulmonary interstitial space is mostly seen as a complication from ventilator therapy. If the gas diffuses into the pleura, it causes pneumothorax, which may need active drainage. Although rare in moderately preterm infants, pneumothorax is the most common cause for sudden deteroriation during ongoing ventilator treatment.[45]

Hypoglycemia

Blood glucose levels in the newborn infant normally decrease immediately after birth but are usually restored within hours. Severe or long-lasting hypoglycemia may cause

brain damage. The definition of hypoglycemia varies but is in Sweden defined as a plasma glucose level <2.6 mmol/L. Symptoms include jitteriness, irritability, feeding difficulties, hypotonia, apnea, bradycardia or seizures but clinical signs can also be absent, especially in preterm infants. Risk factors for hypoglycemia include asphyxia, hypothermia, respiratory distress, diabetic disease in the mother, fetal growth restriction and preterm birth. Infants at risk are treated with early feeding or intravenous fluids and monitored with repeated plasma glucose determinations. In severe or symptomatic hypoglycemia, intravenous glucose is provided.[45,47]

Bacterial infections

Exposure to microorganisms can be transplacental, ascending, intrapartum and/or postnatal. Systemic infections in the neonatal period are subdivided into two groups according to the time of onset: early onset (within 2 days of postnatal age) and late onset (>2 days of postnatal age). Early onset infections are acquired prior to or during delivery and are dominated by microorganisms such as group B streptococci, enterococci and gramnegative bacteria. Septicemia progresses rapidly if antibiotic treatment is not initiated in time. Predisposing factors are prolonged rupture of membranes, maternal urinary tract infection and prematurity. In late onset infections among preterm infants, nosocomial infections with coagulase-negative staphylococci dominate but staphylococcus Aureus, enterobacteriae and Klebsiella species may also occur. Clinical signs of late-onset systemic infections are usually subtle, with irritability, pallor, feeding difficulties, unresponsiveness, jaundice, apneas and/or tachypnea. Antibiotic treatment is given on wide indications before bacterial infection can be excluded. Among suspected cases, only 15-20% are later confirmed by a positive blood or cerebral fluid culture.[45,47]

Patent Ductus Arteriosus (PDA)

In the fetus, the ductus arteriosus connects the pulmonary artery with the aorta, permitting oxygenated blood from the placenta to by-pass the lungs in favor of other internal organs. After term birth, the ductus arteriosus rapidly closes as a result of increased PaO2 and decreased circulating prostaglandin levels. After preterm birth, the ductus arteriosus can sometimes persist. The hemodynamical effects are evaluated by echocardiography. If a PDA becomes hemodynamically significant and symptomatic, treatment with nonselective cyclooxygenase inhibitors (indometacin or ibuprofen), which inhibit prostaglandin synthesis and induce ductal constriction, can be indicated. Should medical treatment fail or if it is contraindicated, surgical ligation of the PDA can be performed.[45,47,52]

Persistent Pulmonary Hypertension of the Newborn (PPHN)

As the newborn infant starts breathing, pulmonary vasodilation occurs and pulmonary blood flow increases many-fold. If this circulatory transition fails or cannot be sustained, the infant may suffer from PPHN. Symptoms usually show early, before 12 hours of age. Clinical signs are severe hypoxia, a normal x-ray film, right-to-left shunting of blood seen on echocardiography in the absence of congenital cardiac abnormality. PPHN is often secondary to other morbidities, such as RDS, septicemia,

meconium aspiration or asphyxia. Treatment with nitric oxide - a potent and selective pulmonary vasodilator - is usually effective.[45,47]

Hyperbilirubinemia

Neonatal jaundice affects approximately two thirds of newborn infants in their first week of life. It is usually a physiological condition with a benign course but can signal underlying infection, metabolic or hemolytic disease. Unconjugated bilirubin accumulates in newborn infants as a result of high turnover of red blood cells, low glucuronosyl transferase activity in the liver and high enterohepatic recirculation. Severe neonatal hyperbilirubinemia may lead to irreversible brain damage, kernicterus, as high levels of unconjugated bilirubin are neurotoxic. Phototherapy is the treatment of choice for hyperbilirubinemia exceeding 150-250 µmol/L in moderately preterm infants, whereas exchange transfusion may be considered, to quickly decrease higher serum bilirubin in severe cases. Kernicterus in very-moderately preterm infants is nowadays extremely rare although this feared complication has been reported to re-occur in near-term and term infants discharged early without follow-up.[45,47,53-55]

Intraventricular Hemorrhage (IVH)

Approximately 20-25% of all infants with a birth weight lower than 1,500 g are diagnosed with IVH and the vast majority are born before 32 weeks of gestation. IVH is graded I-IV according to severity, where grades III-IV are associated with significantly increased risks for adverse neurodevelopmental outcome. The etiology of IVH is complex and involves hypoxia, hypotension, ventilation disturbances and/or acidosis. The highest risk of IVH is within the first 24-48 hours after birth and by the end of the first postnatal week, most cases with IVH have been diagnosed. Given the increasing incidence of IVH at lower gestational ages, preterm infants with a GA <32 weeks are screened with repeated cranial ultrasonography.[45,47,56]

Periventricular leukomalacia (PVL)

PVL refers to white matter injury of the neonatal brain and is more common after preterm birth. PVL is initiated by ischemia and/or inflammation, with resulting cellular toxicity. White matter injury can be either focal or diffuse. In a Swedish study of extremely preterm infants, 14% had moderate or severe white matter changes on cerebral magnetic resonance imaging-examinations at term-equivalent age.[57] White matter injury is associated with increased risks for cognitive and neurological impairment in later life.[45,47,58]

Necrotizing enterocolitis (NEC)

NEC is a rare but potentially dangerous complication of prematurity. Its etiology is still largely unknown but three predisposing factors have been suggested: decreased oxygenation of the gut, invasion of pathogenic bacterial flora and enteral feedings as energy substrate. The disease is characterized by acute inflammation of the intestinal wall, necrosis, perforations and septicemia. Clinical signs include a distended abdomen and blood in the stools. Feeding with human milk decreases risk of NEC and is thought to promote colonization of the intestines with protective lactobacilli and

bifidobacterium species. Accordingly, enteral administration of probiotics has been suggested as a promising intervention to prevent NEC in preterm infants.[45,47,59]

Retinopathy of prematurity (ROP)

ROP is a well-known complication from unlimited oxygen supplementation after preterm birth, characterized by abnormal vascular growth in the retina which may lead to visual impairment or even blindness. In Sweden, all preterm infants born at 32 gestational weeks or less, are routinely screened for ROP. Treatment of ROP with diode laser photocoagulation is effective and reduces the risk of retinal detachment and visual impairment.[45,47,60]

Bronchopulmonary dysplasia (BPD)

Chronic lung disease or BPD is the most common long-term complication from very preterm birth. The disease is histologically characterized by fewer alveoli and abnormal structure of pulmonary microvasculature. BPD is clinically defined as need for oxygen supplementation at 28 days of postnatal age (mild form) or at 36 weeks of postmenstrual age (moderate form) or need for ventilator at 36 weeks gestational age (severe form).[61] Etiological risk factors include prenatal inflammation, preeclampsia, fetal growth restriction, preterm birth and RDS, which all contribute to defect alveolarization and microvascular development. Strategies for prevention and treatment include early nCPAP, mechanical ventilation with permissive hypercapnia, optimized nutrition including vitamin A supplementation and surfactant treatment in cases with RDS. An increased airway resistance and hyperreactivity of the lung are problems that can linger into childhood, adolescence and even adult ages.[45,47,62]

2.5 THE MODERATELY PRETERM INFANT

2.5.1 Epidemiology

The rate of moderately preterm birth according to the definition used in these studies (birth at 30+0 – 34+6 gestational weeks) is approximately 2%, or 2,200 infants in Sweden each year (3.9% in the US[63]). The majority of infants survive their neonatal period and there are today about 36,000 Swedish citizens under 18 years of age that were born moderately preterm.

Moderately preterm infants face substantially higher risks for adverse neonatal outcome than more mature infants.[64-66] In US neonatal units, the moderately preterm infants have been reported to account for 27-38% of neonatal unit admissions.[67]

2.5.2 Maternal, pregnancy and delivery characteristics

Moderately preterm birth has the same etiology as preterm birth in general (section 2.3.3.), but risk factors are differently distributed. In a population-based Finnish study,[68] the most important risk factors for birth at 32-33 gestational weeks were, in multivariate analyses, multiple birth, followed by elective Cesarean section, primiparity, IVF and smoking. Maternal age did not affect risk of preterm birth in this cohort whereas in a Swedish population-based study,[69] maternal age of more than 34 years was a risk factor for moderately preterm birth. Smoking is a preventable risk

factor for preterm birth at 32-36 gestational weeks, and is there is a dose-response relationship between smoking and preterm birth, especially spontaneous preterm birth.[70]

In our cohort of 4,343 moderately preterm and 467,965 late preterm to term singletons born in Sweden in 2004-2008 (Paper IV), maternal, pregnancy and delivery characteristics were investigated (unpublished data, Table 1). Significant risk factors for moderately preterm birth compared to late preterm to term birth in univariate analysis were: maternal overweight before pregnancy, self-reported smoking in early pregnancy, maternal chronic disease (asthma was the most common diagnosis), assisted conception, preeclampsia, preterm premature rupture of membranes, clinical chorioamnionitis and Cesarean delivery. Maternal age did not significantly affect risk of moderately preterm birth and multiparity protected against moderately preterm birth in univariate analysis.

Table 1. Maternal and pregnancy characteristics and obstetrical interventions in moderately singleton preterm infants compared to late preterm to term infants, univariate analysis.

	Late Preterm to Term Infants (35-41 weeks) (N = 467,629)		Moderately Preterm Infants (30-34 weeks) (N= 4,679)		Odds Ratio (CI)	
	n	%	n	%	OR	CI
Maternal Characteristics						
Maternal age						
<25	65,312	14	678	14	1.0	(ref)
25-29	132,416	28	1,329	28	1.0	0.9-1.1
30-34	175,946	38	1,552	33	0.8	0.8-0.9
35-	93,954	20	1,120	24	1.1	1.0-1.3
Parity						
Primipara	181,702	39	2,639	56	1.0	(ref)
Multipara	285,927	61	2,040	44	0.5	0.5-0.5
BMI						
≤24.9	274,042	66	2,395	62	1.0	(ref)
25.0-29.9	101,600	25	943	24	1.1	1.0-1.1
≥30	37,632	9.1	527	14	1.6	1.5-1.8
Smoking at admission	32,841	7,6	379	10	1.4	1.2-1.5
Chronic disease	38,765	8.3	501	12	1.4	1.3-1.6
Pregnancy						
IVF	18,135	3,9	235	5.4	1.4	1.3-1.6
Preeclampsia	7,649	1.6	777	18	13	12-14
Preterm premature rupture of membranes	4,557	1.0	1,289	30	43	41-47
Chorioamnionitis	321	0.1	56	1.3	18.8	14-25
Mode of delivery						
Vaginal delivery	426,740	91	2,326	50	1.0	(ref)
Cesarean section after onset of labor	18,464	4.0	1,878	40	18.6	18-20
Cesarean section before onset of labor	18,185	3.9	292	6.2	2.9	2.6-3.3
Cesarean section, unspecified	4,240	0.9	183	3.9	7.9	6.8-9.2

2.5.3 Neonatal outcomes

In contrast to studies of very or extremely preterm infants,[14,71] previous studies in moderately preterm infants are not population-based,[67,72,73] have studied cohorts older than 10 years,[72-74] provide no gestational age specific data[67,73-75] or present only a limited number of morbidity measures.[73,74] In addition, several studies of moderately preterm infants have focused on differences in morbidity between infants born near-term or at term,[72-74] whereas the neonatal outcomes at the crossroads of moderately preterm infants are less well established. Thus, there is a lack of contemporary large population-based studies with detailed and gestational age-specific data on neonatal morbidity and risk factors for complications after moderately preterm birth.[76]

Morbidity and interventions in infants born at 30-34 gestational weeks have previously been investigated in a US study of 1,250 infants born in 2001-2003 where Escobar et al. looked at key in-hospital outcomes and readmissions.[67] They found rates of <1% of major neonatal morbidities, such as NEC, IVH and ROP among surviving infants. Pneumothorax was seen in 1.6%, BPD (defined as oxygen use at 36 weeks GA) in 3.2%, and sepsis/meningitis in 2.4% of infants. Within this group of moderately preterm infants, 46% were treated with ventilator and 19% were treated with nCPAP only. Surfactant was administered to 25% and antenatal steroids to 66%. Approximately half the infants were discharged before 36 weeks' gestational age. Readmissions to hospital care within three months occurred in 11%, predicted by male sex and chronic lung disease. Escobar et al concluded that moderately preterm infants experience substantial neonatal morbidity which deserves more research.

Kirkby et al. performed a study of 4,932 infants with a GA of 32-34 weeks, born in the US between 2001 and 2004.[77] NEC and severe IVH were found in less than 1% of the infants, bacterial sepsis in 1-3.5%, PDA in 2-5.5%, chronic lung disease (defined as need for oxygen therapy at 28 days of life) in 0.5-3.5% (higher rates at lower gestational ages). As in the study by Escobar, mechanical ventilation or nCPAP was common (42%). Kirkby et al. concluded that moderately preterm infants constitute a large proportion of neonatal resource use, are subjected to increased morbidity and that it would be important to learn more of the characteristics of this group of infants.

2.5.4 Long term morbidity

Long-term follow-up of moderately preterm infants have shown poor school performance and an increased risk of enrollment in special education programs as compared to term infants.[78] In addition, subjects born moderately preterm have lower IQ and a higher risk of attention and behavior problems,[79] lower cognitive test results[80] and even increased hazard ratios for cerebral pares, developmental delay/mental retardation and seizures.[64] These reports strongly suggest an impact of moderately preterm birth on brain development. However, in an Australian study, there were no differences in socioeconomic status (SES), psychological functioning and health related quality of life in adulthood among 126 subjects born at a mean gestational age of 34 weeks at birth as compared to term controls.[81]

The first Swedish generation of infants born preterm in the modern era of neonatal care has now become young adults. Population-based studies on their long-term outcomes show high risks for impairment and disability in adulthood,[4] in-hospital care for psychiatric disease,[3] prescription of inhaled corticosteroids[82] and Attention Deficit Hyperactivity Disorder (ADHD) in school-age.[83]

To summarize, the group of moderately preterm infants seem to be at considerable risk not only for acute neonatal morbidity, but also for long term adverse health effects.

2.6 RESEARCH TOOLS FOR PERINATAL EPIDEMIOLOGIC STUDIES

2.6.1 The Swedish personal identification number

Every Swedish citizen is provided with a unique personal identification number at birth or immigration, consisting of birth date (yymmdd) followed by a sex-specific individual three-digit code and a one-digit check number. The personal identification number is used in all situations that require identification of an individual, for example in all contacts with the medical care system and in writing patient's journals.[84]

2.6.2 Swedish Medical Birth Register (MBR)

History and purpose

The Swedish Medical Birth Register was started in 1973, with the purpose to evaluate and improve the health of pregnant women and newborn infants by collecting data on perinatal factors. The registry is owned by the Swedish National Board of Health and Welfare, Centre for Epidemiology. Participation in the register is nation-wide and mandatory, thus, the individuals have no right to deny registration.

