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EVIDENCE BASED CARE OF THE VERY PRETERM INFANT – STUDIES ON THERMAL CARE AND BREASTFEEDING IN EUROPE

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Evidence based care of the very preterm infant – studies on thermal care and breastfeeding in Europe

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Den verkliga upptäcktsresan består inte i att söka efter nya vyer, utan att se med nya ögon

Le véritable voyage de découverte ne consiste pas à découvrir de nouveaux horizons, mais à voir avec des yeux nouveaux
Marcel Proust

To my parents Maija and Juris Ozolins

ABSTRACT

Very preterm birth occurs in approximately 1.5% of all births in Europe. Advances in neonatal intensive care has contributed to a decline in mortality and morbidity, nevertheless very preterm birth (birth before 32 weeks of gestation) is one of the main determinants of infant mortality and short- and long-term morbidity in Europe. Both the early thermal care after delivery and the availability of breast milk and breastfeeding during neonatal care are two areas of importance for morbidity and mortality for the very preterm infant.

The objective of the European collaboration project, Effective Perinatal Care in Europe (EPICE) is to investigate if evidence-based medicine is translated into care in the obstetric and neonatal intensive care units (NICU) caring for very preterm infants. During 2011-2012, perinatal data at an individual level (cohort study) and unit level (unit study) were collected for infants born before 32 weeks of gestation in 19 regions in 11 countries in Europe, of which Stockholm is one of the regions. Paper I is based on EPICE cohort data, paper II and IV on EPICE cohort and unit data, and paper III on cohort data from the Stockholm region.

Paper I investigated the incidence of hypothermia (temperature <36.5°C) at admission to neonatal care and its association with morbidity, overall mortality, and mortality stratified by time of death during neonatal care. Paper II investigated hypothermia prevention strategies after very preterm birth and the association between reported use of prevention strategy and admission temperature to the NICU. Paper III included data from the Stockholm region and examined if early and high intake of mother's own milk and other predictors of breastfeeding were positively related to breast milk feeding near full term age (postmenstrual age (PMA) 36-40 weeks) (PMA= gestational age plus postnatal age), and paper IV studied breast milk feeding rates at discharge and individual and unit factors that might facilitate breast milk feeding at discharged from NICU.

Paper I showed that hypothermia after very preterm birth is common in European settings, more than 50% of infants admitted to the NICU had a temperature below 36.5°C. Infants who had a temperature below 35.5°C had a twofold risk of mortality during the first month of life in comparison with normothermic (36.5-37.5°C) infants. Paper II showed that in units reporting systematic use of hypothermia prevention the incidence of hypothermia at admission was 54% and in units reporting no systematic use (sometimes or in infants <28 weeks/1000g) it was 75%. In adjusted analysis of no systematic use of hypothermia prevention with systematic use as reference group, the odds ratio of hypothermia at admission was 2.19, 95% CI (1.47-3.24). Hyperthermia was seen in 4.8% of all infants admitted to NICU.

In paper III 80% of the infants in the Stockholm region received breast milk at 36 weeks PMA (55% exclusively and 25% partially). High provision of mother’s own milk was associated with exclusive breast milk feeding at discharge. Between PMA 36 and 40 weeks, breast milk feeding decreased overall, but this decrease was not associated with investigated

predictors. Among infants receiving exclusive breast milk feeding at 40 weeks PMA, 76% were breastfed directly from the breast.

Paper IV showed large variations in breast milk feeding rates at discharge across the regions in Europe (36-80%). Mother's own milk, compared to donor milk or formula, at first enteral feed was associated with exclusive breast milk feeding at discharge from the NICU. Infants in units with a Baby Friendly Hospital initiative (BFHI) accreditation were more likely to receive any maternal milk at discharge. In units that used donor milk in the neonatal period, infants were more likely to be exclusively breast milk fed at discharge from NICU. The proportion of breastfeeding directly from the breast varied between the regions (16-93%).

In conclusion, hypothermia at admission is common among infants born very preterm despite availability evidence-based hypothermia preventing strategies. Temperatures <35.5°C at admission were strongly associated with increased mortality. This calls for emphasizing hypothermia prevention and monitoring of the infant's temperature already in the delivery room. Large variations in breastfeeding at discharge were seen between the EPICE regions. Early breastfeeding support improved breast milk feeding at discharge. This illustrates the potential and the key role the NICU has in improving breastfeeding rates after very preterm birth.

The overall conclusion is that there is room for improvement in thermal care and breastfeeding after very preterm birth across neonatal units in Europe.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers. The papers will be referred to by their Roman numerals (1-IV)

I. Emilija Wilson, Rolf F Maier, Mikael Norman, Bjoern Misselwitz, Elizabeth A Howell, Jennifer Zeitlin, Anna-Karin Edstedt Bonamy on behalf of the Effective Perinatal Intensive Care in Europe (EPICE) Research Group.
Admission hypothermia in very preterm infants and neonatal mortality and morbidity.
The Journal of Pediatrics 2016; 175:61-7.

II. Emilija Wilson, Jennifer Zeitlin, Aurélie Piedvache, Bjoern Misselwitz, Kyllike Christensson, Rolf F Maier, Mikael Norman, Anna-Karin Edstedt Bonamy, and the EPICE Research Group.
Strategies to prevent hypothermia in the delivery room after very preterm birth: results from the EPICE study.
Manuscript.

III. Emilija Wilson, Kyllike Christensson, Lena Brandt, Maria Altman, Anna-Karin Edstedt Bonamy.
Early provision of mother's own milk and other predictors of successful breast milk feeding after very preterm birth: a regional observational study.
Journal of Human Lactation 2015; 31:393-400.

IV. Emilija Wilson, Anna-Karin Edstedt Bonamy, Mercedes Bonet, Liis Toome, Carina Rodrigues, Elizabeth A Howell, Marina Cuttini, Jennifer Zeitlin, and the EPICE Research Group.
Room for improvement in breast milk feeding after very preterm birth in Europe - results from the EPICE cohort.
Submitted.

CONTENTS

LIST OF ABBREVIATIONS

BFHI	baby friendly hospital initiative
BMI	body mass index
BPD	bronchopulmonary dysplasia
C	Celsius
CI	confidence interval
CPAP	continuous positive airway pressure
ELBW	extremely low birth weight
IQR	interquartile range
IUGR	intrauterine growth retardation
IVH	intraventricular haemorrhage
KMC	kangaroo-mother-care
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
OR	odds ratio
PDA	patent ductus arteriosus
PMA	postmenstrual age
PPROM	preterm prelabour rupture of membranes
RDS	respiratory distress syndrome
ROP	retinopathy of prematurity
SC	stratum corneum
SD	standard deviation
SGA	small for gestational age
VLBW	very low birth weight

1 INTRODUCTION

Thermal care to prevent hypothermia after birth (1) and the availability of breast milk and breastfeeding (2) during neonatal care are two areas of great importance to infants, regardless of setting.

In the beginning of the 20th century, the French neonatologist Pierre Budin described the importance of thermal care, and for half a decade it has been known that cold has adverse effects on the newborn infant, and hypothermia at admission to neonatal care has been associated with mortality and morbidity.

In 1990, the Innocenti declaration of the protection, promotion and support of breastfeeding was adopted by international policy makers and agencies (3). At the same time, the United Nations declared breastfeeding as a legal right to the child and that appropriate measures should be taken to facilitate breastfeeding in working parents and to protect from improper breastfeeding information (4). The provision of breast milk and breastfeeding contributes to short- and long term health for both the infant and the mother (5).

In addition, thermal care and breastfeeding are interventions beneficial to the whole society in terms of improved outcomes for the infants and their families, acknowledging the role of the family and also in terms of cost-effectiveness.

Advances in obstetrics and neonatal intensive care have contributed to a decline in newborn mortality and morbidity. Nevertheless, very preterm birth (infants born two or more months before full term) is one of the main determinants of infant mortality and short- and long term morbidity in Europe. The severity of impairment increases with decreasing gestational age.

In perinatology, there is a long tradition of publishing clinical reviews, regularly synthesising evidence. Systems to grade the quality of evidence underlying the decision of a new guideline or recommendation have been developed. However, there are challenges when translating scientific knowledge in to practice, even in areas where there are convincing results from research.

The overall objective of this thesis is to study thermal care and breastfeeding after very preterm birth in Europe. The general research question is to investigate if and how thermal and breastfeeding interventions are implemented in the care of the very preterm infant in European neonatal intensive care units.

2 BACKGROUND

2.1 EVIDENCE-BASED MEDICINE/CARE/PRACTICE

In the beginning of the 1990's, a new paradigm of medical practice rose from the growing influence of systematic search and use of evidence in medical decision-making and clinical practice (Evidence-Based Medicine Working Group, 1992). The new paradigm was called "evidence-based medicine" (EBM) and was defined by Sackett et al. as "The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (6). EBM is not restricted to randomised trials and meta-analyses, but acknowledges the best available knowledge that could answer clinical questions. The integration of the scientific evidence with the expertise from the individual clinician and the patients' values and preferences is emphasised (Figure 1) (6).