Contents

Mothers are identified by the Swedish personal identification number and the infant's identification number is linked to the mother's. The registry contains data on social factors, maternal history, pregnancy, delivery and infant. The data source is standardized individual obstetric and pediatric forms that are completed and sent to the register for the large majority of all Swedish births.[85]

Quality

The quality of the Swedish Medical Birth Register has been evaluated and validated against original medical journals three times.[86,87] A more detailed English summary on contents and quality of included variables can be found at the webpage of the Swedish National Board of Health and Welfare.[87] Records have been found missing in approximately 1.4% of all births. For estimation of gestational length, the majority of women in the last decades have undergone ultrasound scanning.[6] The Birth Register uses a hierarchical model to estimate gestational age, which in essence first uses information on ultrasound estimation, then the last menstrual period, and thereafter uses stated information on length of gestation as recorded at the delivery ward. Many variables, such as maternal identification number, birth weight, date of admission to delivery unit and discharge date, hospital codes, multiple birth status and infant sex

have high quality. Use of tobacco products in early pregnancy had 4-9% of missing values. Other variables have a larger proportion of missing data, such as maternal drug use and infants ICD-10 diagnoses[87] and reporting of ICD-diagnoses has been found to differ between hospitals.[86]

2.6.3 Swedish Perinatal Quality Register (PNQ)

History

PNQ was created in 2000 as a local hospital register collecting data from infants that had been admitted to the neonatal unit. Soon, the register grew to include more clinics and by 2004, 21 out of 34 Swedish neonatal units reported all their patients to PNQ. From January 2008 and forward, PNQ contains data on all patients from all Swedish neonatal units.

Purpose

The main purpose is to evaluate quality of neonatal care in Sweden on a continuous basis. The database is located on the internet, which facilitates both reporting and searching for data. Open-access reports on some quality-related outcomes are regularly published online. Clinics have access to the database to see and analyse results and outcomes of their home clinic patients. In addition, it is possible to request a specified unidentified dataset from the PNQ for research purposes.

Contents

PNQ contains information on approximately 60,000 newborn infants (December 2010). The register holds detailed data on maternal characteristics, pregnancy, delivery, acid-base status, neonatal resuscitation, hospital stay, breathing, mechanical ventilation and nCPAP, infections, treatment of infections, neurology, specified pharmacological treatment, treatment with hypothermia, other specified morbidity, other specified interventions, diagnoses (including congenital malformations) classified by ICD-10, discharge data, and detailed data on deceased infants.

Quality

Diagnostic criteria for all morbidity measures are predefined to avoid variation in diagnoses between centres or users. The data is obtained from standardized questionnaires prospectively filled out by physicians during neonatal care and at hospital discharge of each infant. The questionnaires are transmitted to an electronic form and into the database. So far, the PNQ Register has not been properly validated or evaluated.

2.6.4 Comparison of MBR and PNQ

Individually linking information from MBR and PNQ, using the Swedish personal identification number, creates a powerful, population-based tool for studies on perinatal epidemiology. The Medical Birth Register contributes with detailed and valid data on the mother and pregnancy and the PNQ brings a large amount of data on the neonatal period for all infants who have been admitted to neonatal care. The similarities and discrepancies in data between the two registers have not previously been described.

We have compared the correspondence of some variables that can be found in both registries. Information on 4,679 singleton moderately preterm infants born in 2004-2008 was collected from PNQ and linked to the Medical Birth Register. Data on infant characteristics and diagnoses was extracted and compared between the registers.

Infant sex

Reports on sex correlated in 99% of the infants.

Birth weight

The correlation of birth weight between the registers was good (r=0.97, p < 0.001).

Gestational age

The study group was defined by gestational age in PNQ (30-34 weeks). Gestational age was similar in the two registers in 81% of the infants. This finding is consistent with a previous validation of MBR and original journals.[87] The correlation coefficient was 0.83 (p<0.001), but the range of GA in MBR was 27 to 40 gestational weeks. The majority (91%) of the misclassified GA data differed only one week from GA in PNQ. Of the misclassified GA, 84% were classified as one week higher GA in MBR than in PNQ. It is not possible to determine which register that has the more accurate data on gestational age without looking into original records and using information from original ultrasound estimations of pregnancy length.

When comparing gestational age in days, the correlation between the registers was improved. Mean gestational age was 233 (SD 9.4) in PNQ and 234 (9.8) in MBR. The 25th, 50th and 75th percentiles only differed 1 day between the registers and the correlation coefficient was 0.92 (p < 0.001).

Neonatal diagnoses and interventions

For TTN, RDS, BPD, nCPAP and ventilator therapy, calculations on sensitivity and specificity were performed, given the hypothesis that PNQ would have the most accurate data on neonatal diagnoses and interventions. Definitions of sensitivity and specificity are presented in textboxes below.

Sensitivity =	*Specificity =*
True positive	True negative
(True positive + false negative)	(True negative + false positive)
Pos PNQ	Neg PNQ
(Pos PNQ + Pos PNQ – Pos PNQ&MBR)	(Neg PNQ + Pos MBR - Pos PNQ&MBR)

Results are presented in Table 2. The quality of registration of neonatal diagnoses in MBR shows considerable variation when compared to PNQ. Sensitivity and specificity of TTN and RDS are high, whereas BPD, nCPAP and ventilator therapy have low sensitivity but very high specificity.

Table 2. Sensitivity and specificity of reported diagnoses and interventions in 4,679 infants in the Swedish Medical Birth Register (MBR) as compared to the Swedish Perinatal Quality Register (PNQ)

	Positive cases in PNQ & MBR (n)	Positive cases in MBR (n)	Positive cases in PNQ (n)	Sensitivity	Specificity
TTN	479	636	663	96%	96%
RDS	526	593	630	94%	98%
BPD 28d	13	30	57	68%	99%
BPD 36w	11	30	47	73%	99%
nCPAP	405	432	2,034	56%	99%
Ventilator	59	68	275	57%	100%

2.7   HEALTH ECONOMICAL ASPECTS

2.7.1 Costs of neonatal care in Sweden

Budgets and money is of central concern for health policy decisions. The allocation of resources must be directed towards areas that are necessary but also cost-effective. Evaluations of consequences, effectiveness, utility and benefit of specific actions can guide decisions toward this goal. Results of these evaluations affect the routines and methods in every-day work at the health care units.[88] For example, new pharmaceutical treatments can be more expensive than the older medication but may also have less side effects or better results in long-term evaluations and thus cost less in the end. Building an organized Home Care unit with trained staff, vehicles and equipment is expensive but as more infants can be discharged earlier from the neonatal unit, costs for overall health care may still decrease.

A simplified approach to study costs of neonatal care would be to calculate average length of stay and multiply by the average daily cost at the neonatal unit. In addition to this, other direct costs such as medications, investigations, use of equipment and specially trained staff etc. must be added to come closer to an estimation of the true costs. Indirect costs falling on budgets outside the hospital should also be added, such as travels to and from the hospital, loss of production, sick/maternity pension for parents and future readmissions of the infant. The third category is intangible costs, which are much more difficult to estimate. They refer to the costs of suffering and loss of quality of life after a disease or treatment. Methods to calculate intangible costs use quality adjusted life years (QALY) as an approximation of loss or gain of quality of life during a specified number of years.[88]

An American study from 2007[77] found that infants of 32-34 gestational weeks represented 25% of admissions to neonatal units. The average cost per case was 31,000 USD, representing 22% of total neonatal unit costs. The conclusion was that moderately preterm birth adds a large contribution to neonatal costs and that it may be possible to optimize care to decrease use of resources.

2.7.2 Impact of length of hospital stay on neonatal costs

In a Swedish evaluation of costs of neonatal care and length of hospital stay in preterm infants born 1998-2001, the correlation between gestational age and costs is clearly negative. The preterm infants had a four times longer stay compared to term infants. Length of hospital stay corresponded well to the estimated costs of care, calculated by measures of charge.[89]

At Karolinska University Hospital in Stockholm, Sweden, patients from other Swedish health regions are sometimes admitted for neonatal care. The patient's home health care region pays Karolinska University Hospital for the hospital stay and the price can be used as an approximation of the average costs for neonatal care. In 2011, it has been set to 15,244 SEK (2450 USD)/24 hours for neonatal intensive care of infants >28 gestational weeks or >1500 g and to 10,712 SEK(1700 USD)/24 hours for neonatal care (not intensive care). If ventilator treatment is needed, a cost of 17,510 SEK(2800 USD)/24 hours is added.

3 AIMS

Determinants of length of hospital stay, contemporary measures of morbidity by gestational week and risk factors predicting neonatal morbidity in moderately preterm infants have been poorly studied. The overall purpose of this thesis was to fill these gaps in knowledge to make neonatal care more effective, and to improve short- and long-term outcomes for moderately preterm infants.

The specific aims of the included studies were:

- To determine trends in length of hospital stay for moderately preterm infants during the last twenty years and to identify factors that contributed to changes over time (Paper I);

- To determine postmenstrual age at hospital discharge for moderately preterm infants and its relation to perinatal risk factors and to organization of care (Paper II);

- To determine the gestational age specific risks for neonatal morbidity and use of interventions in infants born moderately preterm (Paper III); and

- To investigate risks of respiratory diseases in moderately preterm infants and to identify maternal, obstetric and neonatal risk factors for acute respiratory morbidity (Paper IV).

4 METHODS

4.1 STUDY COHORTS

All papers in this thesis are based on infants born moderately preterm, at 30+0 to 34+6 gestational weeks and days, and in Sweden. Ethical approval was obtained from the regional ethical vetting board prior to the initiation of all studies.

The characteristics of the study cohorts are presented in Table 3. Paper I includes a longitudinal, in part historical, population and Papers II-IV are contemporary but with different exclusion criteria, which creates four different cohorts of moderately preterm infants.

The mean values of maternal age, gestational age and birth weight were approximately equal in the four study populations, except for a decrease in maternal age and a small increase in birth weight in Paper IV, probably due to the exclusion of multiple births. Mean maternal age increased from 29.7 to 32.2 between 1983 and 2002 in Paper I. The rates of multiple birth and SGA were robust. A low Apgar score indicating asphyxia was less common in Paper II, probably as a result of the exclusion criteria. Paper I had the same exclusion criteria but there were no infants with malformations or major surgery in the original register to exclude and the study population may not be large enough to study such rare events as asphyxia. In Papers I-IV, SGA was defined as birth weight for gestational age more than 2 SD below the mean according to Swedish standards for normal fetal growth of both sexes.[90]

Table 3. Characteristics of study cohorts in Paper I-IV

	Paper I	Paper II	Paper III	Paper IV
Birth years	1983, 1988, 1993, 1998, 2002	2004-2005	2004-2008	2004-2008
Setting	Danderyd Hospital	National data	National data	National data
Subgroup	Exclusion of: malformations, major surgery, neonatal death	Exclusion of: malformations, major surgery, neonatal death	All live births included	All live born singletons included
N of included infants	564	2,388	6,674	4,679
Maternal age*	31 (5.4)	31.2 (5.4)	31.2 (5.4)	30.5 (5.5)
Multiplets	27%	26%	26%	-
Gestational age*	33.0 (1.3)	32.8 (1.3)	33.1 (1.4)	32.8 (1.3)
Birth weight*	2,030 (453)	2,086 (476)	2,062 (471)	2,117 (484)
SGA	12%	13%	13%	13%
Male sex	52%	52%	54%	56%
Apgar score 0-3 at 5 minutes' age	1.0%	0.6%	1.0%	1.1%

*mean (SD)

4.2 DATA SOURCES

The Perinatal Quality Register has been the primary source of data on participating infants in Papers II-IV of this thesis. In addition, Paper I was partly based on

prospectively registered data in a local hospital register similar to PNQ, used to assemble information on infants born during the years 1983-1998. In Paper IV, information on mother, pregnancy and delivery characteristics was added from the Swedish Medical Birth Register.

Definition of diagnoses in PNQ
Diagnostic criteria for all morbidity measures are predefined in the PNQ register to avoid variation in diagnoses between centers and/or users (Table 4).

Table 4. Definitions of diagnoses in PNQ

Diagnose	Definition
Transient tachypnea of the newborn (TTN)	An acute, non-infectious respiratory disorder with positive x-ray findings and decreasing need for supplemental oxygen therapy in the first 24 hours after birth
Respiratory distress syndrome (RDS)	An acute, non-infectious respiratory disorder with progressively increasing central cyanosis in room air or need for supplemental oxygen to maintain $PaO2 \geq 6.6$ kPa in the first 24 hours after birth, and a typical x-ray
Hypoglycemia	Plasma glucose < 2.6 mmol/L at a postnatal age ≥ 3 h
Bacterial infection	Relevant positive cultures and/or clinical criteria for meningitis, septicemia, pneumonia, pyelonephritis, osteomyelitis, pemphigus, omphalitis or arthritis
Patent ductus arteriosus (PDA)	Requiring medical or surgical treatment
Hyperbilirubinemia	Requiring phototherapy or exchange transfusion
Intraventricular hemorrhage (IVH)	Graded in accordance with Papile[91]
Periventricular leukomalacia (PVL)	In accordance with de Vries[92]
Necrotizing enterocolitis (NEC)	In accordance with Bell[93]
Retinopathy of prematurity (ROP)	In accordance with the International Classification for Retinopathy of Prematurity[94]
Bronchopulmonary dysplasia (BPD)	Defined as oxygen supplementation at 36 weeks of gestation

4.3 LENGTH OF HOSPITAL STAY
In Papers I-II, LOS was calculated in days. However, as LOS for infants born at 30 gestational weeks is usually longer than for infants born at 34 gestational weeks, and because infants born at 34 weeks exceed the infants born at lower gestational weeks in numbers, the distribution of LOS in days is skewed. Accordingly, we also used postmenstrual age (PMA) at discharge as outcome. This variable was almost normally distributed (Figure 6) and similar for infants of all gestational ages.

4.4 PAPER I
Study design
To determine longitudinal trends in LOS for moderately preterm infants during the last twenty years, a study group was assembled from one of Karolinska University Hospital's neonatal units, located at Danderyd Hospital. Danderyd Hospital is situated in the northern part of Stockholm and responds to all deliveries greater than

26 gestational weeks. The population of the recruitment area is mostly Caucasian, middle to upper class.

A total of 564 moderately preterm infants admitted for neonatal care during five years were included: 1983 (n = 51), 1988 (n = 114), 1993 (n = 115), 1998 (n = 148) and 2002 (n = 154). Exclusion criteria were life threatening malformations (n = 0), chromosomal anomalies (n = 0) and death during initial hospitalization (n = 10). Four infants were excluded due to incomplete information regarding LOS. In 1983 and 1988, GA was calculated from menstrual dates, which resulted in an age estimate of completed gestational weeks. In the following cohorts, antenatal ultrasound in early second trimester was used for GA estimation and was expressed as completed weeks and days.

Data collection and analysis
For the 1983 to 1998 cohorts, data was collected from the local register and hospital charts and in the 2002 cohort, from PNQ. Information on maternal age, multiple pregnancy, GA, birth weight, infant sex and neonatal morbidity and treatment including Apgar score, RDS, nCPAP-therapy, ventilator therapy and BPD was collected. Infants treated with intravenous antibiotic therapy were also noted as an indicator of infection rate.

All data was initially analyzed separately in the five different cohorts according to birth year. LOS in days and PMA were calculated individually and considered as outcomes. Infants with LOS >75 days or a PMA at discharge exceeding 42 weeks (>3 interquartile distances above the median) were considered as outliers and excluded from statistical calculations (n = 6).

4.5   PAPER II
Study design and population
This cross-sectional study of LOS in moderately preterm infants in different Swedish hospitals was based on data from PNQ. During the years 2004-2005, 21 of 34 neonatal units in Sweden reported all their in-patients to the register. We extracted information on all moderately preterm infants admitted to these units. Infants with one or more of the following diagnoses were excluded: major malformation, (renal n=15, cardiac n=126, central nervous system n=5, gastrointestinal n=39, cleft palate n=13, miscellaneous n=42), chromosomal anomalies (n=21), major surgery (n=35) or death (n=36) during neonatal unit (NU) hospitalization. We also excluded infants with missing information on LOS (n=20). After exclusion, 2,388 infants were included in the study.

Risk factors and outcomes
Maternal age, multiple birth, GA, birth weight and sex were considered as potential risk factors. Neonatal morbidity was defined according to Table 4.