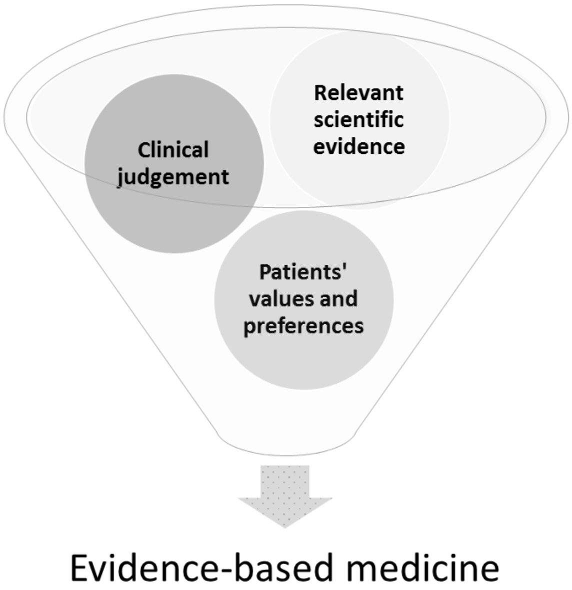

Figure 1. Principles of evidence-based medicine. Adapted from Sackett et al. BMJ, 1996.

In perinatology, there is a long tradition of performing clinical reviews. During the 1970-80's, a British project for systematic reviews developed into an international collaboration of perinatal trials, the Oxford Database of Perinatal Trials, and this further developed into the Cochrane Collaboration in the 1990's (7). Among the first entities to be established were the Cochrane Pregnancy and Childbirth and Cochrane Neonatal groups. The Cochrane Neonatal reviews synthesise evidence and regularly update reviews to improve practice in medical care (8). During the 1990's, the term evidence-based practice was also introduced as the ideas of EBM extended to other professional disciplines, e.g. nurse and midwife practice (9).

The challenges of translating evidence in to practice have been highlighted in several medical areas. There may be barriers on a number of different levels, e.g. organisational, cultural or personal, even in areas where there are convincing results from research (10-12).

In a systematic review about nurses' individual research utilisation, nurses' attitudes to research were consistently related in a positive way with the use of research. Other factors that related to research utilisation were having a graduate degree, working in a specialty area, being satisfied at work, and attending conferences (13).

In a review about factors associated with physicians' adherence to guidelines, three themes were identified: knowledge, attitude and behaviour (11). Barriers affecting *knowledge* were lack of awareness and familiarity, barriers affecting *attitudes* were disagreement, lack of self-efficacy, lack of outcome expectancy and inertia/slowness of previous practices, and barriers affecting *behaviour* were external factors with an impact on the ability to adhere to a guideline. The latter were subcategorised as related to *(a) guidelines*: not easy to adopt or use the guideline); *(b) patient*: inability to reconcile patient wishes with the recommended guideline; and *(c) environmental*: factors beyond control.

Grimshaw et al. suggested that implementation research should focus on a better theoretical understanding of the behavioural change of health care personnel and organisation, so that researchers can identify which factors are modifiable in the work of implementing guidelines (14).

Before implementing a new guideline or recommendation there is a need for evaluation of the evidence underlying the decision. Not evaluating the quality of evidence could lead to improper recommendations (15). There are tools that support the assessment of the quality of evidence before creating clinical guidelines and recommendations. One such commonly used tool, used by the WHO (World Health Organization) and many other organisations and authorities is the GRADE system, the Grading of Recommendations, Assessment, Development and Evaluation system (www.gradeworkinggroup.org).

In GRADE, meta-analyses have the highest grade of evidence. RCTs are considered as high quality, but the evidence grade can decrease due to study limitations, heterogeneity of results, indirectness of evidence (e.g. studying a proxy measure instead of the outcome you want to achieve), imprecision, and reporting bias. Observational studies are usually considered as of lower quality, but can be upgraded if the size of the treatment effect is very large, there is a confirmed dose-response relationship (15) or if "all plausible residual confounding would further support inferences regarding treatment effect" (16).

There is, however, still a gap in knowledge about how, and if, evidence is implemented in European obstetric and neonatal units. Despite medical advances in perinatal care over the past decades, very preterm birth is one of the main determinants of infant mortality and morbidity in Europe and globally, suggesting that there is room for improvement (17, 18).

2.2 EPIDEMIOLOGY OF PRETERM BIRTH

Length of pregnancy

A pregnancy normally lasts for 40 weeks, counted from the first day of the last menstrual period. Estimation of gestational age using ultrasound in the first trimester is the recommended method for best accuracy (19, 20). When ultrasound is not available, the estimation will be based on methods with lower accuracy, such as the last menstrual period (LMP) and/or clinical examination (fundal height measurement). If not assessed during pregnancy, a neonatal examination could be used for an approximate estimate of pregnancy length after birth (21).

An accurate estimation of gestational age during pregnancy is of great importance for clinical practice and evaluation of public health programs (22). Using ultrasound for dating pregnancies has been shown to move the distribution of gestational age to the left, and thereby increase the preterm birth rate (23). On the other hand, it might decrease the preterm birth rate by reducing measurement errors and misclassification of term infants as preterm (24). Registration practices of live births, stillbirths and terminations of pregnancy vary across Europe and affects the preterm birth rate (25).

2.2.1 Classification of preterm birth

Preterm birth is defined by the WHO as birth before 37 completed weeks of gestation (26) (WHO, 1977). Globally, approximately 15 million (11%) of all births are preterm (27). In the United States, the preterm birth rate is around 12%, and in Europe between 5 and 11% (28, 29). The WHO further divides preterm birth in: moderately-, very-, and extremely preterm, as shown in Figure 2. In Europe, approximately 1.5% of all live born infants are born very preterm (<32 weeks) (25).

<table>
<tr><td colspan="21">Gestational duration in weeks</td></tr>
<tr><td colspan="6">Extremely preterm <28</td><td colspan="4">Very preterm 28-<32</td><td colspan="5">Moderately to late Preterm 32-<37</td><td colspan="2">Early Term 37-38</td><td colspan="2">Full Term 39-40</td><td>Late term</td><td>Post-term</td></tr>
<tr><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td><td>27</td><td>28</td><td>29</td><td>30</td><td>31</td><td>32</td><td>33</td><td>34</td><td>35</td><td>36</td><td>37</td><td>38</td><td>39</td><td>40</td><td>41</td><td>42</td></tr>
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<tr><td colspan="10">very preterm birth</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="15">preterm birth</td><td colspan="5">term</td><td></td></tr>
</table>

Figure 2: Gestational duration in weeks.

Preterm birth can be classified as *spontaneous preterm birth* with spontaneous onset of labour with intact membranes, or with preterm prelabour rupture of the membranes (PPROM) before onset of labour, or as *provider-initiated preterm birth* i.e. induction or caesarean section. In provider-initiated preterm birth, a delivery would likely not have occurred without an intervention, but is necessary due to maternal or foetal illness (27, 30).

2.2.2 Causes of preterm birth

The cause of preterm birth is in many cases unknown, but strong risk factors for spontaneous preterm birth are previous preterm deliveries (there is an interplay between genetic and environmental factors) (31), multiple pregnancy, infections in the urinary tract, and inflammation and/or intrauterine infections (27).
Being a younger or older mother, having low or high maternal body mass index, short interval between pregnancies, alcohol consumption and smoking have all been associated with preterm birth (31, 32). Infants with congenital malformations are more likely to be born preterm (33).

Underlying causes for provider-initiated preterm birth are preeclampsia, placental abruption, intrauterine growth restriction and foetal distress, and cholestasis of pregnancy (31). Obesity, diabetes and hypertension are maternal conditions increasing the risk of obstetric complications and indicated preterm birth (27, 31).

Preventing preterm birth is one of the greatest challenges in healthcare today. The implementation of strategies to reduce preterm birth involves multi-disciplinary teams from various medical fields, and policy makers on both a local and national level (34). In a review investigating the interventions to prevent preterm birth, graded according to the quality of evidence of the studies, six preventive measures with various level of evidence were found and they encompassed: progesterone supplementation, use of fertility treatment, cervical cerclage, tobacco control, prevention of non-medically indicated preterm birth; and dedicated preterm birth prevention clinics. Mentioned interventions are applicable in low-, middle- and high-income countries depending on intervention (34, 35).

In addition, the need for a new classification system of preterm birth, based on clinical phenotype has been discussed and defined as a system based on “one or more characteristics of the mother, foetus, placenta, and the presentation of delivery” rather than the cause of preterm birth, as this is often not known. Furthermore, the mode of delivery should not be part of the classification system (30).

In summary, the aetiology of preterm birth and its classification are complex. However, gestational age at birth is often the most determining factor for the infant’s short- and long -term outcome (36); with increasing gestational age the risks associated with the preterm birth decrease sharply (37-39).

2.2.3 Foetal growth and birth weight

The infant’s size at birth reflects the duration of the pregnancy and the rate of foetal growth (the increase in size over time). The birth weight can for a certain gestational age be too low. The term used for this condition is small for gestational age (SGA). SGA is defined as a birth weight less than the 10th percentile or below -2 standard deviations (SD) (approximately the 3rd percentile) below the mean birth weight for gestational age. The SD score or the Z-score is birth weight expressed in units of SDs for gestational age and can be stratified on other factors of interest, e.g. infant sex (40, 41).

$$\text{Z-score (or SD-score)} = \frac{\text{(observed value - mean value of the reference population)}}{\text{standard deviation value of reference population}}$$

Intrauterine growth restriction (IUGR) is a pathologic condition and refers to a growth arrest or a change in longitudinal growth rate, i.e. growth between two time points, usually measured by ultrasound. Being SGA does not always mean that the foetus has been subjected to IUGR, as being small at birth can be caused by several other factors. Maternal and infant genetic and environmental factors, such as maternal body composition, ethnicity, nutritional status during pregnancy, smoking, and infant sex influence birth weight (42-44).

SGA can be defined according to growth curves based on intrauterine estimation of foetal weight- or by growth curves based on postnatal observations of birth weight by gestational age. For the postnatal estimation there are doubts about the representativeness of normal intrauterine growth. Postnatal references, except for the term period, are based on deliveries with an overrepresentation of pathologic conditions, linked to preterm birth. Many preterm infants are growth restricted, but a diagnosis of small-for-gestational age can only be made if healthy full term infants at the corresponding gestational age are used as a reference group. Thus the importance of using intrauterine growth curves when assessing birth-weight for gestational age in preterm infants (45, 46).

The WHO classifies low birth weight (LBW) as birth weight less than 2500 g regardless of gestational age (47) and can further be classified as: very low birth weight (VLBW) less than 1500 g and extremely low birth weight (ELBW), below 1000 g (48).

2.2.4 Mortality and morbidity after very preterm birth

Advances in obstetric and neonatal intensive care in the last decades have contributed to an important decline in infant mortality and morbidity among infants born very preterm, such as administration of antenatal corticosteroids to women with a threatening preterm birth (below 33-34 weeks of gestation) for foetal lung maturation (49) and the use of surfactant after birth to further support lung function (50, 51). Lower rates of neonatal mortality and morbidity have been reported in low-income countries when LBW/preterm infants receive Kangaroo-care (infant skin-to-skin with mother) (52) compared to infants receiving conventional care (53-55).

Very preterm birth is one of the main determinants of infant mortality, and short- and long-term morbidity in Europe. The mortality and morbidity rates have been showed to vary by a factor greater than two across regions (17, 25, 37). There is a slightly decreasing trend in this variation, but the differences between regions and countries are still significant. Maternal and infant characteristics only accounted for one fifth of the variation in mortality in the EPICE-cohort, suggesting that there may be an inequity of the quality of care across Europe after very preterm birth (56).

2.2.4.1 Neonatal mortality

The mortality rate in infants born very preterm is approximately 9-15% across Europe (37, 56, 57). Neonatal mortality is defined as a death after live birth during the first four weeks after birth and is further categorised as: early neonatal death, 0 to 7 days after birth; late neonatal deaths after 7 to 28 days after birth (18), and post neonatal mortality from after 28 days to five years of age. Of all neonatal deaths in Europe, between 61 and 85% occurred during the early neonatal period. Approximately 40% of all neonatal deaths were observed in infants born <28 weeks of gestation or <1000 g (25). The mortality rate for infants born preterm from multiple pregnancies are higher than those seen in singleton pregnancies (58).

2.2.4.2 Neonatal short-term morbidity after very preterm birth

Infants born before 32 weeks are in need of extended support to be able to adapt to the extrauterine life. The very preterm infants who survive to admission to neonatal care and throughout hospitalisation face many challenges related to their grade of prematurity and individual condition at birth. They are dependent on support to maintain their basic needs and to be able to maintain or regain homeostasis.

Respiration

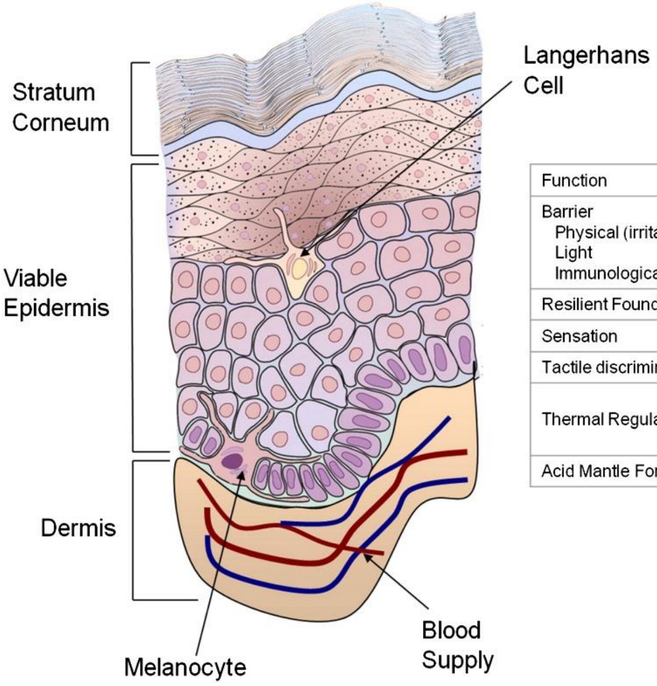
The alveoli and the production of surfactant are immature in infants born very preterm. This puts the infants at risk of developing respiratory distress syndrome (RDS), requiring continuous positive airway pressure (CPAP) or mechanical ventilation for adequate exchange of oxygen and carbon dioxide. Apnoea of prematurity is defined as a cessation of breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia (<100 beats per minute), cyanosis or pallor. The events are often shorter in preterm infants as briefer pauses in airflow already result in bradycardia or hypoxemia. The incidence of apnoea increases with decreasing gestational age (59). Infants are therefore continuously monitored for respiratory rate, heart rate and oxygen saturation with alarms set at specific levels.

Circulation

There are two major changes during the transitional neonatal circulation: clamping of the placental blood flow and the expansion of the lung fields. The transition is often delayed in the preterm infant and the ductus arteriosus frequently remains open: patent ductus arteriosus (PDA). A large PDA may compromise the circulation and can result in decreased perfusion in major organs and is associated with adverse neonatal outcomes. In very preterm infants, PDA is often treated with prostaglandin antagonists or surgery (60).

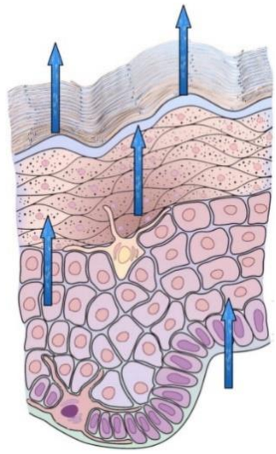
Skin and transepidermal water loss

There are three major layers in the skin, the stratum corneum (SC) which is the main barrier, the epidermis and the dermis, all with special functions, as illustrated in Figure 3. Functional maturation of the SC begins around 24 weeks of gestation with increasing epidermal cell layers and thickening until term when the SC has 40–60% of adult skin thickness (61). The lower the gestational age, the more brittle the barrier. The immaturity of the skin results in a higher risk of percutaneous absorption of chemicals and the skin is more permeable to gases (62).



Function	Skin Structure
Barrier Physical (irritants) Light Immunological	Stratum corneum and epidermis Melanocytes (epidermis) Langerhans cells (epidermis)
Resilient Foundation	Dermis
Sensation	Sensory nerves (epidermis & dermis)
Tactile discrimination	Stratum corneum & sensory nerves
Thermal Regulation	Eccrine sweat glands (dermis) Blood supply (dermis) Adipose fat below dermis
Acid Mantle Formation	Stratum corneum & epidermis

Figure 3: Structure of skin. Image taken from *Clinics in Dermatology* Newborn infant skin: Physiology, development, and care. Visscher et al. 2015. Reprinted with permission from Elsevier©



Transepidermal water loss is most pronounced in the lowest gestational ages (Figure 4). The heat loss/heat exchange is proportional to the amount of water evaporated from the infant's skin surface. A high ambient humidity reduces heat loss and water loss, leading to a reduction in the risk of hypertonic dehydration (63).

Figure 4: Transepidermal water loss. Image taken from *Clinics in Dermatology* Newborn infant skin: Physiology, development, and care. Visscher et al. 2015. Reprinted with permission from Elsevier©

The very preterm infant may suffer from a variety of morbidities due to their prematurity such as *Intraventricular haemorrhage* (IVH), which results from bleeding in the germinal matrix, into the ventricles (grades 2-3) or the surrounding brain tissue (grade 4). IVH occurs in about 25% to 30% of all VLBW preterm infants, and in 45% of ELBW preterm infants. Both mild (grades 1-2) and severe (grades 3-4) IVH were associated with adverse long-term outcomes compared with infants who did not have IVH. (64).

Necrotising enterocolitis (NEC) is a very serious bowel disorder with an incompletely understood pathogenesis. Epidemiological studies have suggested multifactorial and interacting origins. NEC is characterised by intestinal inflammation, ischemia, necrosis, and in some cases perforation. The incidence of NEC in infants weighing between 500 and 1500 g is approximately 7% and in infants born <34 weeks of gestation the incidence is 5% (39, 65). Mortality associated with NEC ranges between 20 and 30%, with the highest rate among infants in need of surgery (66). Long term complications and morbidity are short bowel syndrome (67) and neurodevelopmental delay (66). Feeding with mother's own milk has been shown to reduce NEC, when compared with infants receiving formula (68, 69).