All 21 NUs reporting to the PNQ also responded to a questionnaire concerning organization of care. The individual NUs' identities were blinded to the investigator during data collection and analysis. The participating NUs were categorized according to unit level I-III.[10] Unit size was characterised by numbers of yearly admissions of infants with a GA of 30-34 completed weeks (less than 50 or at least 50), facilities for co-care of mother and infant, use of NIDCAP, fixed criteria for home discharge, and/or home care program.

PMA at discharge was considered main outcome measure and was defined as number of days from last menstrual period, corrected for by early second trimester ultrasound in all women. To specify the PMA at discharge, the destination at hospital discharge (other clinic/hospital, home care or home without support) was investigated. Because bottle fed preterm infants have been reported to have shorter hospital stay,[95] outcome data was stratified and analyzed according to breastfeeding or not.

The purpose of this study was to investigate risk factors for PMA at hospital discharge to home. Infants discharged to other clinics (n=125) were therefore excluded from the risk factor analyses. Infants with a LOS of 3 interquartile distances above the 75th percentile (n=10) were considered outliers and were also excluded from these analyses. The final number of infants for statistical analyses was 2,253.

4.6   PAPER III
Study design and population
To explore neonatal morbidity and interventions stratified by gestational week, we extracted PNQ information on all 6,677 infants born at 30-34 weeks in 2004-2008. Three infants born at 31-32 weeks, having birth weights for gestational age > +5.5 SD[90] and 3-5 days length of hospital stay were excluded due to strong suspicion of misclassification. After exclusion, 6,674 infants remained in the study group.

Outcomes
The following neonatal diagnoses were considered as outcomes: TTN, RDS, hypoglycemia, bacterial infection, PDA, hyperbilirubinemia, IVH, PVL, NEC, ROP, BPD, malformations (specified by ICD-10 codes Q00-Q89), chromosomal aberrations (specified by ICD-10 codes Q90-Q99) and death before discharge to home. Secondary outcomes were the following treatments and interventions provided before or at birth or during the neonatal hospitalization period: antenatal steroids, nCPAP, ventilator treatment, surfactant, antibiotics, pharmacological or surgical treatment of PDA, and exchange transfusion.

Birth weight standard deviation scores
Birth weight for gestational age was stratified into the following standard deviation groups: <-2; -2 to <-1; -1 to +1; >+1 to ≤+2; and >+2SD. Morbidity outcomes were then presented by birth weight for gestational age, which also was stratified and presented by GA.

4.7 PAPER IV

Study design and population

This project was designed as a population-based study of acute respiratory morbidity in live born infants in Sweden between 2004 and 2008, with a GA at birth from 30 to 41 completed gestational weeks. Using information about mothers' personal identification number and infant's birth date, it was possible to link information from PNQ to MBR. In the process of linking the two registers, 318 infants were excluded because of lack of reliable identification data. After linkage, 6,362 very to moderately preterm infants (30-34 weeks) remained in the study group. From the MBR, 472,318 late preterm to term infants (gestational age 35-41 completed weeks) born during the same time period were identified. We chose to restrict all analyses to single births because neonatal morbidity may differ between multiple and singleton born infants and because the reliability of identification of same-sex twins was uncertain when the two registers were linked together. After exclusion of all multiple births, there were 4,679 very to moderately preterm infants and 467,629 late preterm to term infants.

Outcomes and risk factors

First, we compared risks of respiratory diseases between infants born at 30-34 weeks and 35-41 weeks. In these comparisons, information about infant respiratory diseases was derived from MBR, using ICD-10. The following diseases were included as outcomes: TTN (ICD-10 code P22.8), RDS (ICD-10 code P22.0), pneumothorax and PIE (ICD-10 codes P25.1 and P25.0), pneumonia (ICD-10 code P23 and J12-J18), meconium aspiration syndrome (ICD-10 code P24.0), PPHN (ICD-10 code P29.3B), and BPD (ICD-10 code P27.1).

Second, within the group of moderately preterm infants, we studied risks of the most common respiratory diseases, TTN and RDS. In these analyses, data on outcomes was obtained from PNQ.

The following possible risk factors for TTN and RDS in the neonatal period were included in univariate and multivariate analysis: maternal age (<24; 25-29; 30-34; and ≥35 years); parity (primiparity and multiparity); body mass index in early pregnancy (<25; 25-29; ≥30); chronic disease of the mother (asthma n=321 [7.3% of all mothers to very to moderately preterm infants]; renal disorders n=31 [0.7%]; diabetes n=83 [1.9%]; ulcerative colitis n=36 [1.0%]; systemic lupus erythematosus n=8 [0.2%]; and chronic hypertension n=65 [1.5%]), assisted conception (hormonal stimulation of ovaries; surgical treatment of infertility; intracytoplasmatic sperm injection and/or other form of assisted conception); preeclampsia (including eclampsia); premature rupture of membranes before onset of labor (regardless of time to delivery); mode of delivery (vaginal delivery; Cesarean section after onset of labor; Cesarean section before onset of labor; unspecified Cesarean section); antenatal steroid treatment; SGA status; infant sex; Apgar score at 5 minutes' age (0-3; 4-6; 7-10); and gestational age in completed weeks.

4.8 STATISTICAL ANALYSES

Data are presented as means (SD or 95% confidence intervals) or proportions (numbers and percent). Student´s t-test and ANOVA were used to compare variables with a normal distribution. The Mann-Whitney U-test and Kruskal Wallis test were used to compare non-parametric variables. Chi-Square test was used to compare proportions.

In Papers I and II, linear regression analyses were used to evaluate contributions to LOS from the neonatal morbidity, hospital level and size, as well as organization of care. Covariates with p-values < 0.20 were subsequently entered into stepwise forward multiple regression models. In the multivariate model, we included maternal age, multiple pregnancy, GA, SGA, sex and neonatal morbidity and studied contributions from these risk factors to LOS. Subsequently, data regarding hospital characterization were added to the multiple regression models.

In Paper III, logistic regression was used to obtain odds ratios and 95% confidence intervals for morbidity outcomes and interventions at 30, 31, 32 and 33 gestational weeks as compared to 34 weeks. Because infants were actively screened for some morbidity outcomes (IVH, PVL and ROP) when born at 30, 31 and 32 weeks but not thereafter, 32 weeks was used as reference and risks at 33 and 34 weeks were omitted for these outcomes. Similarly, 32 weeks was used as reference in antenatal steroids because it was standard treatment in expected deliveries before 33 weeks but not in later gestational weeks.

In Paper IV, risk factors for TTN and RDS were divided into maternal (maternal age; parity; BMI; daily smoking in early pregnancy; chronic disease; assisted conception; preeclampsia; premature rupture of membranes; and mode of delivery) and infant related risk factors (antenatal corticosteroid therapy; SGA status; sex; Apgar score at 5 minutes' age; and gestational age). When building the multivariate models, we restricted the analysis to either maternal or infant related risk factors. Gestational age was found to be the strongest and most robust risk factor for TTN and RDS in all analyses and was included in all multivariate models. Accordingly, maternal risk factors were adjusted for gestational age and maternal risk factors but not for infant related risk factors. Infant related risk factors were adjusted for gestational age in model 1 and for all infant characteristics in model 2 but not for maternal risk factors. Logistic regression was used to obtain odds ratios and 95% confidence intervals in multivariate analyses. Effect modification was tested by likelihood ratio interaction test and stratification.

A P-value <.05 was considered significant. All analyses were performed with Stata 9.2 software (Stata-Corp, College Station, Texas).

5 RESULTS

5.1 STUDY COHORTS

Table 5 demonstrates how characteristics among moderately preterm infants compare to those of late preterm and term infants in a cohort of singletons born in Sweden 2004-2008. The risk of being SGA, male, having a congenital malformation and/or an Apgar score of 0-3 at 5 minutes' age were significantly increased in the moderately preterm infants as compared to late preterm to term infants.

Table 5. Infant characteristics in moderately preterm infants compared to late preterm to term infants.

	Late Preterm to Term Infants (35-41 weeks) (n = 467,965)		Moderately Preterm Infants (30-34 weeks) (n = 4,343)		Odds Ratio (CI)	
	n	%	n	%	OR	CI
Infant characteristics						
SGA status	7,771	1.7	589	13	8.6	7.8-9.4
Male sex	230,629	49	2,628	56	1.3	1.2-1.4
Congenital malformation	14,783	3	473	10	3.4	3.1-3.8
Apgar < 4 at 5 minutes	427	0.1	52	1.1	13	9.4-17
Gestational age						
30 weeks			382	8.8		
31 weeks			560	12		
32 weeks			732	17		
33 weeks			1,091	25		
34 weeks			1,578	36		
35 weeks	5,069	1.1				
36 weeks	9,967	2.1				
37 weeks	19,370	4.1				
38 weeks	78,275	16				
39 weeks	124,687	27				
40 weeks	134,718	29				
41 weeks	95,879	20				

5.2 LENGTH OF HOSPITAL STAY

5.2.1 Length of stay in a longitudinal perspective (Paper I)

During the five study years, 24,368 deliveries occurred at Danderyd Hospital and a total number of 2,958 (2,701 inborn) infants were admitted to the NU. Twenty percent of the admitted infants were moderately preterm. Of the total number of bed-days, moderately preterm infants consumed almost fifty percent (figure 5).

Figure 5. Proportions of moderately preterm infants admitted to the neonatal unit and their proportion of the total bed-days at the neonatal unit.
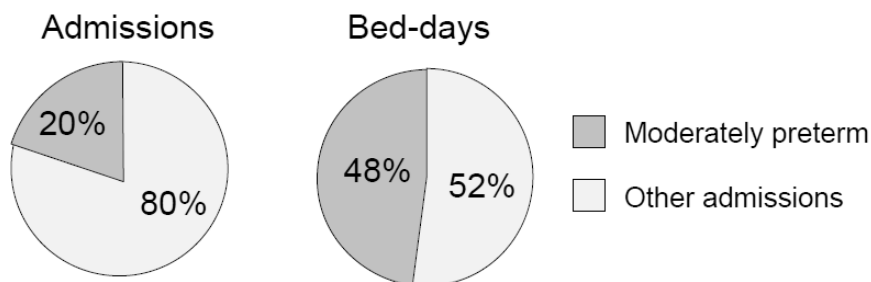
Infant morbidity and interventions
The rates of low Apgar scores and RDS did not differ significantly between the year cohorts. During the 20 year study period, antibiotic treatment decreased ($p<0.05$), use of nCPAP increased ($p<0.05$) and the need for ventilator therapy decreased ($p<0.05$, Pearson Chi-Square test). Transfers between hospitals increased somewhat. In 2002, a lower proportion of infants were discharged directly to home (85%), as compared to the other year cohorts (mean 94%, $p<0.05$).

There were no significant differences in perinatal characteristics (birth weight, GA, SGA, twinning rate), morbidities (low Apgar score, RDS) or interventions (antibiotic, nCPAP and ventilator treatments) among infants that were transferred to other units as compared to those discharged directly to home. In addition, infants transferred to other units in 2002 did not have any indirect or direct factors suggesting higher morbidity (such as lower birth weight, lower Apgar scores, higher frequency of RDS or nCPAP treatment), compared to infants transferred to other units in 1983-1998. This speaks against the possibility that infants in 2002 were selectively referred to other units because of higher morbidity.

Length of stay
The overall LOS for moderately preterm infants was 24 (13) days and postmenstrual age at discharge was 36.6 (1.5) weeks. In 2002, LOS and postmenstrual age at discharge were significantly lower than in the earlier cohorts ($p<0.05$). Excluding infants transferred to other units did not alter these findings (Table 6).

Table 6. Length of hospital stay in moderately preterm infants according to year of birth

	1983	1988	1993	1998	2002
All infants (n = 564)					
LOS, days	26 (13)	25 (11)	28 (12)	26 (13)	17 (13)*
GA at discharge, Weeks	37.2 (1.8)	36.8 (1.2)	37.1 (1.2)	36.6 (1.5)	35.8 (1.4)*
After exclusion of infants transferred to other units (n = 513)					
LOS, days	28 (10)	26 (11)	29 (12)	26 (12)	19 (13)*
GA at discharge, Weeks	37.7 (1.2)	36.9 (1.1)	37.1 (1.2)	36.7 (1.2)	36.0 (1.2)
Healthy, inborn singletons discharged to home (n = 179)					
LOS, days	28 (11)	23 (8)	24 (10)	20 (10)	14 (7)*
GA at discharge, Weeks	37.9 (1.3)	36.7 (1.0)	36.9 (1.1)	36.5 (1.5)	35.8 (1.0)*

LOS = Length of stay, GA = Gestational Age
Mean (SD) values
* = p < 0.05 versus all other year cohorts.

Risk factors associated with significantly longer LOS were in multivariate regression analysis: twin birth (+2.1 days, p<0.001), SGA (+1.6 days, p=0.008), and nCPAP treatment (+1.7 days, p<0.001). Factors associated with shorter LOS were: birth year 2002 (-4.2 days, p<0.001), gestational age (-5.2 days/week increase in GA, p<0.001) and transfer to other unit (-5.9 days, p<0.001). Taken together, these variables explained 55% ($r^2 = 0.55$, p<0.001) of the variation in LOS. Restricting the analysis to healthy (no ventilatory support) inborn singletons discharged to home, the change in LOS over the years became more evident: it decreased from 28 (11) days in 1983 to 14 (7) days in 2002 (p<0.05).

Risk factors associated with significantly higher PMA (in weeks) at discharge were: GA (+0.18 weeks, p<0.001), twin birth (+0.27 weeks, p<0.001) and nCPAP treatment (+0.23 weeks, p<0.001). Factors associated with lower PMA at discharge were: birth year 2002 (-0.64 weeks, p<0.001) and transfer to other unit (-0.88 weeks, p<0.001). Taken together, 29% ($r^2=0.29$, p<0.001) of the variation in PMA could be explained by these variables.

### 5.2.2 Length of hospital stay – a multicenter survey (Paper II)
Maternal and neonatal risk factors and PMA at discharge
The mean (±SD) value of PMA at hospital discharge was 36.9 (1.7) weeks. Postmenstrual age at discharge had an approximately normal distribution with a median value of 36.7 (range 30.3 to 46.7) weeks (Figure 6). Female and male infants had the same mean value of PMA at discharge (36.9 weeks).

Figure 6. Distribution of postmenstrual age (days) at discharge.

Discharged home, n=2141

Discharged to Domiciliary Care, n=110
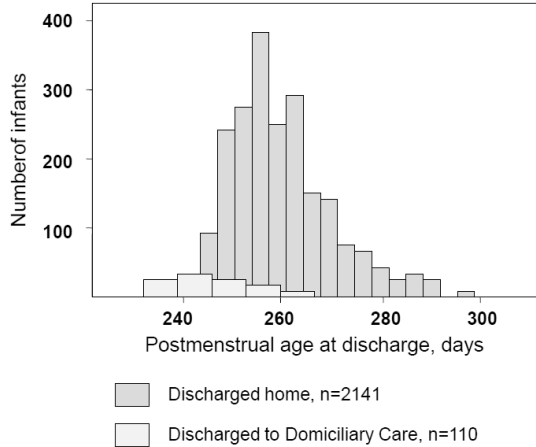
In both uni- and multivariate analyses, a higher PMA at discharge was associated with high (≥35 years) maternal age, multiple gestation, SGA and neonatal morbidity.

Low GA at birth was associated with a higher PMA at discharge in univariate analysis but not after controlling for neonatal morbidity. Thus, the effect of GA on PMA at discharge could be explained by higher neonatal morbidity in more immature infants. Maternal and neonatal risk factors could only explain 13% (R^2=0.13, p<0.001) of the total variation in PMA at discharge (Table 7).

Table 7. Maternal, neonatal and hospital characteristics in moderately preterm infants and their significance for postmenstrual age (PMA) in days at hospital discharge to home (n = 2,253).