2.2.4.3 Long-term morbidity after very preterm birth

Long-term morbidities steeply rise with decreasing gestational age. One of the most common sequelae is *bronchopulmonary dysplasia* (BPD). BPD is defined as oxygen dependency at 36 weeks PMA (moderate below 30% oxygen; severe $\geq$30% oxygen or positive pressure ventilation) (70, 71). The aetiology of BPD has not yet been fully uncovered, but is considered to be multifactorial (72). The strongest predictor of BPD is the degree of prematurity.

Retinopathy of prematurity (ROP) is a vascular disease of the eye, and very preterm infants are more susceptible due to an incomplete neurovascular development of the retina at birth. Oxygen treatment, low gestational age, and low birth weight for gestational age are major risk factors. Genetic factors might also have an effect on the development of ROP (73).

The *brain* of the very preterm infant is more vulnerable than the brain of a term infant, because of the limited capacity of autoregulation of cerebral blood flow, which is further impaired if hypoxia or hyper- or hypocapnia is present (74). Many potential mechanisms are involved in brain injury, such as intraventricular haemorrhage, perinatal infections or inflammation and metabolic disorders. In extremely preterm infants who are discharged alive from neonatal care, 5-10% develop cerebral palsy (75). Also among infants without severe disabilities, developmental, cognitive or behavioural difficulties in childhood still may be seen (76, 77). Furthermore, being born very preterm is associated with an increased risk of cardiovascular and metabolic disease later in life (78-81).

2.3 LEVEL OF CARE AND CENTRALISATION

The classification of NICU level of care varies internationally. One commonly used definition is the American Academy of Pediatrics classification from 2004, updated in 2012, defined as *level I*: basic care of well newborn*; level II* is divided in two categories *IIa*: specialty care of stable or moderately ill newborn infants ≥ 32 weeks of gestation or birth weight ≥1500 g and *IIb* units who have the same capability as a level IIa unit but with additional ability to provide assisted ventilation including CPAP. *Level III* subspecialty care of infants born <32 weeks of gestation <1500 g at birth or having medical or surgical conditions regardless of gestational age, *level IV* include the same capability as a level III unit but with the addition of providing surgery for complex conditions (e.g. congenital cardiac malformations) (82). The definitions consider the "*overall evidence for risk appropriate care through the availability of appropriate personnel, physical space, equipment, technology and organisation*" (83).

The care of the very preterm infant has during the past decade been driven towards centralisation. A large study from the US, including 72 431 infants with a birth weight between 500 and 1499 g, aimed to investigate the independent effects of the birth hospital's volume of VLBW deliveries and the level of NICU on the risk of neonatal mortality and morbidity. The authors concluded that the annual volume of deliveries of VLBW infants had a greater association with mortality risk than the level of NICU (84).

In a birth-register study from Finland, results showed the one-year mortality after live birth was higher in level II hospitals compared with level III hospitals. In addition, the total mortality rate was higher among infants born outside the office hours. Translating this in to practice i.e. births in level III instead of level II hospitals could mean a yearly prevention of 69 of the 170 total deaths (85).

2.4 PARENTS IN THE NEONATAL CARE

"When nothing turned out as planned"

Preterm birth and latter NICU hospitalisation are associated with psychological and emotional stress and are for some parents highly traumatic and distressing ((86). Developmental research in the 1990s contributed to the introduction of the family-centred care, and approaches promoting physical care involving the parents as a central aspect of care were introduced. Closeness in the NICU can be *physical*: skin-to-skin or by the presence close to the infant without direct contact, and *emotional*: emphasising all the feelings that can be experienced (87).

In interviews with parents about their experiences of neonatal care, three themes were identified as positive: the parent's involvement in the care of their premature child, staff competence and efficiency, and interpersonal relationships with the staff (88). Dominating medical-technical care, a shortage of staff, lack of space and the absence of strategies to develop optimal conditions for parental presence have been identified as barriers for the parents to take part in neonatal intensive care (89). A European study about parental presence in the NICU and parent-infant closeness in 11 units in 6 countries revealed that there were large variations between countries and between units in countries in regard to the possibility for the parent to stay with the infant in the NICU. The strongest factor to support parent-infant closeness was the possibility to stay overnight (90).

2.5 THERMOREGULATION

After birth, one of the main challenges for the newborn infant is to maintain a neutral thermal environment. The infant has to rely on interventions to be protected from cold, i.e. unintended hypothermia*. The WHO defines normothermia as a body temperature of 36.5-37.5°C, hypothermia as <36.5°C and hyperthermia as >37.5°C.

2.5.1 Heat production in the healthy newborn

Most of the metabolic energy is produced by oxidative metabolism of glucose, fat and protein by the brain, heart, and liver and muscles. The quantity of produced heat fluctuates with health status, activity and the temperature surrounding the infant. When exposed to a cold environment the infant increases muscle activity and crying, which generates heat. Infants may try to minimize their exposed surface area by cuddling up in a flexed position, leading to conservation of heat (91).

Peripheral vasoconstriction occurs in response to cooling, reducing the blood flow to the skin and thereby decreasing the heat loss from the skin. Non-shivering thermogenesis is when heat is produced by metabolism of brown fat. The hypothalamus receives impulses from thermal receptors, which in turn stimulates the sympathetic nervous system to noradrenaline release from brown fat. The release of noradrenaline activates lipase and this results in lipolysis and fatty acid oxidation generating heat, instead of storing the energy as adenosine-5-triphosphate (ATP) (91-94).

2.5.2 Heat loss

hermoregulation is the balance measure of the balance between the heat loss and the production of heat. When facing the colder environment after birth, the skin temperature of the newborn infant can drop at a rate of 0.3°C per minute and the core body temperature 0.1°C per minute if no action of thermal care is taken (95, 96). The very preterm infant is even more susceptible to heat loss due to the high surface area to weight ratio, immature skin and little or no subcutaneous fat. Furthermore, there are limited or no brown fat deposits, impeding the heat production by non-shivering thermogenesis. In addition, the immature thermal centre limits self-regulation of body temperature.

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*As the focus of this thesis is unintended hypothermia after very preterm birth and therapeutic hypothermia for brain protection is not applicable in the very preterm population, therapeutic hypothermia will not be addressed.

The infant loses heat through evaporation, convection, conduction and radiation, (26, 63, 95, 96) Figure 5.

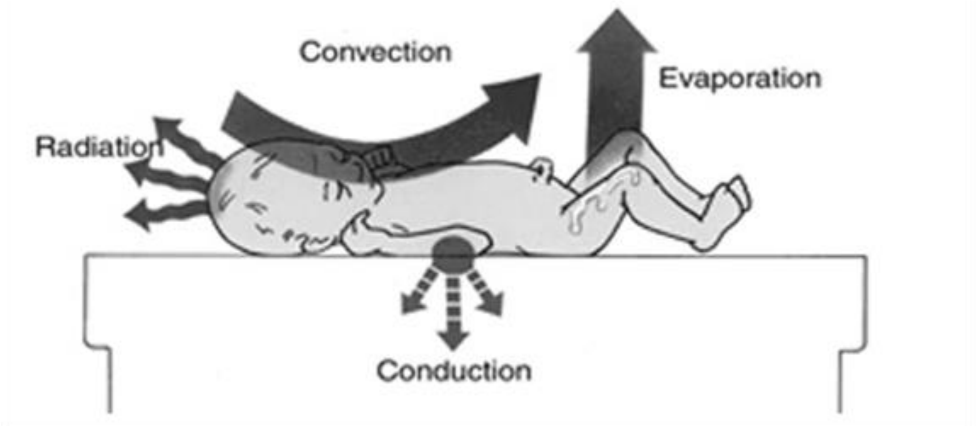

Figure 5: Mechanisms of heat loss from a newborn infant's skin. (Source: WHO, 1997, Safe Motherhood: Thermal Protection of the Newborn, a Practical Guide (26).

- **Evaporation:** when wet surfaces are exposed to air and the surface dries. At birth the infant is "bathing" in amniotic fluid and as the amniotic fluid evaporates from the infant's skin, the infant loses heat. This is more pronounced in the lowest gestational ages.
- **Convection:** when air moves against the infant's skin, heat is lost/transferred away from the body.
- **Conduction:** when the infant comes in direct contact with an object cooler than their skin.
- **Radiation:** Heat radiates away from the infant's body towards cooler surfaces in the environment and depends on the differences in temperature between skin and the surrounding environment.

2.5.3 Hypothermia

As a consequence of a colder body temperature, several physiological reactions can be induced. With already limited stores of glucose and the increased demands in the adjustment to extrauterine life, the very preterm infant is at high risk of developing hypoglycaemia. In addition, cold stress increases the demand for oxygen, which can lead to hypoxia, anaerobic metabolism and metabolic acidosis with the constriction of the pulmonary blood vessels with a decreased surfactant production (93, 94, 97).