	Univariate analyses β = regression coefficient (p-value)	Multivariate Analysis β = regression coefficient (p-value)
Maternal and pregnancy data		
Maternal age ≥35	3.08 (<0.001)	2.39 (<0.001)
Maternal age 25-29	-1.74 (<0.001)	-0.75 (ns)
Multiple birth	4.54 (<0.001)	4.16 (<0.001)
Gestational age at birth	-0.74 (<0.001)	-0.26 (ns)
Small for gestational age	6.28 (<0.001)	5.42 (<0.001)
Neonatal morbidity		
Respiratory distress syndrome	4.88 (<0.001)	3.67 (<0.001)
Infection	3.69 (<0.001)	2.27 (0.001)
Hypoglycemia	2.00 (0.001)	1.87 (0.001)
Hyperbilirubinemia	1.52 (<0.001)	1.07 (0.010)
Severe neonatal morbidity*	12.7 (<0.001)	9.70 (<0.001)
Hospital characteristics		
Level 3 neonatal unit	-2.26 (<0.001)	-1.47 (0.001)
Fixed discharge age criteria	4.66 (<0.001)	3.27 (<0.001)
Small unit	0.43 (ns)	-
Domiciliary care	-9.76 (<0.001)	-9.62 (<0.001)
Intercept (days)		263.8 (p<0.001)

R^2 in total multivariate model=0.21 and without hospital characteristics = 0.13. A p-value > 0.05 was considered non-significant (ns).
*Severe neonatal morbidity include infants with one or more of the following diagnoses: ROP grade 3-4, IVH grade 3-4 or BPD.

Organization of care and PMA at discharge

The result of the questionnaire that was answered by all 21 neonatal units included in Paper II is presented in figure 7.

Figure 7. Results of a survey to the participating neonatal units regarding organization of care for moderately preterm infants.

Survey of Neonatal Care of Moderately Preterm Infants in Sweden 2004-2005
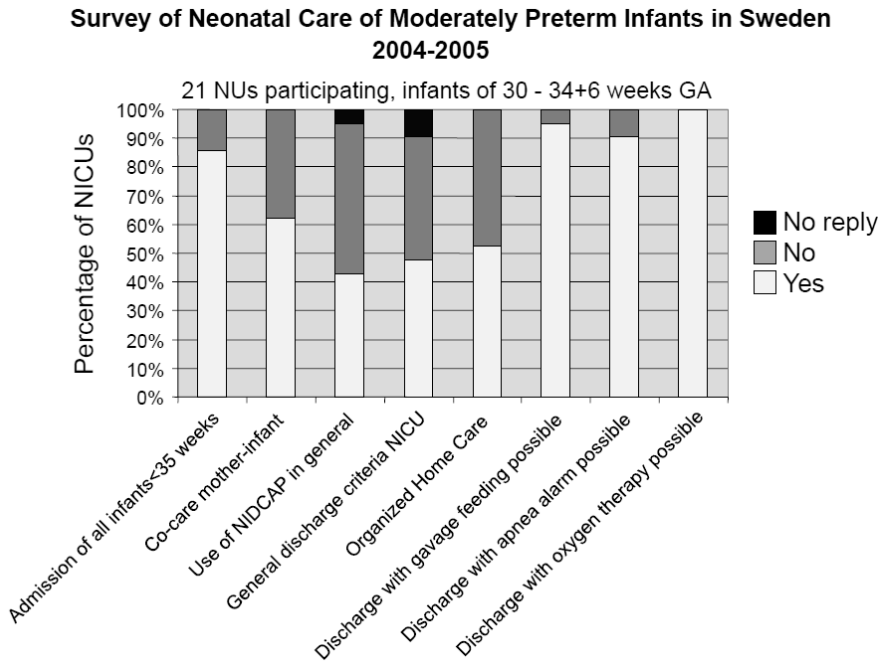
The mean PMA at discharge differed up to 2 weeks between hospitals (Figure 8). We found an overrepresentation of multiplets (27 vs 22%, p=0.03) and infants with hypoglycemia (19 vs. 15%, p=0.02) in hospitals with medium to high PMA at discharge as compared to hospitals with low PMA at discharge. There were no other statistically significant differences in perinatal risk factors between low and medium-high PMA hospitals.

Figure 8. Differences in postmenstrual age at discharge between neonatal units
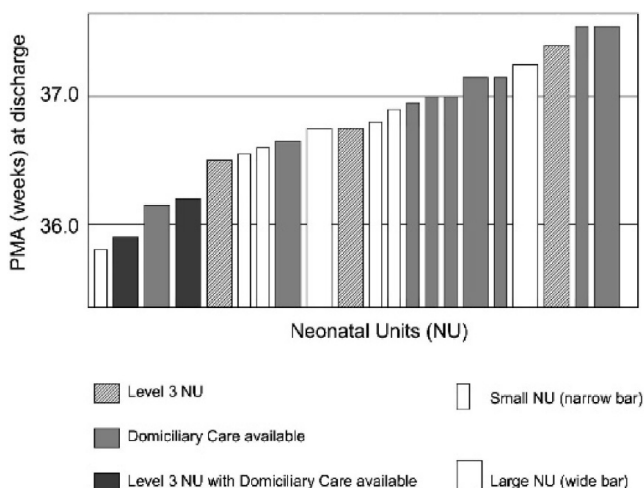
Comparing hospitals with low to hospitals with medium-high PMA at discharge, level 3 neonatal units, larger hospitals and hospitals without fixed criteria for discharge were overrepresented in the lower tertile for PMA at discharge (Table 8). These differences were not statistically significant, possibly due to limitations in statistical power. Practice of co-care of mother and infant, NIDCAP in use and available organized home care did not differ between hospitals with low as compared to medium-high PMA at discharge.

Table 8. Organization of care for moderately preterm infants in hospitals with low (n=7) as compared to medium-high (n=14) postmenstrual age (PMA) at discharge to home

	Low PMA at discharge*	Medium-high PMA at discharge**	P-value
Level 3 Hospital	3/7 (43 %)	2/14 (14 %)	Ns
Unit size:≥ 50 infants/year	4/7 (57 %)	6/14 (43 %)	Ns
Co-care mother-infant‡	5/7 (71 %)	8/14 (57 %)	Ns
NIDCAP in general use‡	3/6† (50 %)	6/14 (43 %)	Ns
Fixed criteria for discharge	0/7	3/14 (21 %)	Ns
Domiciliary Care available‡	3/7 (43 %)	8/14 (57 %)	Ns
Mean birth weight (g)	2087 (480)	2090 (466)	Ns
Mean weight at discharge (g)	2450 (395)	2619 (447)	<0.001

Values are numbers of hospitals (proportions) or mean values (SD). P-values were calculated by chi-square test (proportions) or t-test (mean values) and considered non-significant (ns) if >0.05.
*Low PMA at discharge consisted of 7 hospitals with a low mean value of PMA at discharge (n of infants = 781), ranging from 35.7 to 36.6 postmenstrual weeks
**Medium-high PMA at discharge consisted of 14 hospitals with a medium or high mean value of PMA at discharge (n of infants = 1472), ranging from 36.7 to 37.6 postmenstrual weeks.
†One hospital in the study group did not report on NIDCAP use.
‡Although item could be provided, the number of infants actually receiving each item could be lower.

However, comparing characteristics of organization of care on a hospital level may have introduced misclassification bias. Whereas there was no individual information on co-care of mother-infant or use of NIDCAP, infants admitted to home care could be

identified in the PNQ-register. An option for organized home care was reported by 11 of 21 hospitals. However, only 110 infants were actually discharged to home care and PMA at discharge for these infants was on average 9.8 days lower as compared to infants discharged home without organised support (p<0.001). By adding NU characteristics available on an individual level into the multivariate regression model with maternal and neonatal risk factors, the r^2–factor for PMA at discharge increased from 13% to 21%.

Breastfeeding and PMA at discharge
Exclusive breastfeeding at discharge was seen in 56% of the infants and 22% were partly breastfed (missing data for 199 infants). Infants that were (exclusively or in part breastfed) had on average 2,7 days lower PMA at hospital discharge as compared to infants that were not breastfed (p<0.001). When controlling for maternal risk factors and neonatal morbidity in multivariate analysis, the difference in PMA at discharge between breastfed and not breastfed infants decreased to 1.9 days.

5.3   NEONATAL MORBIDITY
A comparison of neonatal morbidity between the different study populations is shown in Table 9. Overall, the rates of morbidity and interventions were robust. RDS was more common in Paper I, possibly due to misclassification (there is no data on TTN to compare with the more recent cohorts). Treatment with nCPAP, ventilator and antibiotics was slightly less common in Paper II, probably reflecting the exclusion of the most complicated cases.

Table 9. Neonatal morbidity among moderately preterm infants in Paper I-IV

	Paper I	Paper II	Paper III	Paper IV
Birth years	1983, 1988, 1993, 1998, 2002	2004-2005	2004-2008	2004-2008
Setting	Danderyd Hospital	National data	National data	National data
Subgroup	Exclusion of: malformations, major surgery, neonatal death	Exclusion of: malformations, major surgery, neonatal death	All live births included	All live born singletons included
N of included infants	564	2,388	6,674	4,679
Antenatal steroids	No data	37%	38%	36%
TTN	No data	14%	14%	17%
RDS	17%	12%	14%	13%
Infection	No data	13%	15%	15%
Hypoglycemia	No data	18%	16%	20%
Hyperbilirubinemia	No data	59%	59%	61%
BPD	0.5%	0.9%	1%	0.6%
nCPAP therapy	42%	38%	43%	43%
Ventilator therapy	6.9%	3.3%	5.5%	5.9%
Antibiotic treatment	32%	28%	30%	31%

Respiratory morbidity in moderately preterm in relation to late preterm-term infants (Paper IV)

Rates of neonatal respiratory morbidity in moderately preterm infants compared to late preterm to term infants are presented in Table 10. Overall, the most common respiratory diseases were TTN, followed by RDS. Compared with late preterm to term infants, very to moderately preterm infants had substantially increased risks of all respiratory diseases. Specifically, the risks of TTN and RDS were 23 and 180 times higher in very to moderately preterm infants compared to the reference population.

Table 10. Risk of respiratory morbidity in moderately preterm infants as compared to late preterm to term newborn infants (singletons only).

	Late Preterm to Term Infants (35-41 weeks) n = 467,629		Moderately Preterm Infants (30-34 weeks) n = 4,679			
	n	%	N	%	OR	95% CI
Transient Tachypnea of the Newborn	3,899	0.83	781	16.7	23	30-35
Respiratory Distress Syndrome	376	0.08	593	12.7	180	158-206
Pneumothorax/PIE	657	0.14	116	2.48	18	15-22
Pneumonia	629	0.13	45	0.96	7.2	5.3-9.8
Persistent Pulmonary Hypertension	210	0.04	43	0.92	21	15-29
Meconium Aspiration Syndrome	297	0.06	5	0.11	1.7	0.7-4.1
Bronchopulmonary Dysplasia[a]	37	0.01	30	0.64	82	50-132

OR = Odds Ratio; CI = Confidence interval; PIE = Pulmonary Interstitial Emphysema
[a]need of oxygen at 36 weeks gestational age

5.3.1 Neonatal morbidity by gestational week (Paper III)

Rates and risks of morbidity at each gestational week are presented in Table 11. With the exception of hypoglycemia, all morbidity outcomes had a significantly decreasing trend towards higher GA (p <0.05). Compared to infants born at 34 weeks, infants born at 30 weeks had a twelve-fold increased risk of RDS, a four-fold increased risk of infections and a more than three-fold risk of hyperbilirubinemia. Major neonatal morbidity - defined as IVH, PVL, NEC, BPD and/or ROP – was reported to be rare (< 0.5%) at 33-34 weeks of GA. Compared to infants born at 32 weeks, infants born at 30 weeks had a two-fold increased risk of any IVH, a six-fold increased risk of NEC and an eight-fold increased risk of any ROP or BPD. In contrast, GA did not influence risks for IVH grade 3-4, PVL and ROP ≥ grade 3. Death before discharge to home occurred in 76 (1.1%) infants (15 [2.4%] at 30 weeks, 9 [1.1%] at 31 weeks, 18 [1.7%] at 32 weeks, 20 [1.2%] at 33 weeks and 14 [0.5%] at 34 weeks). Forty-eight of the 76 infants died during the first 6 completed days of life and 14 died within 7 to 27 completed days of life.

Table 11. Neonatal morbidities in 6,674 infants born moderately preterm

	30 weeks n=623		31 weeks n=822		32 weeks n=1045		33 weeks n=1564		34 weeks n=2620		Total n=6674
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%
Transient tachypnea of the newborn	19	2.1 (1.7-2.7)	19	2.0 (1.7-2.5)	18	2.0 (1.6-2.5)	13	1.3 (1.1-1.6)	10	**1.0 (ref)**	14
Respiratory distress syndrome	40	12.2 (9.6-15)	26	6.5 (5.1-8.2)	16	3.6 (2.8-4.6)	9	1.8 (1.4-2.3)	5.1	**1.0 (ref)**	14
Hypoglycemia*	12	0.7 (0.5-0.9)	14	0.8 (0.7-1.0)	14	0.9 (0.7-1.0)	17	1.0 (0.9-1.2)	17	**1.0 (ref)**	16
Infection	31	4.3 (3.5-5.4)	21	2.6 (2.0-3.2)	17	2.0 (1.6-2.5)	13	1.5 (1.2-1.8)	9.3	**1.0 (ref)**	15
Patent ductus arteriosus	8.8	23.0 (12-44)	4.3	10.5 (5.3-21)	1.8	4.4 (2.1-9.3)	0.6	1.5 (0.6-3.6)	0.4	**1.0 (ref)**	1.9
Hyperbilirubinemia	76	3.4 (2.8-4.1)	72	2.7 (2.3-3.2)	66	2.1 (1.8-2.4)	60	1.6 (1.4-1.8)	48	**1.0 (ref)**	59
Intraventricular haemorrhage											
- any	2.4	8.6 (2.5-30)	1.1	3.8 (1.0-14)	0.3	**1.0 (ref)**	0.2	-	<0.1	-	0.5
- severe†	<0.1	0.8 (0.1-9.2)	<0.1	0.6 (0.1-7.0)	0.2	**1.0 (ref)**	0	-	0	-	<0.1
Periventricular leukomalacia	1.6	1.5 (0.6-3.6)	1.1	1.0 (0.4-2.5)	1.0	**1.0 (ref)**	0.3	-	0.1	-	0.5
Necrotizing enterocolitis	1.9	5.7 (2.4-14)	0.5	1.4 (0.4-4.6)	0.8	1.7 (0.7-4.2)	0.3		0.3	**1.0 (ref)**	0.6
Retinopathy of prematurity											
- any	8.3	2.4 (1.6-3.8)	6.2	1.8 (1.2-2.8)	3.5	**1.0 (ref)**	0.6	-	<0.1	-	2.1
- severe‡	<0.1	-	<0.1	-	0	-	0	-	0	-	<0.1
Bronchopulmonary dysplasia§	3.9	8.7 (4.3-18)	2.2	4.9 (2.3-10)	0.4	2.2 (0.9-5.8)	0.3	0.8 (0.3-2.2)	0.5	**1.0 (ref)**	0.5
Death before discharge	2.4	4.6 (2.2-9.6)	1.0	2.1 (0.9-4.8)	1.2	3.3 (1.6-6.6)	0.5	2.4 (1.2-4.8)	0.5	**1.0 (ref)**	0.6

Numbers are proportions of patients (percent); OR odds ratios; CI confidence intervals.
* Hypoglycemia was defined as plasma glucose level <2.6 at an age of ≥3 hours.
† Severe intraventricular hemorrhage was defined as grade 3-4.
‡ Severe retinopathy of prematurity was defined as grade 3-5.
§ BPD was defined as need for oxygen supplementation at 36 weeks of gestational age.

Table 12. Interventions and treatments by gestational week in 6,674 infants born moderately preterm

	30 weeks n=623		31 weeks n=822		32 weeks n=1,045		33 weeks n=1,564		34 weeks n=2,620		Total n=6,674
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%
Antenatal steroids	70	1.6 1.3-2.0)	68	1.5 (1.3-1.8)	58	**1.0 (ref)**	39	0.4 (0.4-0.5)	12	0.1 (0.1-0.1)	38
nCPAP	80	10.5 (8.5-13)	68	5.8 (4.9-6.9)	53	3.2 (2.7-3.7)	38	1.7 (1.5-2.0)	27	**1.0 (ref)**	43
Ventilator	16	7.6 (5.5-11)	10	4.4 (3.2-6.2)	6.3	2.7 (1.9-3.8)	3.6	1.5 (1.0-2.2)	2.4	**1.0 (ref)**	5.5
Surfactant	17	12.9 (8.9-19)	11	7.8 (5.4-11)	5	3.3 (2.2-5.0)	3.8	2.5 (1.7-3.8)	1.6	**1.0 (ref)**	5.2
Antibiotics	64	8.3 6.8-10)	47	4.1 (3.4-4.8)	36	2.7 (2.3-3.1)	26	1.6 (1.4-1.9)	18	**1.0 (ref)**	30
Pharmacological closure of patent ductus arteriosus	4.3	40 (12-130)	2.0	17.3 (5-60)	1.1	10.1 (2.9-36)	0.3	2.2 (0.5-10)	0.1	**1.0 (ref)**	0.9
Surgical ligation of patent ductus arteriosus	0.6	4.2 (1.1-17)	0.2	1.6 (0.3-8.7)	0.2	1.3 (0.2-6.9)	0.1	0.8 (0.2-4.6)	0.2	**1.0 (ref)**	0.2
Exchange transfusion for hyperbilirubinemia	0.2	0.3 (0-2.0)	0.5	0.8 (0.3-2.4)	1.0	1.7 (0.8-3.7)	0.4	0.6 (0.2-1.6)	0.6	**1.0 (ref)**	0.6

Numbers are proportions of patients (percent); OR odds ratios; CI confidence intervals.

Malformations

Two hundred infants (3.0%) had one or more malformations (including malformations of the central nervous system n=11, eye/ear/neck/face n=10, cardiovascular n=96, airway including cleft palate n=26, gastrointestinal n=56, external genitals n=30, renal/urinary tract n=28, musculoskeletal n=52, and miscellaneous n=7) and/or chromosomal aberrations (n=33 [0.5%], including trisomy 21 [n=16], trisomy 18 [n=1], trisomy 13 [n=8] and Klinefelter syndrome [n=2]). Infants with malformation diagnoses or chromosomal aberrations had a higher mortality (n=23, 12%) than other infants (n=53, 0.8%).

Treatments and interventions

Treatment and intervention outcomes according to GA are presented in Table 12. With the exception of exchange transfusion, all interventions were more commonly used towards lower gestational ages (p <0.05 when tested by a non-parametric test for trend).

5.3.2 Risk factors for neonatal morbidity (Paper III + IV)

Intrauterine growth and morbidity (Paper III)

SGA (birth weight for gestational age more than 2 SD below the mean for normal fetal growth) was seen in 8% of infants born at 34 and in 23% of infants born at 30 weeks (test for trend: p < 0.05) in Paper III. Compared to infants with birth weight for gestational age between -1 and +1 SD, SGA infants had an almost doubled risk of infection, a doubled risk of PDA and IVH, a three-fold increased risk of NEC or ROP and a five-fold increased risk of BPD (Table 13). Risks for these diagnoses were not significantly increased in other birth weight for gestational age groups. Compared to infants with birth weights for gestational age between -1 and +1 SD, SGA infants (<-2 SD) had a five-fold and infants with birth weights >+2SD had a four-fold increased risk of BPD. Respiratory distress syndrome, severe IVH and PVL did not correlate to birth weight standard deviations.

Table 13. Neonatal morbidity in moderately preterm infants by birth weight for gestational age.

	<-2SD n=840	-2 to <-1SD n=1,501	-1 to +1SD n=3,700	>+1 to ≤+2SD n=456	>+2SD n=177	Test for trend
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value
RDS	1.2 (0.9-1.4)	1.0 (0.8-1.2)	**1.0**	1.0 (0.7-1.3)	0.6 (0.4-1.1)	0.092
Infection	1.6 (1.3-1.9)	1.1 (0.95-1.34)	**1.0**	0.9 (0.7-1.2)	1.5 (1.0-2.2)	0.001
PDA	2.1 (1.4-3.3)	1.2 (0.8-1.9)	**1.0**	0.4 (0.1-1.2)	0.3 (0.0-2.3)	<0.001
IVH						
any	2.5 (1.7-3.8)	1.2 (0.8-1.8)	**1.0**	1.0 (0.5-2.1)	1.3 (0.5-3.6)	0.001
severe*	1.8 (0.7-4.5)	1.0 (0.4-2.5)	**1.0**	1.6 (0.5-5.6)	1.4 (0.2-11)	0.685
PVL	1.5 (0.6-3.7)	1.0 (0.4-2.3)	**1.0**	1.4 (0.4-4.6)	3.5 (1.0-12)	0.556
NEC	2.9 (1.4-5.8)	0.9 (0.4-2.0)	**1.0**	1.0 (1.0-1.0)	2.1 (0.5-9.0)	0.013
ROP						
any	3.2 (1.3-8.0)	1.6 (0.6-4.0)	**1.0**	1.0 (1.0-1.0)	1.9 (0.2-15)	0.013
severe†	-	-	**1.0**	-	-	0.052
BPD‡	4.9 (2.7-8.8)	1.7 (0.9-3.3)	**1.0**	1.9 (0.7-4.9)	3.9 (1.3-11)	0.001

Intrauterine growth characterized by standard deviation (SD) from expected birth weight. Numbers are proportions of patients (percent) and p-values. Test for trend across standard deviation groups is non-parametric. RDS = Respiratory Distress Syndrome; PDA = Patent Ductus Arteriosus; IVH = Intraventricular Haemorrhage; PVL = Periventricular Leukomalacia; NEC = Necrotizing Enterocolitis; ROP = Retinopathy of Prematurity; BPD = Bronchopulmonary Dysplasia
* Severe intraventricular hemorrhage was defined as grade 3-4
† Severe retinopathy of prematurity was defined as grade 3-5
‡ Bronchopulmonary dysplasia was defined as need for oxygen therapy at 36 weeks of gestational age

Maternal risk factors for TTN (Paper IV)

Among very to moderately preterm infants, maternal age ≥35 years, multiparity, preeclampsia and all forms of Cesarean deliveries increased risk of TTN in the univariate analysis and premature rupture of membranes decreased the risk. In the adjusted analysis, multiparity increased the risk of TTN by 30%, Cesarean section after onset of labor increased the risk with 30% and Cesarean section before onset of labor increased the risk by 60%. Maternal BMI between 25.0-29.9 decreased the risk of TTN.

Maternal risk factors for RDS (Paper IV)

In univariate analyses, multiparity; BMI >30; chronic disease; preeclampsia; Cesarean section before; and after onset of labor were associated with increased risks for RDS and premature rupture of membranes was associated with a decreased risk of RDS. In the adjusted analysis, Cesarean section after onset of labor doubled the risk of RDS, Cesarean section before onset of labor more than doubled the risk and premature rupture of membranes decreased the risk of RDS by 50 % (Table 14).

Table 14. Maternal, pregnancy and delivery-related risk factors for Transient Tachypnea of the Newborn and Respiratory Distress Syndrome among moderately preterm infants.

	Transient tachypnea of the newborn (n = 663) Odds Ratios (95% CI)		Respiratory distress syndrome (n = 630) Odds Ratios (95% CI)	
	Crude	Adjusted	Crude	Adjusted
Maternal age				
<24	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
25-29	0.85 (0.64-1.12)	0.82 (0.60-1.12)	1.01 (0.76-1.33)	0.99 (0.71-1.37)
30-34	1.21 (0.93-1.57)	1.09 (0.81-1.47)	1.11 (0.85-1.47)	0.91 (0.65-1.26)
≥35	1.36 (1.04-1.79)	1.02 (0.74-1.41)	1.25 (0.94-1.65)	0.84 (0.60-1.20)
Parity				
Primiparous	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Multiparous	1.38 (1.17-1.63)	1.28 (1.05-1.56)	1.41 (1.19-1.67)	1.46 (1.18-1.81)
BMI				
≤24.9	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
25.0-29.9	0.86 (0.69-1.07)	0.79 (0.62-0.99)	1.00 (0.79-1.25)	0.95 (0.75-1.22)
≥30.0	1.05 (0.81-1.38)	0.92 (0.69-1.21)	1.40 (1.09-1.81)	1.10 (0.82-1.46)
Daily smoking in early pregnancy	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
No	1.12 (0.84-1.49)	1.15 (0.85-1.56)	1.05 (0.78-1.42)	0.82 (0.59-1.16)
Yes				
Chronic disease				
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.06 (0.83-1.37)	1.05 (0.80-1.38)	1.37 (1.08-1.75)	1.31 (1.00-1.73)
Assisted conception				
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.12 (0.79-1.59)	1.24 (0.86-1.79)	0.84 (0.57-1.24)	0.81 (0.52-1.25)
Preeclampsia				
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.33 (1.08-1.63)	0.99 (0.76-1.28)	1.63 (1.33-1.99)	0.84 (0.64-1.09)
PPROM				
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	0.76 (0.63-0.92)	0.81 (0.65-1.02)	0.42 (0.34-0.52)	0.50 (0.38-0.66)
Mode of delivery				
Vaginal delivery	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
CS after onset of labor	1.50 (1.25-1.79)	1.27 (1.02-1.58)	2.74 (2.27-3.31)	2.13 (1.67-2.72)
CS before labor	2.00 (1.47-2.73)	1.59 (1.10-2.30)	3.40 (2.49-4.65)	2.57 (1.75-3.77)
Unspecified CS	1.70 (1.14-2.54)	1.50 (0.96-2.33)	1.59 (0.99-2.54)	1.26 (0.74-2.15)

The multivariate model is adjusted for maternal age, parity, BMI, daily smoking in early pregnancy, chronic disease, assisted conception, preeclampsia, premature rupture of membranes, mode of delivery and infant's gestational age.

Infant related risk factors for TTN (Paper IV)

In univariate analyses, antenatal steroids; male sex; Apgar score 4-6 at 5 minutes; and gestational age 30-33 weeks were associated with increased risks for TTN among very to moderately preterm infants. After adjustment for gestational age only, antenatal corticosteroids was no longer associated with an increased risk of TTN. Male sex increased the risk of TTN by 30 % and Apgar score 4-6 increased the risk by 75 %. Adding infant characteristics (antenatal corticosteroid therapy; SGA status; sex; and Apgar score at 5 minutes' age) to the adjusted model with gestational age, did not change the risk estimates significantly.

Infant related risk factors for RDS (Paper IV)

Among very to moderately preterm infants, antenatal steroids; male sex; Apgar score 0-3 and 4-6; and gestational age 30-33 weeks (compared to 34 weeks) were associated with increased risks for RDS in univariate analyses. After adjustment for gestational age only, antenatal steroid therapy and SGA decreased the risk of RDS by 30 %, whereas an Apgar score between 0-3 almost tripled the risk and an Apgar score between 4 and 6 almost doubled the risk of RDS. Male sex still increased the risk by 30 %. As with risks for TTN, adding antenatal corticosteroid therapy; SGA status; sex; and Apgar score at 5 minutes' age to the multivariate model on risk of RDS, did not change risk estimates significantly but the difference in risks between gestational age weeks increased (data not shown, Table 15). Tests for interaction between SGA and GA on the risk of RDS were performed but no effect modification was detected.

Table 15. Infant related risk factors for Transient Tachypnea of the Newborn and Respiratory Distress Syndrome among moderately preterm infants.

	Transient tachypnea of the newborn (n = 663)			Respiratory distress syndrome (n = 630)		
	OR (95% CI)			OR (95% CI)		
	Crude	Adjusted model 1	Adjusted model 2	Crude	Adjusted model 1	Adjusted model 2
Antenatal corticosteroid therapy						
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.4 (1.2-1.6)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.5 (1.3-1.8)	0.7 (0.6-0.9)	0.8 (0.6-0.9)
SGA status						
No	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	1.1 (0.8-1.4)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.1 (0.8-1.4)	0.7 (0.5-0.9)	0.7 (0.6-1.0)
Sex						
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.3 (1.1-1.6)	1.4 (1.2-1.7)	1.4 (1.2-1.7)	1.4 (1.2-1.7)
Apgar score 5 min						
0-3	1.3 (0.6-2.7)	1.2 (0.6-2.4)	1.1 (0.5-2.4)	3.4 (1.9-6.1)	2.8 (1.5-5.3)	3.1 (1.6-5.9)
4-6	1.7 (1.2-2.4)	1.6 (1.1-2.2)	1.6 (1.1-2.2)	2.3 (1.6-3.1)	1.9 (1.3-2.6)	1.8 (1.3-2.6)
7-10	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Gestational age						
30 weeks	2.2 (1.7-3.0)		2.3 (1.7-3.1)	9.4 (7.1-12.4)		11.3 (8.2-15.5)
31 weeks	2.0 (1.6-2.6)		2.0 (1.5-2.7)	5.4 (4.1-7.0)		6.5 (4.9-8.8)
32 weeks	1.8 (1.4-2.3)		1.9 (1.4-2.4)	3.0 (2.3-3.9)		3.4 (2.6-4.6)
33 weeks	1.2 (1.0-1.6)		1.2 (0.9-1.5)	1.5 (1.2-2.0)		1.6 (1.2-2.2)
34 weeks	1.0 (ref)		1.0 (ref)	1.0 (ref)		1.0 (ref)

Model 1 adjusts for gestational age.
Model 2 adjusts for antenatal corticosteroid therapy, SGA status, sex, Apgar score at 5 minutes' age and gestational age.

6   GENERAL DISCUSSION

6.1   LENGTH OF HOSPITAL STAY

In our longitudinal study of length of hospital stay in moderately preterm infants in a one-hospital setting, the main finding was that length of stay was significantly shorter in 2002 compared to previous year cohorts. The difference in length of stay (or postmenstrual age at discharge) between 1983 and 2002 was 9 days. This could not be attributed to healthier infants in 2002. In a population-based study of 2,388 moderately preterm infants born 2004-2005, we found that postmenstrual age at discharge differed up to two weeks between hospitals and that perinatal risk factors and neonatal morbidity only had a limited impact on length of hospital stay for these infants.

Previous studies have suggested that length of stay for preterm infants is much less influenced by morbidity and neonatal risk factors than expected.[96,97] There is general consensus that all preterm infants should have achieved physiological stability before they are sent home. But there are no accepted definitions of temperature and respiratory stability in Sweden. Accordingly, there may be variations in the margins of safety; including the time elapsed after documented physiologic temperature and respiratory stability, before discharge.[98,99]

Hospitalisation is stressful for both infants and parents. The ambition should always be to restrain the LOS as much as safety allows.[18] Early hospital discharge has been reported to increase the risk of readmission for late preterm infants.[100] Costs for neonatal care are closely related to length of stay.[77,89,101,102] In Sweden, 2% of all live-born infants are moderately preterm, but they account for almost 50% of total bed-days in the NU (Paper I). Shortening length of stay for moderately preterm infants by nine days – the effect associated with organized home care in previous studies[25] – would reduce the total need for neonatal beds by 15%. This permits reallocation of NU resources to the growing number of infants surviving extremely preterm birth.