In the 1950's, an RCT from Silverman et al. showed that infants cared for in incubators with higher temperatures (31.7°C) had a higher survival rate than infants in incubators with lower temperatures (28.9°C) and that the difference was more prominent in infants weighing below 1001 g (98). Since then, several observational studies have shown an association between hypothermia at admission to neonatal care and mortality and morbidity (99-101). Laptook et al. showed that for each 1 degree decrease in admission temperature below 36.0°C, there was an increased risk of mortality by 28% (102). The authors of these studies have speculated whether hypothermia is a causal factor in mortality or a marker for increased risk of mortality.

2.5.4 Thermal care

In the beginning of the 20th century, the French neonatologist Pierre Budin described the importance of thermal care of the newborn infant in his book “The Nursling”. Since then, several different strategies have been suggested to protect infants from getting cold after delivery. Standard thermal care has been described by the WHO as providing a warm delivery room - preferably not lower than 25°C, drying the infant, removing wet blankets, pre warming blankets, limiting the contact with surface areas, and avoiding draught and being close to outside walls (26). Guidelines from the European resuscitation council on how to preserve infant body temperatures between 36.5-37.5°C after very preterm birth, recommend polyethylene wrapping of the head (not face) and body without drying the infant, along with placing the infant under a radiant heater (103).

Two reasons for not being able to prevent hypothermia have been suggested 1) inadequate use of existing hypothermia prevention measures and 2) the need to increase the awareness about thermal management among personal involved in the resuscitation of the newborn infant (104).

2.5.4.1 Barriers to heat loss

Barriers focus mainly on the reduction of evaporative heat loss and include wraps/bags and/or caps (head cover). A Cochrane review from 2010, investigating interventions of hypothermia prevention, concluded that placing infants <28 weeks in plastic bags without drying resulted in higher temperatures at admission to neonatal care (105). This was recently confirmed in the to date largest RCT, in which infants who received the occlusive wrap/plastic bag intervention had higher body temperatures at admission to neonatal care. The temperatures were 36.3°C in the wrap group vs 35.7°C in the no wrap group (106).

2.5.4.2 External heat source

External heat sources include heated mattresses, (107, 108) in addition to or replacing radiant warmers, to reduce radiant and conductive heat loss. Skin-to-skin care has in the last years been suggested also in the lower gestational ages to reduce heat loss and to promote temperature stabilisation (109), which has previously been shown to be advantageous in low risk infants with hypothermia (55).

2.5.4.3 Intervention bundles

Quality improvement work, using bundles of interventions such as educating staff, plastic wraps, consistent room temperature and transfer to the NICU in a warmed incubator in different constellations (103, 110, 111) have been associated with lowering the incidence of hypothermia.

2.5.5 Hyperthermia

In attempts to lower the incidence of hypothermia, studies have reported that there is a risk of overwarming (112, 113). The same factors that make the very preterm infant susceptible to hypothermia: large surface area to body weight ratio and limited insulation along with a limited ability to sweat makes the infant susceptible also to excessive heat (62). There are fewer studies on the adverse effects associated with hyperthermia in the preterm infant, but there are reasons to believe that hyperthermia may increase the risk of neurological damage (114).

Admission temperature has been suggested as a quality indicator and as a predictor of outcome in newborn stabilisation (103).

2.6 BREAST MILK FEEDING

Breast milk feeding has important benefits for the infant and their mothers (2). The WHO recommends colostrum and breast milk as the perfect nutrition, for term as well as preterm infants, and feeding should start in the first hour after birth if possible (115).

2.6.1 Lactogenesis and lactation

During pregnancy, luteal and placental hormones stimulate breast development. The production of breast milk depends on mammogenesis and lactogenesis. Mammogenesis is the growth and development of the milk producing glandular breast tissue, and lactogenesis is the breast milk secretion, in its different phases. Growth of the ductal (milk collection) system is stimulated by oestrogen, and progesterone stimulates the milk production system.

Lactogenesis I occurs in mid-pregnancy, when the mammary gland differentiates and secretes specific milk components. The milk is held back by high plasma concentrations of circulating progesterone. At birth, the progesterone levels decrease abruptly when the placenta is delivered. The second phase, lactogenesis II is the onset of copious milk secretion trigged by this rapid drop of progesterone. (116).

The frequency and the quality of the nipple stimulation is reflected in the amount of prolactin released during the first weeks postpartum, and may also relate to the development of prolactin receptors. Preterm delivery, maternal obesity and pre pregnancy diabetes mellitus have been shown to be associated with delayed lactogenesis II (117, 118). The first two phases of lactogenesis are hormonally driven, while the third phase lactogenesis III/lactation is the secretion and maintenance of milk production under autocrine control, locally in the breast, and occurs in the following weeks after delivery (116).

2.6.2 Breast milk

The first milk is called colostrum and is rich in immunologic components and growth factors. The transitional milk occurs typically from 5 days to 2 weeks postpartum and has increased carbohydrate and lipid content to meet the needs of the growing infant. By 4-6 weeks postpartum, the milk is considered fully mature and remains relatively similar in its composition in contrast to the shifts observed in the first month postpartum (119). Breast milk contains a number of components contributing to the decreased morbidity seen in breast milk fed infants. They will not be further investigated in this thesis, but the main components include antimicrobial agents, anti-inflammatory components and immunomodulating agents (120).

Milk volume

On average, the maternal milk production by the second week postpartum, in a mother to a full term infant, is around 30 ml/hour, or 700-800 ml/day. Mothers of preterm infants who achieved a milk production of ≥500 ml/day two weeks postpartum had a tripled chance to provide their infants with human milk at discharge from the neonatal unit, compared to mothers who did not achieve this amount of milk (121).

2.6.2.1 Benefits of breast milk and breastfeeding

Breastfeeding protects against child infections, is associated with higher intelligence and a probable reduction in diabetes, but there are conflicting results in regard to child overweight and obesity (2, 122, 123). For the mother, an increased duration of breastfeeding is associated with a reduced risk of breast cancer, ovarian cancer and cardiovascular disease (5, 124, 125).

Breast milk is beneficial for infants born very preterm, as it reduces the risk of NEC (68, 69, 126, 127) and is associated with lowering the incidence of late-onset sepsis (128, 129), and ROP (130). In addition, breast milk feeding promotes brain growth and neurodevelopment (57, 131, 132).

2.6.3 Breast milk feeding after very preterm birth

As the very preterm infant is too immature to breastfeed fully from the breast during the NICU hospitalisation, most of the mothers in the NICU who provide their own milk are pump dependent, both for the initiation and for the maintenance of milk production. The pump dependency, together with several other factors, predispose to delayed onset of lactogenesis II and low milk volume (118, 133) (134, 135). It is recommended that milk expression should start within one hour after birth if possible. In a study investigating the effect of early breast milk expression among mothers of VLBW infants born <32 of gestation, mothers were randomised to either early start (beginning to express within 60 min after delivery) or later start at 1 to 6 hours, the results showed that mothers in the early initiation group produced twice the amount of milk during the first week compared with mother who started expressing at 1 to 6 hours after delivery. Further findings from this randomised study showed that mothers who started to express within 1 hour after birth decreased time to lactogenesis II, in comparison with the group who started express between 1 and 6 hours after delivery (133) . Several observational studies indicate that adequate milk output during the first two postnatal weeks predicts adequate milk volumes during late NICU hospitalisation (136-138).

It is of utmost importance to distinguish what an adequate milk volume implies, as there can be a discrepancy between the mother's view and the staff, and in addition in between staff members, as well (134). Meier et al. stresses the importance of communicating with the mother about two types of milk volume targets. First, the lactating mother needs to provide enough breast milk for her infant in the NICU, which may be very small amounts because of prematurity, surgical complications, or fluid restrictions, but then she needs to be informed about the importance of protecting the milk supply by early programming and to reach amounts sufficient for her infant to receive mother's own milk exclusively after the NICU hospitalisation (134, 139).
To be able to maintain an adequate milk supply, a minimal milk volume is of 350 ml per day and volumes closer to 1000 ml per day (134) could be recommended as targets, to ensure

breastfeeding throughout the first 6 months by protecting mothers' milk supply. In the NICU, the most common reason for discontinuing breast milk feeding is inadequate milk supply, as it also is for breastfeeding cessation after discharge (140-142).

2.6.3.1 Pump frequency and technique

Breast milk can be expressed using the hand, i.e. manually, or by a manual or electrical pump. A recent Cochrane review of methods of milk expression for lactating women concludes that a suitable method for milk expression depend on time since birth, the reason of expression and the individual mother-infant dyad. Health care staff need to be able to justify the use of a breast pump for the individual mother, rather than to see it as a routine (143). Becker et al. were not able to report any pooled estimates due to the heterogeneity in interventions, participants and outcome measures reported. However, greater milk volumes were expressed if the initiation started sooner after birth, if the mother pumped frequently with a suitable breast shield size, had a protocol for relaxation, listened to music, warmed the breast and massaged the breast when the infant was not able to feed directly from the breast. Further, simultaneous pumping compared with sequential pumping did not show a difference in obtained milk. Nevertheless, double pumping is time saving.