In Paper I, morbidity in terms of asphyxia, RDS and BPD did not change over time. Use of nCPAP treatment increased in later years, probably replacing some of the need for ventilator treatment. It is conceivable that the introduction of surfactant therapy during the latter half of the study period may have contributed to shorter LOS. However, rates of RDS was on average fairly low (17%) and it did not change over time. In addition, the course of RDS was usually mild to moderate. Accordingly, surfactant therapy was uncommon and could only have had a marginal, if any, effect on length of stay in these moderately preterm infants. Treatment with antenatal steroids in preterm labor was introduced in 1985 at our hospital and could therefore not explain the later drop in length of hospital stay.

It is well known that a low birth weight for gestational age predicts a higher risk of morbidity and mortality.[103] This was reflected also in Paper I, which found longer LOS for SGA infants. Likewise, the longer LOS found among infants treated with nCPAP reflects their underlying respiratory or circulatory fragility.

Breastfeeding has important short and long term health implications for preterm infants.[104,105] Establishment of successful breastfeeding in preterm infants should therefore be given high priority in neonatal care.[106] In contrast to previous reports,[95,107,108] we found that breastfed infants in Paper II had a lower PMA at discharge as compared to those not breastfed. After controlling for neonatal morbidity, the difference between the two groups decreased. This suggests that the lower PMA at discharge in breastfed infants may partly be due to that breastfed infants are healthier and more mature as compared to not breastfed infants. In addition, a majority of the preterm infants were exclusively breastfed before discharge, thereby allowing for discharge at home as soon as physiologic stability had been achieved.

Apnea of prematurity has been reported to significantly increase LOS in moderately preterm infants and that diagnosis of apnea varies considerably between hospitals.[99] The register from which we extracted data did not contain information on the proportion of infants with apnea of prematurity, which precludes an analysis of the effects of this diagnosis on PMA at discharge. Even though it is clear that morbidity is not the main determinant of LOS, we cannot exclude that neonatal morbidity below 32 weeks of GA may be more important for LOS than presently reported. A more detailed analysis of morbidity data in each GA strata and its relation to LOS is a topic for further research.

6.2   ORGANIZATIONAL ASPECTS ON NEONATAL CARE

From the findings that LOS was shortened during the last 20 years without a corresponding decrease in neonatal morbidity, we hypothesized that changes in organization of care for moderately preterm infants may have had some impact on the decrease in length of stay. In Paper II, organization of care seems to be equally or even more important than perinatal risk factors for length of hospital stay.

Increasing admission rates and overcrowding in the NU may have contributed to the development of shorter hospital stay in Paper I. But there was also a growing parental demand for earlier discharge and a proactive search for new and safe strategies to avoid unnecessary hospitalisation of infants and parents. Two major changes in nursing care were made during the study period that may have been of importance for the decrease in length of stay: the introduction of organized home care in 1998 and the incorporation of routine use of NIDCAP into nursing care.

Organized home care can be a strategy to discharge infants earlier with maintained safety and to counteract readmissions. Early discharge has been associated with lower risk of nosocomial infection,[25] a better parental preparedness and a tendency to perceive the infants as being healthier.[26] Moreover, early discharge to home care has not been reported to increase readmissions.[25] Designed to decrease stress for the preterm infant, NIDCAP customizes care to match individual needs, involves parents more in the care of their infant and may save costs and resources.[109]

At Danderyd Hospital, Stockholm (Paper I), transfer of infants to other secondary level neonatal units before discharge to home became somewhat more common in 2002 than the years before due to a rising number of births without a corresponding increase of NU beds. This was a contributing factor to the overall decrease in length of stay during 2002. However, shorter hospital stay because of patient transfer does not decrease costs for the society because the care continues in another unit. In addition, parents often experience increased stress and anxiety in these situations and transfer of infants between units and hospitals should be limited to those instances in which there is a medical indication.

In Paper I, length of neonatal stay for moderately preterm infants decreased in average 14 days from 1983 to 2002. Assuming that 2200 moderately preterm infants are born in Sweden every year and that the average length of stay is reduced by 14 days, national savings would be worth an estimated 330 million SEK (52,8 million USD)/year. In Paper II, mean postmenstrual age at discharge differed almost two weeks between the most extreme clinics. With the assumption that these hospitals had 50 admitted moderately preterm infants every year, and that costs for neonatal care is the same as in Karolinska Hospital, the clinic with the highest LOS would have costs that are 7.5 million SEK (1.2 million USD) higher than the clinic with the shortest LOS every year. It should be noted that this difference is calculated only in the moderately preterm group. Although these examples are crude, the savings and/or costs for society that can be calculated this way are nonetheless worth a thought.

In Sweden and in other countries, centralization of neonatal care to improve outcome is only recommended for extremely preterm infants. As demonstrated in Paper III, significant morbidity – qualifying many infants for neonatal intensive care – also occurs in very preterm infants. Reassuringly, infant mortality has not been found to differ between regional centers of excellence and general hospitals in infants born at 28-31 weeks gestational age in Sweden.[15] However, based on our findings, the discussion of how to organize neonatal care should perhaps not be restricted to the most immature group but also include very preterm infants.

6.3 NEONATAL MORBIDITY

The major finding in our national population-based study of 6,674 infants was that moderately preterm infants still have substantially increased risks for neonatal morbidity, despite general advances in perinatal care. Rates of neonatal morbidity for each gestational week were similar to results of previous reports.[67,72,75,77] The morbidities increased as GA decreased from 34 to 30 weeks. In Paper IV, risks of TTN and RDS among moderately preterm infants were increased by 23 and 180 times, respectively, when compared with late preterm to term infants (born at 35-41 weeks). Nasal CPAP was the major treatment for respiratory problems, which differed markedly from other studies.[67,77]

In a US study of infants born at 30-34 completed weeks, Escobar et al. found lower rates of IVH and ROP as compared to our study.[67] In the US study, bronchopulmonary

dysplasia (defined similarly in both studies) was three times more common and infants were more often treated with ventilator than with nCPAP as compared to Sweden. In addition, 5 times more infants in the US study received surfactant compared to Sweden. These differences in acute management of respiratory disorders most likely reflect different care traditions.[110] Nasal CPAP is frequently used in Sweden, not only for acute respiratory disorders but also to stabilize and decrease work of breathing and for treatment of apnea of prematurity. Such practice is poorly evidence-based in moderately preterm infants, but spontaneously breathing extremely preterm infants have been shown to benefit from nCPAP as compared to being mechanically ventilated from start.[111] Kirkby et al.[77] reported rates of PDA, BPD and NEC that were higher and rates of PVL and severe IVH that were lower than in our data for the same GAs. Similar to Escobar's study, ventilator treatment was much more common than in our study.

In Paper III, the overall rate of hypoglycemia was 16%, which is similar or higher as compared to rates previously reported in late preterm infants (6.8-16%)[72,75] but lower than that seen in extremely preterm infants (41%).[112] In view of these figures and of the fetal growth distributions, the finding of a trend towards gradually *increasing* prevalence of hypoglycemia in more mature infants, is intriguing. In Sweden, all preterm infants, also those without any symptoms, are repeatedly screened for hypoglycemia, the first blood test being performed within 3 hours after birth. However, we cannot exclude that there are GA-related differences in screening procedures that could have contributed to the unexpected trend of increasing prevalence of hypoglycemia at higher GA. Prevention of hypoglycemia may also have been more effective at lower GA because of more frequent use of intravenous glucose infusions in infants with acute respiratory disorders. Finally, we had no data on the distribution of maternal diabetes – a known risk factor for neonatal hypoglycemia – in relation to GA.

6.4 RISK FACTORS FOR ACUTE RESPIRATORY MORBIDITY

The very to moderately preterm infants represent a large group at the neonatal unit that generally has a good prognosis. However, a substantial part of these infants experience medical problems and complications resulting from their prematurity. Among these problems, acute respiratory disorders stand out as a leading morbidity category.

In our national population-based study, analyses of risk factors for the two most common respiratory disorders within the group of moderately preterm infants, TTN and RDS, revealed three important findings: first, increased risks for both TTN and RDS were associated with low GA, low Apgar scores and delivery by Cesarean section, as well as with multiparity and male sex. Second, vaginal delivery, premature rupture of membranes, antenatal corticosteroid therapy and SGA status were associated with a reduced risk of RDS. Finally, maternal age, obesity, assisted reproduction, smoking in pregnancy, chronic disease or preeclampsia did not affect the risk of acute respiratory morbidity in moderately preterm infants.

Cesarean section, both before and after onset of labor, more than doubled the risk of RDS. In addition, TTN was also more common after Cesarean section. This is in line with previous studies of term infants that have reported increased risks for neonatal respiratory morbidity after Cesarean section as compared to vaginal delivery, also after adjustment of other risk factors and confounders.[113,114] There are several proposed explanations for the association between Cesarean section and neonatal respiratory disease. These include lack of mechanical squeezing of lung fluid during the passage through the birth canal, absence of molecular promotion of alveolar fluid drainage by activation of sodium channels,[46] and lack of the physiological surge of stress hormones[115] seen in the fetus during labor and vaginal delivery.

Increasing Cesarean section rates[116] could be one explanation for the increment in rates of both TTN and RDS found in moderately preterm infants. Since RDS is common with overall rates varying from 40% at 30 weeks of GA to 5% at 34 weeks of GA (Paper III), the added risk after Cesarean section carries a significant contribution to neonatal respiratory morbidity in absolute numbers.

The finding that multiparity is associated to a higher risk of general respiratory morbidity has been reported by others.[72,117] In our study, this association was restricted to TTN. Possible underlying mechanisms remain unclear, and other studies have found higher risks for general neonatal morbidity in nulliparous women.[118] Few studies have focused on the association between parity and neonatal respiratory morbidity.

The male disadvantage in neonatal respiratory morbidity is well known from previous studies. RDS and other respiratory diseases are more common in boys than in girls.[119] Preterm boys need more respiratory support than girls.[120] The cause of this sex difference is so far largely unknown, but sex-specific hormonal influences on fetal lung development have been proposed.[121]

PPROM has been associated with an increased risk[118] or no risk[122] for RDS in preterm infants. In contrast, our study showed that PPROM was protective of RDS. The risk of neonatal respiratory disease after PPROM is modified by many factors, such as GA, SGA status, latency period to delivery,[118] presence of histological chorioamnionitis[122] and use of antibiotic therapy.[48] Prenatal exposure to cytokines and inflammatory mediators during subclinical or clinical chorioamnionitis after prelabor premature rupture of membranes has been thought to accelerate fetal lung maturation and decrease the incidence of RDS,[123] However, clinical observations have been contradictory and both beneficial and detrimental effects of inflammation on the fetal lung have been shown.[124-126]

Although there is evidence that antenatal corticosteroid treatment is effective for RDS-prevention in preterm infants,[48,127] antenatal steroids were only administered to one third of the moderately preterm infants. This is most likely reflecting variations in practice with respect to the upper GA limit for steroid administration. We have previously found that 39% of Swedish pregnant women at 33 weeks and 12% at 34

gestational weeks were treated with antenatal corticosteroids (Paper III). In a recent US study, infant mortality and respiratory distress syndrome rates were studied in preterm infants of 33-34 gestational weeks between 1995-97 and 2002-04. The conclusion was that treatment with antenatal steroids may be beneficial also in this group of moderately preterm infants.[128] Given the high number of infants and a RDS-rate of 5-9 % (Paper III) at these gestational weeks, as well as the short and long-term safety of one-course antenatal corticosteroid treatment,[48,50,127] current practice and recommendations in Sweden should be discussed.

Intrauterine growth restriction (IUGR) has previously been regarded as a protective factor for RDS, according to similar lung maturation theories as with inflammation.[129,130] Recently, the opinion seems to have changed towards a more cautious interpretation of the effect of IUGR on RDS. Studies have shown both increased and decreased RDS rates in SGA infants, and that the effect of IUGR may vary by gestational age.[131] Animal models have shown that IUGR in fact does not accelerate lung maturation but delays it.[132,133] In Paper III, SGA was significantly more common at lower GA and being born SGA was associated with increased risks for most of the observed neonatal diagnoses (but not RDS).

6.5 INTERNAL AND EXTERNAL VALIDITY

The two major threats to the validity of a scientific study are systematic and random errors. Random errors usually disappear with a larger sample size and are discussed further under "precision". Systematic errors are also called bias, and will not decrease if the study sample is increased. Examples of common bias are selection bias, misclassification bias, recall bias and confounding. Selection bias occurs when participation in a study is associated to the incidence of exposure or outcome studied. Misclassification bias is occurring when data on the study subjects holds errors in a systematic way. Recall bias is when study subjects are asked questions in retrospect and the quality of collected data systematically differ between those with and without the disease. Confounding is when the association between a risk factor and an outcome is influenced by one or more other factors. There are many more examples of bias that will not be presented herein.[134] In the study design, researchers must take all possible precautions to avoid bias. For example, measurements of risk factors and outcomes can be specified and standardized, study subjects blinded to the purpose of the study, data collectors blinded to the individual's outcome, data collected prospectively and confounding factors identified and controlled for in statistical analyses.

Internal validity

If the result of a study can be trusted to be close to the true value in the studied population, the internal validity is said to be high. Bias, especially misclassification, recall bias and confounding, have a negative effect on internal validity.

In this thesis, we have tried to improve the internal validity in several ways. In Paper I, the dating of pregnancies was made by last menstrual period in 1983-88 and by ultrasound scanning in most pregnancies in the later cohorts. To some degree, this could have confounded the comparisons of postmenstrual age at discharge between

early and later year cohorts. However, the decrease in postmenstrual age at discharge also appeared between 1993 and 2002, when ultrasound dating was generally used to estimate gestational age. The dating of pregnancies by last menstrual period resulted in an age estimate of completed gestational weeks. In the following cohorts, antenatal ultrasound was used for gestational age estimation and was expressed as completed weeks and days. To avoid underestimation of the postmenstrual age at discharge for the 1983 and 1988 cohorts, 3.5 days was added to the completed gestational weeks for those infants.

The internal validity of studies II-IV depends mainly on the quality of the PNQ register. The prospective design and predefined diagnostic criteria for outcome measures minimizes the risk of recall bias. We have found very few missing data in Papers II-III. However, there has been no proper validation of the register. Another limitation is that infections could not be separated into subcategories and were presented in one group, including both life-threatening and relatively harmless infections.

External validity

When performing a study on a population sample, for example a group of patients with a specific diagnosis in a local hospital, the aim is always to extrapolate the results to a larger population, for example individuals with the same diagnosis all over the country, or even all over a continent. This is not always possible – populations are different, diagnostic tools vary across countries, clinical routines regarding diagnosis and treatment may differ between hospitals and even between doctors. The external validity is especially sensitive to selection bias.

Paper I is based on data from a local Swedish hospital and it is perhaps not possible to generalize the results to a larger population. However, we suspect that similar results on length of hospital stay for moderately preterm infants can be found in at least the neonatal units in Stockholm County. Analogous results on admissions and utility of neonatal resources have also been found in the US.[135]

As we cover a majority (63% in Paper II and 81% in Paper III-IV) of all Swedish moderately preterm infants born in recent years, the results of this thesis can be generalized to contemporary Scandinavian populations of infants born at 30-34 gestational weeks.

Precision

Random errors are the variability in study results that cannot be explained by bias. The easiest way to deal with random errors is to increase the study sample. The minimum sample size must be estimated in advance before initiation of a study and is done by a power calculation. A properly performed statistical analysis is the next step to avoid random errors.

The number of included infants in the studies of this thesis was large, which provided high precision in estimates and a low risk of random errors. However, in Paper II, the number of included hospitals was too low to allow analyses on hospital level.

6.6 CLINICAL IMPLICATIONS

Moderately preterm births account for a large proportion of the growing population of preterm infants, as well as children and adults once born preterm. Contemporary reports on their neonatal period have been sparse in the recent decades but in the last years, we have observed an increased interest for these infants. Well-performed studies on their neonatal outcome and resource utilization may be helpful to renew medical knowledge and customize obstetric and neonatal care to the specific needs of moderately preterm infants.