Not all studies reported whether support for the mothers was provided in regard to a place to rest near the infant, and availability of staff with knowledge about pumping. None of the studies asked mothers if they had achieved their own goals for expressing milk (143).

2.6.3.2 Donor milk

Mother's own milk is the first choice of feeding in preterm infants, and strong efforts should be made to encourage and support lactation. In those circumstances when mother's own milk is not available, donor human milk is the preferred option, received from well-established human milk banks to ensure the safety of the donated milk (115, 144). The provision of donor milk involves several aspects that need to be mentioned, but will not be further described in this section and comprises: screening, storage, impact on morbidity and growth (compared with mother's own milk), acceptability of donor milk in family and staff, impact of its availability on the provision of mother's own milk, as well as the costs involved (145).

2.6.4 Direct breastfeeding

There are two types of sucking. Nonnutritive sucking is when there is sucking activity, but no nutrition or fluid is received by the infant, and nutritive sucking when nutrition reaches the infant (146). Very preterm infants have shown that they can establish breastfeeding at lower gestational ages than previously expected. In a cohort study of infants born between 26-31 weeks of gestation investigating the development of breastfeeding capacity, all infants were introduced to breastfeeding at a postmenstrual age (PMA), (Figure 6) of 29 to 33 weeks. (147).

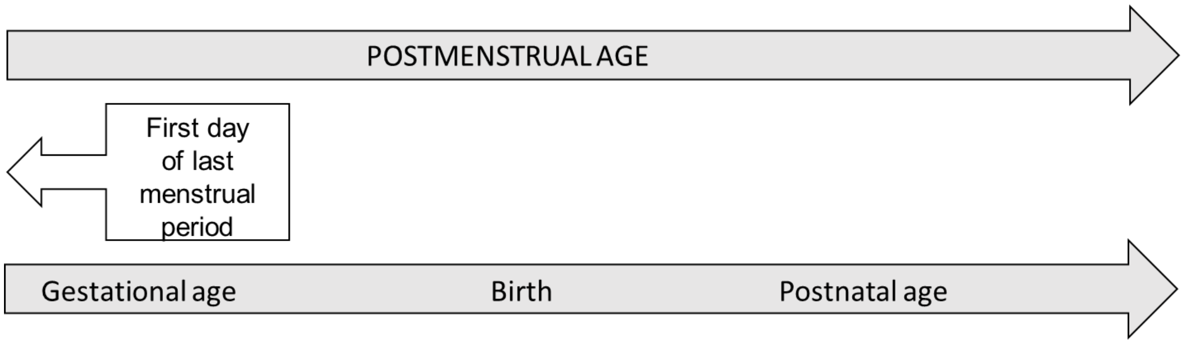

Figure 6. Age terminology during and after pregnancy.

Being skin to skin is the first step towards breastfeeding. Kangaroo-mother-care (KMC) is a highly contributing factor to increased breastfeeding rates in VLBW-infants (148) (149).Despite known benefits the breast milk feeding rates vary across Europe (150, 151). This raises the question of if, and how, breastfeeding support is implemented in European neonatal units.

It has been suggested that feeding infants with mother's own milk during hospitalisation in the NICU would not only reduce the disease burden for the infants and their families, but it could also be a cost-effective intervention in this group of infants, as it reduces morbidities associated with very preterm birth (121, 152). Patel et al. demonstrated a dose-response relationship between the average daily dose of mother's own milk and a reduction of sepsis and associated NICU costs. For every 10 ml/kg/day increase in mother's own milk, the odds of sepsis decreased by 19% (153).

After very preterm birth, where nothing turned out as it was planned, every care aspect that can facilitate and help mothers who wish to provide their infant with mother's own milk and later breastfeeding directly from the breast should be acknowledged.

As the survival after very preterm birth has increased and in many settings plateaued, there is an increasing focus on obtaining the best health outcome after very preterm birth; disease free survival. Prolonging the pregnancy for as long as possible without jeopardising the safety of the mother and child is the primary target. Thermal care and breastfeeding have been acknowledged as two of the determinants that could improve infant health if fully implemented.

3 AIMS

The overall objective of this thesis was to study thermal care and breastfeeding after very preterm birth. The general research question was to investigate if and how thermal care and breastfeeding interventions are implemented in the care of the very preterm infant in European neonatal intensive care units, and how this implementation related to outcomes after very preterm birth.

The specific aims of the included studies were:

- To examine the incidence of admission hypothermia after very preterm birth in Europe, and its relation to overall mortality, mortality stratified by postnatal age of death, and neonatal morbidity. *Paper I*

- To investigate the presence of guidelines and hypothermia preventing strategies in European neonatal units and their association with infant body temperature at admission to neonatal care. *Paper II*

- To investigate the association between maternal and infant characteristics, early provision of mother's own milk and breast milk feeding at discharge from neonatal care. Paper *III*

- To investigate breast milk feeding rates after very preterm birth in Europe and to explore how maternal, obstetric, infant and unit policies are associated with breast milk feeding at discharge. *Paper IV*

4 METHOD

4.1 STUDY DESIGN AND SETTING

All studies in this thesis are based on data collected for the European collaboration project EPICE (Effective Perinatal Intensive Care in Europe www.euruproject.com).

Overview of the four studies included in the thesis				
Paper	**Research question**	**Exposure**	**Outcomes**	**Statistics**
I	To investigate incidence of hypothermia <36.5°C in European settings, and the hypothesis that hypothermia is associated with early and later neonatal mortality and morbidity.	Infant body temperature measured at admission to neonatal care.	Overall neonatal mortality and mortality stratified by time of death. Infant morbidity.	Descriptive statistics, multi-variable adjusted mixed effect Poisson regression
II	To investigate reported use and the efficacy of different hypothermia prevention strategies in preventing infant hypothermia after very preterm birth.	Reported hypothermia prevention strategies in the obstetric and neonatal unit.	Body temperature at admission to neonatal intensive care.	Descriptive statistics, multi-variable adjusted logistic regression.
III	To investigate if early provision of mother's own milk predicts later breast milk feeding success.	Breast milk feeding with mothers' own milk at day 3 and 7 after birth and individual characteristics of mother and infant.	Breast milk feeding at near term age (36 to 40 weeks PMA* *postmenstrual age	Descriptive statistics, multi-variable adjusted logistic regression
IV	Does breastfeeding support in the NICU lead to improved breast milk feeding rates at discharge from European NICU.	Breast feeding promotion strategies in the neonatal unit. Individual-level factors (maternal, obstetric and infant).	Breast milk feeding at discharge from neonatal care.	Descriptive statistics, multi-variable adjusted mixed effect Poisson regression

The EPICE study investigated and collected determinants of evidence-based practices in a cohort of infants born very preterm below 32 weeks of gestation), in 11 countries in 19 European regions (Figure 9) during 2011-2012 at three levels: region, unit and patient. The study encompassed a prospective cohort study (perinatal data, 2-year follow-up), a unit study (survey of maternity and neonatal units and a qualitative study) and case studies of regional governance. This thesis uses the perinatal cohort and unit data. The aim of the EPICE-project, Figure 7.

To improve very preterm infants' survival and long-term health and development by ensuring that available medical knowledge is translated into effective perinatal care.

Figure 7. The aim of the EPICE-project.

Included EPICE regions: Belgium (Flanders); Denmark (Eastern Region); Estonia (entire country); France (Burgundy, Ile-de-France and the Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm region) and the United Kingdom (East Midlands, Northern, and Yorkshire & Humber regions) Figure 8.

Figure 8. Included EPICE regions by country.

The interventions that were further investigated in the EPICE-project were selected as follows: The Cochrane neonatal reviews, reviews of observational studies of the care of very preterm infants and the clinical knowledge of the project participants were used as a starting point to create a broad list of interventions that are used in obstetrics and neonatology before or after very preterm birth. The following criteria were used to select a short-list of interventions that were studied further in EPICE:

- Clinical importance: significant impact on health outcomes and/or widely implemented in many units.
- Quality of evidence: well established evidence exists for their use (or non-use) from RCTs, or observational data accompanied by expert reviews.

All four papers included in the thesis have an observational design and are based on cohort and unit data (paper II and IV) from the EPICE collaboration project.

4.1.1.1 Data collection

Maternal, obstetric and infant data were abstracted from medical records for the cohort study. A structured data collection instrument was used, pretested and jointly revised in the EPICE-group. All investigators double-checked numbers of inclusions for stillbirths and livebirths against delivery ward registers, registry offices or another equivalent external data source. For the unit study, questionnaires were sent to the heads of the units to collect information about medical and care interventions. When collecting and registering data, we had a codebook to ascertain that all variables were specified and collected in the same way across units and countries. For paper III (Stockholm region) additional data on nutrition were collected.

4.1.1.2 EPICE database

The database was administered, checked and updated by an INSERM (French National Institute of Health and Medical Research) statistician, and by corrections received from users of the database in the different regions.

4.2 STUDY POPULATION

In all four studies, infants born at less than 32 weeks and surviving until admission to neonatal care were included. The follow-up time in *paper I* was until death/discharge, *paper II* until admission to neonatal care unit, *paper III* to a postnatal age of 40 weeks and in *paper IV* until discharge from the neonatal unit. In the unit studies in *paper II* and *IV*, units with at least 10 very preterm admissions per year were included.