Our findings on length of hospital stay suggest that organization of neonatal care can be adapted to shorten hospital stay, for the benefit of infant, family and neonatal unit resources. The findings that neonatal morbidity has only a small impact on length of hospital stay and that postmenstrual age at discharge varies considerably between hospitals, can stimulate new evaluations of hospital stay in infants of all gestational ages, and local overviews to streamline organization of care. Organized home care and individualized care for newborn infants may decrease length of hospital stay with maintained safety level, and thereby allocate resources from healthy and relatively mature infants to more severely ill infants. In addition to well-known positive effects on health, nutrition and mother-infant relationship, our results indicate that breastfeeding is associated with a shorter length of hospital stay.

As demonstrated in this thesis, moderately preterm infants are at high risk of neonatal morbidity. It seems that the general expectancy on outcome of moderately preterm birth is better than the actual numbers shown in this thesis. To highlight risks of neonatal morbidity, the results of the included studies may be used in specific education programmes. Based on our findings that infants in the lower gestational weeks of our study population are at such high risk of neonatal intensive care, centralization of care for infants born below 30-32 gestational weeks may be discussed in Sweden.

Results on neonatal morbidity in this thesis may also add to knowledge and arguments in discussions between neonatologists and obstetricians when it comes to elective preterm delivery. This is most applicable in cases of relative maternal indication of moderately preterm delivery, such as pain, humanitarian causes or general discomfort. In these cases, a postponed delivery may be argued for on the basis of our results, which show that infants born at 30-34 gestational weeks by no means can be regarded as "almost term" or mature. This thesis also attempts to predict the infants most at risk of developing acute respiratory morbidity, which may increase clinical awareness of disease symptoms in exposed infants. In addition, the information provided can be used to individualize risk-assessment when counselling parents facing moderately preterm birth.

More specifically, the included morbidity studies in this thesis indicate that acute respiratory diseases are common in the moderately preterm group. The European guidelines recommend treatment with single-dose antenatal corticosteroids to all mothers giving birth before 35 completed gestational weeks. Given the rather high rate of RDS (5-9%) in infants of 33-34 gestational weeks in our studies, it seems reasonable to discuss an extension of antenatal steroid use to include these gestational ages in Sweden.

7 CONCLUSIONS

- Length of stay at the neonatal unit has decreased significantly for moderately preterm infants over the last twenty years. We did not detect any changes in the panorama of diseases that could explain the shortening of length of stay. We conclude that individualized hospital care and development of home care have contributed to this finding.

- Perinatal risk factors have small overall impact on length of hospital stay in moderately preterm infants. Organization of care is probably an important factor. The number of bed-days differs significantly between centres, which may have effects on quality of care and health economy.

- Despite general advances in perinatal care, moderately preterm infants still face increased risks for neonatal morbidity and need for neonatal interventions and treatments. Morbidity rates increased as gestational age decreased, SGA was more common at lower gestational ages and being born SGA was associated with increased risks for most of the observed neonatal diagnoses.

- Risks of TTN and RDS among moderately preterm infants (born at 30-34 weeks) were increased by 23 and 180 times, respectively, when compared with late preterm to term infants (born at 35-41 weeks). Delivery by Cesarean section, low gestational age, low Apgar scores, and male sex were associated with higher risks for TTN and RDS. Antenatal corticosteroid therapy was associated with a reduced risk of RDS, and should be considered in all pregnancies with imminent preterm delivery at 34 weeks or less.

8 TOPICS FOR FUTURE RESEARCH

Moderately preterm infants represent a large proportion of all preterm infants and at 30-34 gestational weeks, they account for half the number of bed-days in NU and a third of all preterm infants. The research field of moderately preterm infants includes further areas to be mapped.

The results on length of hospital stay in this thesis indicate that organized home care programs may be a method to reduce the hospital stay. This may have a positive impact on the cost-benefit of neonatal care in general. The modern health care system deals continuously with questions on how to use financial resources in the most effective way. Health economical evaluations on the transition from a full neonatal unit stay to discharge to home care after physiologic stabilization, would answer questions on this topic.

Furthermore, results from our and other studies suggest that care organization is an important factor on length of hospital stay. These factors are often more difficult to evaluate than for examples measures of morbidity. How does staff numbers, workload, clinical and theoretical competence of staff, breastfeeding policies and care strategies affect length of stay? Some of these factors have been evaluated previously[97,136,137] in a smaller context but no study takes them all into account. It would be of interest from a health economical point of view to evaluate which organizational changes can be made to reduce the length of hospital stay, with maintained quality of care, in this large group of infants at the neonatal unit.

The relationship between IUGR and neonatal morbidity seems to be enigmatic. In our studies, SGA was a risk factor for most important neonatal diagnoses, but not all. In contrary, SGA reduced the risk of RDS in moderately preterm infants. Previous studies have shown both increased and decreased RDS incidence in SGA infants, and that the effect of IUGR may vary by gestational age.[131] Further studies focusing on IUGR and risk of specified neonatal morbidity, stratified by gestational age and perhaps supported by genetic and animal studies, may help solve the puzzle. The susceptibility of some infants to adverse neonatal outcomes may not only be environmental, but also genetic. Studies on genetic association, generation studies and twin studies may help explain why some infants have complications from moderately preterm birth and others do not.

As shown in this thesis, moderately preterm infants are at a substantial risk of morbidity and complications in the neonatal period. The next question is how they are doing as pre-school children, school children, adolescents and adults? There are a few studies published on long-term follow-up of moderately preterm infants, indicating that they face a higher risk of long-term disability,[64,79] psychiatric disorder requiring hospitalization in adolescence,[3] diabetes,[2] hypertension,[1] asthma[82] and ADHD in childhood.[83] Further studies on long-term consequences of moderately preterm birth in the modern era of neonatology are needed.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Måttligt för tidig födsel, i den här avhandlingen definierad som födsel i graviditetsvecka 30-34, står för 2% av alla födslar per år i Sverige (~2 000 barn). Den övervägande majoriteten av de måttligt för tidigt födda barnen läggs in på neonatalavdelning för övervakning och tillmognad. Under senare år har man uppmärksammat bristen på vetenskapliga studier av gruppen måttligt för tidigt födda barn efter moderniseringen av västerländsk nyföddhetsvård. Den här avhandlingen avser att belysa de måttligt för tidigt födda barnen ur ett epidemiologiskt perspektiv, med aspekter på vårdtider samt sjuklighet i nyföddhetsperioden.

I delarbete I visar resultaten att nästan hälften av alla barn som ligger inne på nyföddhetsavdelningarna är födda i graviditetsvecka 30-34. Under en 20-årsperiod har dessa barns vårdtider kortats med en dryg vecka utan att sjukligheten minskat. Den största förändringen i vårdtid skedde i slutet av 90-talet och början av 2000-talet. Dessa fynd tillskrivs främst organisatoriska förändringar i vården, såsom införandet av hemsjukvård och individualiserad omvårdnad (NIDCAP) för nyfödda barn.

Med delarbete II, en större studie som innefattar 63% av alla neonatalavdelningar i Sverige, kunde vi visa att vårdtiderna för denna grupp barn skiljde sig med upp till två veckor mellan olika svenska sjukhus. När vi tagit hänsyn till graviditetstidens längd, hade inte barnens sjuklighet i sig någon stor effekt på vårdtidens längd medan organisatoriska faktorer såsom sjukhusstorlek, sjukhusnivå, möjlighet till samvård av mamma och barn samt tillgång till hemsjukvård verkade vara betydelsefulla. Amning minskade tiden på sjukhus jämfört med uppfödning på flaska.

Dessa studier av vårdtider indikerar att man med hjälp av en genomtänkt vårdorganisation och införande av hemsjukvård med möjlighet till syrgasbehandling, sondmatning, apnélarm och stöd av specialutbildad sjuksköterska, kan begränsa tiden på sjukhus för denna grupp barn utan att riskera deras hälsa. Detta ger fördelar för både barnets och familjens välmående samtidigt som man får en trygg övergång från sjukhustiden till att klara av att själv ta hand om sitt barn hemma. Dessutom frigör man resurser och sängplatser från neonatalavdelningen som kan användas till att övervaka och behandla de allra mest ömtåliga, extremt för tidigt födda barnen.

Då ett barn föds i graviditetsvecka 30-34, förväntar sig i allmänhet både föräldrar och vårdpersonal att nyföddhetsperioden ska förlöpa godartat och komplikationsfritt. I landsomfattande svenska studier under tiden 2004-2008 kan vi nu bekräfta data från bland annat USA och visa att de måttligt för tidigt födda bär på en väsentlig risk att insjukna och behöva behandlingsinsatser i nyföddhetsperioden. De vanligaste diagnoserna är, förutom nyföddhetsgulsot och lågt blodsocker, akuta andningssjukdomar, som drabbar 28 % av de måttligt underburna barnen. Risken att drabbas av en komplikation ökar med sjunkande graviditetslängd för majoriteten av diagnoserna. Tillväxthämning under fosterlivet var vanligare bland de mer omogna

barnen och detta tillstånd ökade också risken att insjukna i merparten av de studerade diagnoserna hos de nyfödda.

I delarbete 4 bestämdes risken att drabbas av ett antal andningssjukdomar hos 4,679 måttligt för tidigt födda barn jämfört med en referenspopulation av 467,629 svenska barn födda i graviditetsvecka 35-41 under samma tidsperiod. De måttligt underburna hade en avsevärt ökad risk att drabbas av akuta andningssjukdomar. Risken att drabbas av pulmonell adaptationsstörning (TTN) var 23 gånger större och risken att insjukna i akut lungsjukdom (RDS) var 180 gånger större för måttligt för tidigt födda jämfört med referenspopulationen. Inom gruppen måttligt för tidigt födda barn genomfördes en riskanalys av faktorer hos mamma, graviditet, förlossning och barn. Följande faktorer ökade risken att insjukna i akuta andningssjukdomar (TTN och/eller RDS) inom gruppen måttligt för tidigt födda barn: kejsarsnitt, hög omognadsgrad, låga Apgarpoäng vid födelsen och manligt kön. För tidig hinnbristning, behandling med kortikosteroider före förlossningen samt tillväxthämning var skyddande mot RDS. Mammans ålder, kroniska sjuklighet och rökvanor hade ingen effekt på risken att insjukna i akuta andningssjukdomar.

I det dagliga arbetet på landets sjukhus, kan denna nya information om sjuklighet hos måttligt för tidigt födda både bidra till ett bättre och mer riskanpassat omhändertagande redan vid förlossningen, samt vara ett argument i diskussionerna mellan förlossningsläkare och barnläkare vid hotande för tidig förlossning. Resultaten pekar tydligt på vinsten av att senarelägga förlossningen i de fall då det är möjligt, även vid graviditetslängder som närmar sig fullgångna. Vidare kan nyfödda barn med identifierade riskfaktorer hållas under särskild uppsikt med avseende på akuta andningssymtom, och få snabbare behandling med bättre resultat. Föräldrar som står inför risken att föda i graviditetsvecka 30-34 kan bättre informeras om vad som kan vänta deras barn efter förlossningen.

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11 REFERENCES

1.   Johansson S, Iliadou A, Bergvall N, et al. Risk of high blood pressure among young men increases with the degree of immaturity at birth. Circulation 2005;112:3430-6.

2.   Kaijser M, Bonamy AK, Akre O, et al. Perinatal risk factors for diabetes in later life. Diabetes 2009;58:523-6.

3.   Lindstrom K, Lindblad F, Hjern A. Psychiatric morbidity in adolescents and young adults born preterm: a Swedish national cohort study. Pediatrics 2009;123:e47-53

4.   Lindstrom K, Winbladh B, Haglund B et al. Preterm infants as young adults: a Swedish national cohort study. Pediatrics 2007;120:70-7.

5.   Statistiska Centralbyrån, SCB [Vital Statistics Sweden]. Database. (Accessed 2011-03-01, at www.scb.se.)

6.   SBU [Swedish Council on Technology Assessment in Health Care] Rutinmässig ultraljudsundersökning under graviditet [Routine Ultrasound Examination in Pregnancy] Swedish; 1998. Report No.: 139.

7.   Socialstyrelsen. Socialstyrelsen [Swedish National Board of Health and Welfare]:Report 2011-3-19, bilaga 201.

8.   Socialstyrelsen [Swedish National Board of Health and Welfare]: Statistics on Swedish Births (Swedish). (Accessed January 2011, at http://www.socialstyrelsen.se/statistik/statistikdatabas.)

9.   Centers for Disease Control and Prevention. USA National Center for Health Statistics. (Accessed 4/12/2009, at http://www.cdc.gov/nchs/vitalstats.htm.)

10.   Stark AR. Levels of neonatal care. Pediatrics 2004;114:1341-7.

11.   Chien LY, Whyte R, Aziz K, et al. Improved outcome of preterm infants when delivered in tertiary care centers. Obstet Gynecol 2001;98:247-52.

12.   Menard MK, Liu Q, Holgren EA, et al. Neonatal mortality for very low birth weight deliveries in South Carolina by level of hospital perinatal service. Am J Obstet Gynecol 1998;179:374-81.

13.   Bowman E, Doyle LW, Murton LJ, et al. Increased mortality of preterm infants transferred between tertiary perinatal centres. BMJ 1988;297:1098-100.

14.   Fellman V, Hellstrom-Westas L, Norman M, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009;301:2225-33.

15.   Johansson S, Montgomery SM, Ekbom A, et al. Preterm delivery, level of care, and infant death in sweden: a population-based study. Pediatrics 2004;113:1230-5.

16.   Ortenstrand A, Westrup B, Brostrom EB, et al. The Stockholm Neonatal Family Centered Care Study: effects on length of stay and infant morbidity. Pediatrics 2010;125:e278-85.

17.   Als H, Lawhon G, Duffy FH, et al. Individualized developmental care for the very low-birth-weight preterm infant. Medical and neurofunctional effects. JAMA 1994;272:853-8.

18.   Rose C, Ramsay L, Leaf A. Strategies for getting preterm infants home earlier. Arch Dis Child 2008;93:271-3.

19.   Westrup B. Newborn Individualized Developmental Care and Assessment Program (NIDCAP) - family-centered developmentally supportive care. Early Hum Dev 2007;83:443-9.

20.   Westrup B, Bohm B, Lagercrantz H, et al. Preschool outcome in children born very prematurely and cared for according to the Newborn Individualized Developmental Care and Assessment Program (NIDCAP). Acta Paediatr 2004;93:498-507.

21.   Committee on Hospital Care. American Academy of Pediatrics. Family-centered care and the pediatrician's role. Pediatrics 2003;112:691-7.

22.   Als H, Lawhon G, Brown E, et al. Individualized behavioral and environmental care for the very low birth weight preterm infant at high risk for bronchopulmonary dysplasia: neonatal intensive care unit and developmental outcome. Pediatrics 1986;78:1123-32.

23.   Fleisher BE, VandenBerg K, Constantinou J, et al. Individualized developmental care for very-low-birth-weight premature infants. Clin Pediatr (Phila) 1995;34:523-9.

24.   Jacobs SE, Sokol J, Ohlsson A. The Newborn Individualized Developmental Care and Assessment Program is not supported by meta-analyses of the data. J Pediatr 2002;140:699-706.

25.   Ortenstrand A, Waldenstrom U, Winbladh B. Early discharge of preterm infants needing limited special care, followed by domiciliary nursing care. Acta Paediatr 1999;88:1024-30.

26.   Ortenstrand A, Winbladh B, Nordstrom G, et sl. Early discharge of preterm infants followed by domiciliary nursing care: parents' anxiety, assessment of infant health and breastfeeding. Acta Paediatr 2001;90:1190-5.

27.   Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet 2008;371:75-84.