Paper I

EPICE cohort study: The **exposure,** infant body temperature, was measured at admission to neonatal care. Normothermia, 36.5-37.5°, was used as reference group. The **outcome**, infant mortality, was investigated as overall mortality, and stratified by time of death, <24 hours, 1-

6 days, 7-28 days and 28 days until discharge. Major neonatal morbidities were also investigated.

N=7610 infants admitted to neonatal care were eligible for inclusion. After excluding infants transported to another hospital n=868, time to admission >2 hours n=156, severe congenital malformations n=93, infants with no information on vital status at discharge n=2, and infants missing admission temperature N=794, 5697 infants were included in final analysis.

Paper II

EPICE cohort and unit study: The **exposure**, hypothermia prevention strategies used in the neonatal units, was investigated in the unit questionnaire by the following question: "In your hospital, are any of the following strategies used for preventing hypothermia for infants less than 32 weeks' gestational age in the delivery room?" "Whenever possible", "sometimes", and/or "never" use of polyethylene/polyurethane plastic wraps or bags; other plastic wraps or bags; plastic caps; and/or exothermic heat/transwarmer mattresses were the response options. All infants in the unit were considered as exposed to the prevention strategy reported in use. The interventions were categorised as shown below.

Systematic (whenever possible) use of:

Bags/wraps and exothermic heat/mattresses and sometimes cap

- Bags/wraps+exothermic heat/transwarmer mattress+caps
- Bags/wraps+ exothermic heat/transwarmer mattress

Bags/wraps and sometimes cap

- Bags/wraps+caps
- Bags/wraps

Exothermic heat/transwarmer mattress

No systematic use of hypothermia prevention strategy

- Sometimes use of hypothermia prevention
- Use of bags/wraps only if <28 weeks /<1000g

No reported use of hypothermia prevention

The **outcome**, admission temperature was studied both as a continuous variable and dichotomised as hypothermia <36.5°C vs. normothermia 36.5 to 37.5 °C, and in a separate analysis as hyperthermia vs. normothermia. Only infants admitted to the NICU in the same hospital as birth occurred were included.

After exclusions of infants with an admission time >2 hours n=159, missing temperature n= 798, and infants from units missing unit questionnaire n=133, n=5861 were included in analysis. In the regression analysis of hypothermia at admission, infants born in units with no reported use of hypothermia prevention were excluded n=130. The presence of hypothermia prevention guidelines and the association with admission temperature was also investigated.

Paper III

<u>EPICE Stockholm regional cohort:</u> For this study, information on type, volume and route of nutritional intake was additionally collected in the Stockholm region. The association of potential **predictors** of breastfeeding outcome, e.g. early provision of mother's own milk, gestational age and socio-demographic factors, with the **outcome**, breast milk feeding at 36 weeks PMA and 40 weeks PMA was investigated. Breast milk feeding, regardless of route of administration (i.e. breast, gavage), was categorised in three groups; *exclusive* (mother's own milk only, no other food or drink), *partial* (formula or donor milk in addition to mother's own milk); and *no breast milk feeding* (only formula).

After excluding multiple births n=82, infants who deceased n=18, infants lost to follow up n=4, medical contraindications to provide/receive breast milk n=8, and infants with incomplete nutritional data at 36 or 40 weeks postnatal age n=17, there were 138 mother-infant dyads included.

Paper IV

<u>EPICE cohort and unit study:</u> The **exposure**, unit policies regarding breastfeeding and individual-level covariates were investigated with the **outcome**, maternal breast milk feeding at discharge, categorised as exclusive; or partial, a combination of maternal breast milk and formula; or no breast milk feeding, i.e. only formula. Maternal and obstetric covariates were: maternal age, preeclampsia/eclampsia/HELLP, administration of any course of antenatal corticosteroids, type of delivery (vaginal or caesarean), type of birth (single or multiple). Infant covariates were: gestational age, SGA, Apgar <7 at 5 minutes, time of first enteral feed <1 day, 1-6 days or >6 days, mother's own milk at first enteral feed, any major congenital anomaly, any major neonatal morbidity, between hospital transfers any time during neonatal care, and PMA at discharge. Breastfeeding directly from the breast was also investigated.

Investigated unit policies in the unit questionnaire:

- Is there a designated staff member to support mothers who are expressing or breastfeeding while they are hospitalised?
- Are mothers advised to start expressing breast milk within six hours after delivery?
- Do you provide donor milk to feed very preterm infants whose mothers do not express their milk?
- Is your unit accredited Baby Friendly Hospital or national equivalent?

After excluding in-hospital deaths n=837 (11%), infants missing data on vital status n=2, infants never fed n=2, or missing nutritional status n=177 (3%), the final study population consisted of 6592 infants followed until discharge from neonatal care when breast milk feeding status was assessed. In the analysis of unit policies, only infants discharged from the same unit as where the infant spent at least their first 48 hours after birth, and infants linked with answers from both the maternity and neonatal unit were kept to be able to assign the correct exposure from the unit. Data was collected from 82 units with a total of 3765 infants.

Definitions used

SGA

In this thesis, SGA defines infants with a birth weight below 3rd or between 3-10th percentiles for gestational age and sex, adapted to national population values for term birth weight infants (46, 154).

Hypothermia/Admission hypothermia

Admission temperature below 36.5°C.

Mortality

Overall mortality and stratified on time on time of death: <24 hours, 1-6 days, 7-28 days and 28 days until discharge.

Any major neonatal morbidity

IVH grade ≥3 according to Papiles's classification (155), cystic periventricular leukomalacia (cPVL), NEC defined as surgery or peritoneal drainage for NEC; ROP stage ≥3, diagnosis of BPD, defined as receiving oxygen or positive pressure ventilation at 36 weeks PMA.

Breastfeeding

Breastfeeding is receiving breast milk regardless of route of administration. In this thesis the term from/direct at breast, and direct breastfeeding is used when the infant is feeding directly from the breast.

4.2.1.1 Missing data

Missing was low for most of the variables <1% for maternal age, any course of antenatal corticosteroids, mode of delivery. 1-3% for preeclampsia/eclampsia/HELLP, PPROM, IVH, BPD, 5% for Apgar score <7 at 5 minutes and 9% for maternal country of birth. For preeclampsia/eclampsia/HELLP and major infant neonatal morbidities, missing was treated as "no", otherwise complete case analysis was performed.

In paper I, the exposure variable, admission temperature, was missing in 12% of the infants (794/6491). Supplemental mortality analysis with the final models were rerun after imputation of missing data for admission temperature categories, Apgar score <7 at 5 minutes and mode of delivery using chained equations (MICE). The imputed variables were considered to be missing at random in relation to the outcome variable. The concept of multiple imputation is to use the distribution of the observed data to estimate a set of plausible values for the missing data (156).

4.3 STATISTICAL ANALYSIS

Shapiro-Wilks test was used to investigate the distribution of continuous data. This test rejects the hypothesis of normality when the p-value < 0.05. Failing the test of normality allows you to state with 95% confidence that the data does not fit the normal distribution, on the other hand, passing the normality test only allows the statement that no significant deviation from normality was found. Descriptive statistics are presented as mean (SD), median, interquartile range (IQR), number and proportions (%). When testing for differences between groups, non-parametric Wilcoxon-rank sum (two group comparison) and Kruskal-Wallis (three or more groups comparison) tests were used, as the assumption of a normally distribution could not be met for all variables.

Hypothesis testing

The relative risk (RR) indicates the increased or decreased relative risk of an outcome in relation to the exposure. A confidence interval (CI) that does not include 1 gives us the possibility to reject the null hypothesis.

Regression analysis

In paper II and III, when estimating associations between the exposure and the outcome logistic regression presenting odds ratios (OR) with 95% CI was used. In paper I and IV, mixed-effects modified Poisson model with robust standard errors (SE) was used to estimate risk ratios (RR) with 95% CI (157). This model accounted for the clustering in this cohort (Figure 9).

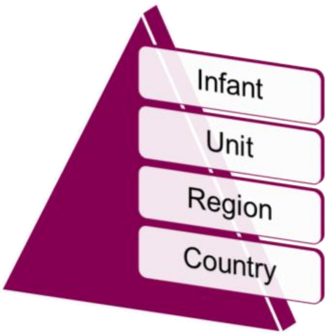

Figure 9. Illustration of levels of clustering in the EPICE cohort study.

Marginal effects

Coefficients from the multivariable adjusted logistic regression model in study IV were used to estimate marginal effects of the different hypothermia prevention strategies and predict the probability of hypothermia at representative values of gestational age (158) , using the margins command in STATA.

All statistical calculations were conducted using STATA IC 14.0 (www.stata.com).

5 RESULTS

This section is an overall description of the EPICE cohort and a summary of the results from the four studies included in this thesis.

In total, the EPICE cohort included 10329 births. Of those, 7900 were live births, 1614 were stillbirths and 815 were terminations of pregnancy. There was a regional variation of number of inclusions, varying from 134 in Marche (Italy), 143 in Burgundy (France) and 308 in Stockholm (Sweden) to 990 in Flanders (Belgium), 921 in the Yorkshire and Humber region and 1468 in Ile-de-France (France).