28.   Engle WA, Tomashek KM, Wallman C. "Late-preterm" infants: a population at risk. Pediatrics 2007;120:1390-401.

29.   Skalkidou A, Kieler H, Stephansson O, et al. Ultrasound pregnancy dating leads to biased perinatal morbidity and neonatal mortality among post-term-born girls. Epidemiology 2010;21:791-6.

30.   Morin I, Morin L, Zhang X, et al. Determinants and consequences of discrepancies in menstrual and ultrasonographic gestational age estimates. BJOG 2005;112:145-52.

31. Savitz DA, Terry JW, Jr., Dole N, et al. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. Am J Obstet Gynecol 2002;187:1660-6.

32. Mercer BM, Goldenberg RL, Meis PJ, et al. The Preterm Prediction Study: prediction of preterm premature rupture of membranes through clinical findings and ancillary testing. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 2000;183:738-45.

33. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG 2006;113 Suppl 3:17-42.

34. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. N Engl J Med 2010;362:529-35.

35. Goldenberg RL, Cliver SP, Mulvihill FX, et al. Medical, psychosocial, and behavioral risk factors do not explain the increased risk for low birth weight among black women. Am J Obstet Gynecol 1996;175:1317-24.

36. Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. N Engl J Med 1999;341:943-8.

37. Wikstrom AK, Stephansson O, Cnattingius S. Previous preeclampsia and risks of adverse outcomes in subsequent nonpreeclamptic pregnancies. Am J Obstet Gynecol 2011;204:148 e1-6.

38. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500-7.

39. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res 2004;6 Suppl 2:S125-40.

40. Wikstrom AK, Cnattingius S, Galanti MR, et al. Effect of Swedish snuff (snus) on preterm birth. BJOG 2010;117:1005-10.

41. Svensson AC, Sandin S, Cnattingius S, et al. Maternal effects for preterm birth: a genetic epidemiologic study of 630,000 families. Am J Epidemiol 2009;170:1365-72.

42. Draper ES. Evaluating and comparing neonatal outcomes. Arch Dis Child Fetal Neonatal Ed 2010;95:F158-9.

43. Kramer MS, Platt RW, Yang H, et al. Registration artifacts in international comparisons of infant mortality. Paediatr Perinat Epidemiol 2002;16:16-22.

44. Kramer MS, Wilkins R, Goulet L, et al. Investigating socio-economic disparities in preterm birth: evidence for selective study participation and selection bias. Paediatr Perinat Epidemiol 2009;23:301-9.

45. Lagercrantz H Hellström-Westas Lena, Norman M (ed). Neonatologi (Swedish): Studentlitteratur; 2008.

46. Jain L, Dudell GG. Respiratory transition in infants delivered by cesarean section. Semin Perinatol 2006;30:296-304.

47.   Rennie JM Roberton NRC (ed). Textbook of Neonatology. 3 ed: Churchill and Livingstone; 1999.

48.   Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 update. Neonatology;97:402-17.

49.   Jobe AH. Lung maturation: the survival miracle of very low birth weight infants. Pediatr Neonatol 2010;51:7-13.

50.   Eriksson L, Haglund B, Ewald U, et al. Short and long-term effects of antenatal corticosteroids assessed in a cohort of 7,827 children born preterm. Acta Obstet Gynecol Scand 2009;88:933-8.

51.   Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50:515-25.

52.   Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010;125:1020-30.

53.   Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114:e130-53.

54.   Sarici SU, Serdar MA, Korkmaz A, et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. Pediatrics 2004;113:775-80.

55.   Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. N Engl J Med 2001;344:581-90.

56.   McCrea HJ, Ment LR. The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol 2008;35:777-92, vii.

57.   Skiold B, Horsch S, Hallberg B, et al. White matter changes in extremely preterm infants, a population-based diffusion tensor imaging study. Acta Paediatr 2010;99:842-9.

58.   Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009;8:110-24.

59.   Bell EF. Preventing necrotizing enterocolitis: what works and how safe? Pediatrics 2005;115:173-4.

60.   Salvin JH, Lehman SS, Jin J, Hendricks DH. Update on retinopathy of prematurity: treatment options and outcomes. Curr Opin Ophthalmol 2010;21:329-34.

61.   Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.

62.   Tibboel D, Jobe AH. Update in pediatric lung disease 2009. Am J Respir Crit Care Med 2010;181:661-5.

63.   Martin JA, Kung HC, Mathews TJ, et al. Annual summary of vital statistics: 2006. Pediatrics 2008;121:788-801.

64.   Petrini JR, Dias T, McCormick MC, et al. Increased risk of adverse neurological development for late preterm infants. J Pediatr 2009;154:169-76.

65.   Soria-Pastor S, Padilla N, Zubiaurre-Elorza L, et al. Decreased regional brain volume and cognitive impairment in preterm children at low risk. Pediatrics 2009;124:e1161-70.

66.   Escobar GJ, Clark RH, Greene JD. Short-term outcomes of infants born at 35 and 36 weeks gestation: we need to ask more questions. Semin Perinatol 2006;30:28-33.

67.   Escobar GJ, McCormick MC, Zupancic JA, et al. Unstudied infants: outcomes of moderately premature infants in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed 2006;91:F238-44.

68.   Jakobsson M, Gissler M, Paavonen J, Tapper AM. The incidence of preterm deliveries decreases in Finland. BJOG 2008;115:38-43.

69.   Cnattingius S, Haglund B. Socio-economic factors and feto-infant mortality. Scand J Soc Med 1992;20:11-3.

70.   Kyrklund-Blomberg NB, Cnattingius S. Preterm birth and maternal smoking: risks related to gestational age and onset of delivery. Am J Obstet Gynecol 1998;179:1051-5.

71.   Costeloe K, Hennessy E, Gibson AT, et al. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000;106:659-71.

72.   Melamed N, Klinger G, Tenenbaum-Gavish K, et al. Short-term neonatal outcome in low-risk, spontaneous, singleton, late preterm deliveries. Obstet Gynecol 2009;114:253-60.

73.   Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 2004;114:372-6.

74.   Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, et al. Effect of late-preterm birth and maternal medical conditions on newborn morbidity risk. Pediatrics 2008;121:e223-32.

75.   Adamkin DH. Late preterm infants: severe hyperbilirubinemia and postnatal glucose homeostasis. J Perinatol 2009;29 Suppl 2:S12-7.

76.   Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006;118:1207-14.

77.   Kirkby S, Greenspan JS, Kornhauser M, Schneiderman R. Clinical outcomes and cost of the moderately preterm infant. Adv Neonatal Care 2007;7:80-7.

78.   Chyi LJ, Lee HC, Hintz SR, Gould JB, Sutcliffe TL. School outcomes of late preterm infants: special needs and challenges for infants born at 32 to 36 weeks gestation. J Pediatr 2008;153:25-31.

79.   van Baar AL, Vermaas J, Knots E, et al. Functioning at school age of moderately preterm children born at 32 to 36 weeks' gestational age. Pediatrics 2009;124:251-7.

80.   Ekeus C, Lindstrom K, Lindblad F, et al. Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19-year-old men. Pediatrics;125:e67-73.

81.   Dalziel SR, Lim VK, Lambert A, et al. Psychological functioning and health-related quality of life in adulthood after preterm birth. Dev Med Child Neurol 2007;49:597-602.

82.   Lindström K. Preterm Birth and Inhaled Corticosteroid usage in 6-19 year-olds. A Swedish National Cohort Study. Manuscript. In; 2011.

83.   Lindström K. Preterm Birth and ADHD in School Children: A National Population-Based Study. Manuscript. In; 2011.

84.   Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659-67.

85.   Socialstyrelsen. [Swedish National Board of Health and Welfare] Graviditeter, förlossningar och nyfödda barn - Medicinska Födelseregistret 1973-2008, Assisterad befruktning 1991-2007. [Pregnancies, Deliveries and newborn infants. The Swedish Medical Birth Register 1973-2008. Assisted Conceptions 1991-2007.] (Swedish)

86.   Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. Scand J Soc Med 1990;18:143-8.

87.   Socialstyrelsen. [Swedish National Board of Health and Welfare] The Swedish Medical Birth Registry. A Summary of Content and Quality. Report 2003-112-3 2003.

88.   Kobelt G. Health economics: An Introduction to Economic Evaluation: Office of Health Economics; 2002.

89.   Ringborg A, Berg J, Norman M, et al. Preterm birth in Sweden: what are the average lengths of hospital stay and the associated inpatient costs? Acta Paediatr 2006;95:1550-5.

90.   Marsal K, Persson PH, Larsen T, et al. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr 1996;85:843-8.

91.   Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.

92.   de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 1992;49:1-6.

93.   Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.

94.   The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.

95.   Collins CT, Ryan P, Crowther CA, et al. Effect of bottles, cups, and dummies on breast feeding in preterm infants: a randomised controlled trial. BMJ 2004;329:193-8.

96.   Powell PJ, Powell CV, Hollis S, Robinson MJ. When will my baby go home? Arch Dis Child 1992;67:1214-6.

97.   Korvenranta E, Linna M, Hakkinen U, et al. Differences in the length of initial hospital stay in very preterm infants. Acta Paediatr 2007;96:1416-20.

98.   Eichenwald EC, Blackwell M, Lloyd JS, et al. Inter-neonatal intensive care unit variation in discharge timing: influence of apnea and feeding management. Pediatrics 2001;108:928-33.

99.   Eichenwald EC, Zupancic JA, Mao WY, et al. Variation in diagnosis of apnea in moderately preterm infants predicts length of stay. Pediatrics 2011;127:e53-8.

100.   Tomashek KM, Shapiro-Mendoza CK, Weiss J, et al. Early discharge among late preterm and term newborns and risk of neonatal morbidity. Semin Perinatol 2006;30:61-8.

101.   Zupancic JA, Richardson DK, O'Brien BJ, et al. Daily cost prediction model in neonatal intensive care. Int J Technol Assess Health Care 2003;19:330-8.

102.   Russell RB, Green NS, Steiner CA, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. Pediatrics 2007;120:e1-9.

103.   Richardson DK, Phibbs CS, Gray JE, et al. Birth weight and illness severity: independent predictors of neonatal mortality. Pediatrics 1993;91:969-75.

104.   Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. Am J Clin Nutr 1999;70:525-35.

105.   Kramer MS, Chalmers B, Hodnett ED, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. JAMA 2001;285:413-20.

106.   Akerstrom S, Asplund I, Norman M. Successful breastfeeding after discharge of preterm and sick newborn infants. Acta Paediatr 2007;96:1450-4.

107.   Weiss M, Ryan P, Lokken L, Nelson M. Length of stay after vaginal birth: sociodemographic and readiness-for-discharge factors. Birth 2004;31:93-101.

108.   Howard CR, Howard FM, Lanphear B, et al. Randomized clinical trial of pacifier use and bottle-feeding or cupfeeding and their effect on breastfeeding. Pediatrics 2003;111:511-8.

109.   Westrup B, Stjernqvist K, Kleberg A, et al. Neonatal individualized care in practice: a Swedish experience. Semin Neonatol 2002;7:447-57.

110.   Vanpee M, Walfridsson-Schultz U, Katz-Salamon M, et al. Resuscitation and ventilation strategies for extremely preterm infants: a comparison study between two neonatal centers in Boston and Stockholm. Acta Paediatr 2007;96:10-6; discussion 8-9.

111.   Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;358:700-8.

112. Alexandrou G, Skiold B, Karlen J, et al. Early hyperglycemia is a risk factor for death and white matter reduction in preterm infants. Pediatrics 2010;125:e584-91.

113. De Luca R, Boulvain M, Irion O, et al. Incidence of early neonatal mortality and morbidity after late-preterm and term cesarean delivery. Pediatrics 2009;123:e1064-71.

114. Morrison JJ, Rennie JM, Milton PJ. Neonatal respiratory morbidity and mode of delivery at term: influence of timing of elective caesarean section. Br J Obstet Gynaecol 1995;102:101-6.

115. Irestedt L, Dahlin I, Hertzberg T, et al. Adenosine concentration in umbilical cord blood of newborn infants after vaginal delivery and cesarean section. Pediatr Res 1989;26:106-8.

116. MacDorman MF, Menacker F, Declercq E. Cesarean birth in the United States: epidemiology, trends, and outcomes. Clin Perinatol 2008;35:293-307, v.

117. Farchi S, Di Lallo D, Franco F, et al. Neonatal respiratory morbidity and mode of delivery in a population-based study of low-risk pregnancies. Acta Obstet Gynecol Scand 2009;88:729-32.

118. Melamed N, Ben-Haroush A, Pardo J, et al. Expectant management of preterm premature rupture of membranes: is it all about gestational age? Am J Obstet Gynecol.

119. Perelman RH, Palta M, Kirby R, Farrell PM. Discordance between male and female deaths due to the respiratory distress syndrome. Pediatrics 1986;78:238-44.

120. Elsmen E, Hansen Pupp I, Hellstrom-Westas L. Preterm male infants need more initial respiratory and circulatory support than female infants. Acta Paediatr 2004;93:529-33.

121. Shinwell ES, Reichman B, Lerner-Geva L, et al. "Masculinizing" effect on respiratory morbidity in girls from unlike-sex preterm twins: a possible transchorionic paracrine effect. Pediatrics 2007;120:e447-53.

122. Zanardo V, Vedovato S, Cosmi E, et al. Preterm premature rupture of membranes, chorioamnion inflammatory scores and neonatal respiratory outcome. BJOG;117:94-8.

123. Andrews WW, Goldenberg RL, Faye-Petersen O, et al. The Alabama Preterm Birth study: polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. Am J Obstet Gynecol 2006;195:803-8.

124. Kramer BW, Kallapur S, Newnham J, Jobe AH. Prenatal inflammation and lung development. Semin Fetal Neonatal Med 2009;14:2-7.

125. Thomas W, Speer CP. Chorioamnionitis: Important Risk Factor or Innocent Bystander for Neonatal Outcome? Neonatology;99:177-87.

126. Bracci R, Buonocore G. Chorioamnionitis: a risk factor for fetal and neonatal morbidity. Biol Neonate 2003;83:85-96.

127.   Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454.

128.   Joseph KS, Nette F, Scott H, Vincer MJ. Prenatal corticosteroid prophylaxis for women delivering at late preterm gestation. Pediatrics 2009;124:e835-43.

129.   Gortner L, Wauer RR, Stock GJ, et al. Neonatal outcome in small for gestational age infants: do they really better? J Perinat Med 1999;27:484-9.

130.   Ley D, Wide-Swensson D, Lindroth M, et al. Respiratory distress syndrome in infants with impaired intrauterine growth. Acta Paediatr 1997;86:1090-6.

131.   Sharma P, McKay K, Rosenkrantz TS, Hussain N. Comparisons of mortality and pre-discharge respiratory outcomes in small-for-gestational-age and appropriate-for-gestational-age premature infants. BMC Pediatr 2004;4:9.

132.   Orgeig S, Crittenden TA, Marchant C, et al. Intrauterine growth restriction delays surfactant protein maturation in the sheep fetus. Am J Physiol Lung Cell Mol Physiol;298:L575-83.

133.   Gortner L, Hilgendorff A, Bahner T, et al. Hypoxia-induced intrauterine growth retardation: effects on pulmonary development and surfactant protein transcription. Biol Neonate 2005;88:129-35.

134.   Rothman KJ. Epidemiology an Introduction: Oxford University Press; 2002.

135.   Gray JE, McCormick MC, Richardson DK, Ringer S. Normal birth weight intensive care unit survivors: outcome assessment. Pediatrics 1996;97:832-8.

136.   Merritt TA, Raddish M. A review of guidelines for the discharge of premature infants: opportunities for improving cost effectiveness. J Perinatol 1998;18:S27-37.

137.   Profit J, Zupancic JAF, McCormick MC, et al. Moderately premature infants at Kaiser Permanente Medical Care Program in California are discharged home earlier than their peers in Massachusetts and the United Kingdom. Archives of Disease in Childhood-Fetal and Neonatal Edition 2006;91:F245-F50.