A total of 532 maternity units and 270 neonatal units were located in the participating EPICE regions. The criterion for inclusion in the unit study was at least 10 very preterm neonatal unit admissions over the 12-month study period. One hundred thirty-five maternity- and 135 neonatal units fulfilled that criterion. The response rates on the unit questionnaires were 134/135 (99%) for neonatal units and 124/135 (92 %) for the maternity units.

5.1 OBSTETRIC, MATERNAL AND INFANT CHARACTERISTICS

The following description of obstetric, maternal and infant characteristics includes all infants that were admitted to neonatal care in the EPICE region; N=7637, without any study specific exclusions (please refer to sections below for results for each paper).

Most of the mothers (73 %) were <35 years of age. Regarding pregnancy complications, 15% had preeclampsia/eclampsia/HELLP (preeclampsia (hypertension with proteinuria) /eclampsia (hypertension associated with one or more convulsions (seizures) or coma) /HELLP (Hemolysis Elevated Liver enzymes Low Platelet count-syndrome based on laboratory abnormalities), 25% had PPROM and 88% received at least one dose of antenatal corticosteroids. Multiples accounted for 31% of all infants. Vaginal delivery was seen in 33% of all deliveries and caesarean section in 67%, of which 41 % were prelabour and 26 % intrapartum.

The median gestational age was 29 weeks (IQR 27-30). Thirty percent were born below 28 weeks of gestation and 2 % of the infants were born at 22-23 weeks of gestation. The median birth weight was 1195 g (IQR 910-1490). During hospitalisation, 11% of the infants deceased. Among infants surviving until discharge, the median PMA at discharge was 37 weeks (IQR 36-39). In the Stockholm region, the corresponding PMA at discharge was 36 weeks, IQR (IQR 35-38), and 73% of the infants in the Stockholm region were discharged home with home-based neonatal care. In Ile-de-France, 15% were discharged home with home-based care, and for the other regions it was below 5% or no infants discharged home with home-based care

Paper I

Among 5679 infants with registered admission temperature, 53.4% had an admission temperature below 36.5°C and 13% had a temperature below 35.5°C. The incidence of admission hypothermia varied between the regions from 30 to 90%.

PPROM, any course of antenatal corticosteroids, higher gestational age and birth weight were associated with higher admission temperatures. Lower admission temperatures were seen among infants to mothers having preeclampsia/eclampsia/HELLP, singletons, SGA and infants having an Apgar score <7 at 5 minutes. Time to admission was in this cohort not associated with admission temperature.

Infants with an admission temperature below 35.5°C had a two-fold risk of mortality during the first month of life after adjustment for gestational age, birth weight Z-score, infant sex, multiple birth, antenatal corticosteroids, preeclampsia/eclampsia/HELLP (Figure 10)

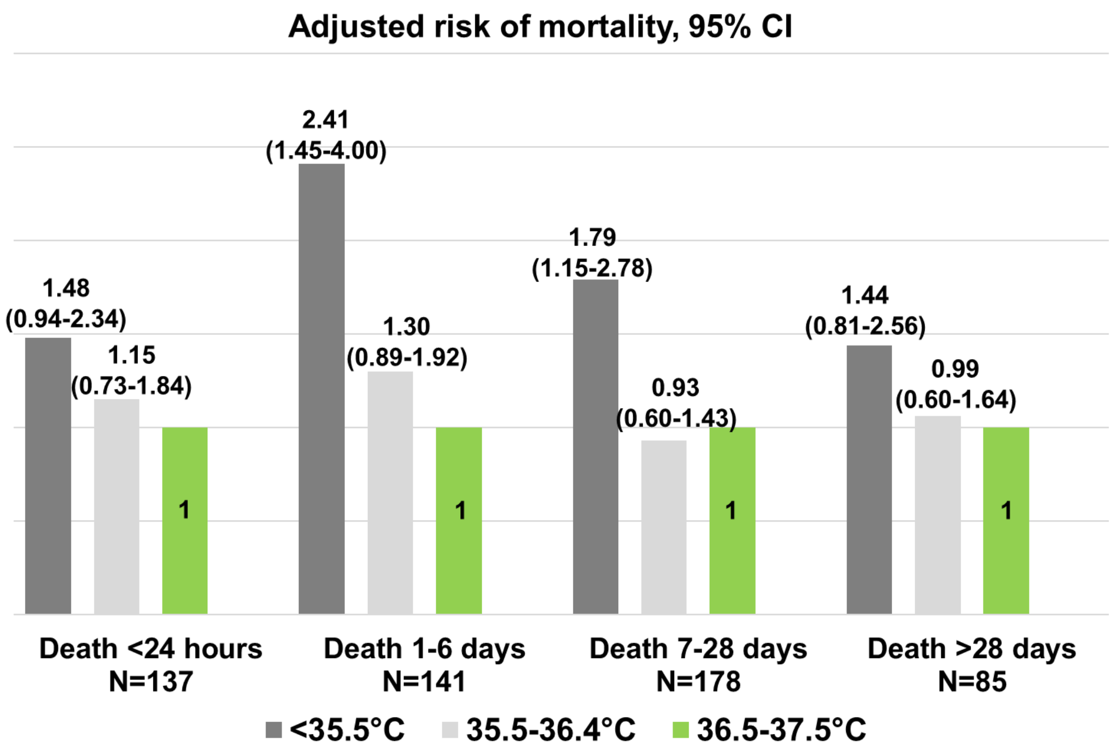

Figure 10. Association of admission temperature and in-hospital mortality, risk ratios, 95% CI.

Infants with a temperature below 35.0°C had the highest incidence of morbidity. After adjusting for obstetric characteristics, gestational age, birth weight Z-score and infant sex, the association between admission temperature and morbidity was no longer present.

In the sensitivity analysis, including infants with imputed admission temperatures, Apgar and mode of delivery, the risk estimates for mortality were slightly attenuated, but followed the same pattern as in the complete case analyses.

Paper II

The median admission temperature was 36.4°C (35.9-36.8°C). The distribution of admission temperatures is shown in Figure 11.

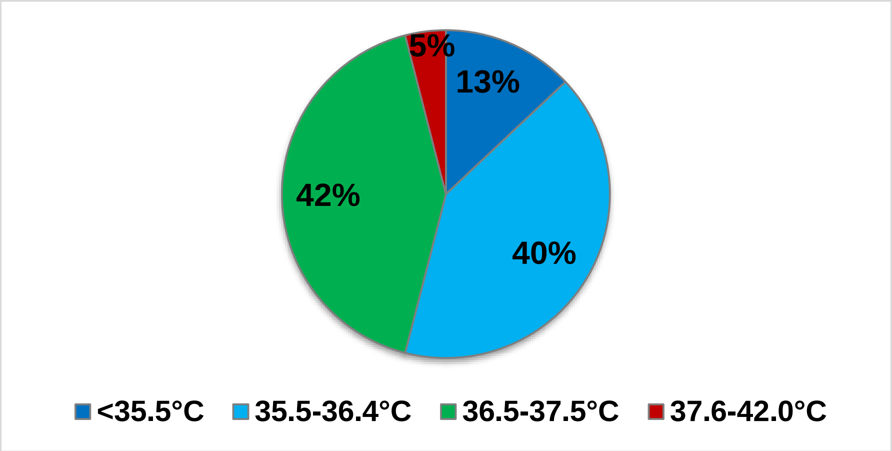

Figure 11. Distribution of admission temperatures.

The type of hypothermia prevention used, varied across EPICE regions. Eighty-eight percent reported systematic (whenever possible) use of a strategy, or a combination of strategies, 9.6% reported no systematic use (sometimes use oruse of bags/wraps only if <28 weeks /<1000g) and 2.2% reported no use of investigated strategies.

The incidence of hypothermia was high across all the hypothermia prevention groups (41.2-56.7%). Infants born in units reporting systematic use of hypothermia prevention strategies had significantly higher admission temperatures 36.4 (36.0-36.9°C) than infants born in units with sometimes or no use of hypothermia prevention 36.0 (35.5-36.5°C), (p<0.001).

Among the 10.2% of infants born in units with no systematic use of hypothermia prevention, the percentage of infants with hypothermia at admission was 74.5% (413/554). In the systematic use (whenever possible) the incidence of hypothermia was 53.7% (2629/4895). Odds ratios of admission hypothermia to NICU in infants born in units reporting systematic use vs no systematic use of hypothermia prevention (Table 1).

	N=5449	Odds ratio of admission temperature <36.5°C	
		Unadjusted	**Adjusted[a]**
SYSTEMATIC (WHENEVER POSSIBLE) USE			
Bags/wraps+exothermic heat/transwarmer mattress and sometimes cap Bags/wraps and sometimes cap Exothermic heat/transwarmer mattress	4895 (89.8)	Ref. (1.00)	Ref. (1.00)
NO SYSTEMATIC USE OF HYPOTHERMIA PREVENTION			
Use of bags/wraps only if gestational age <28 and/or birth weight <1000g Sometimes use of hypothermia prevention	554 (10.2)	2.52 (2.07-3.08)	2.19 (1.47-3.24)

Table 1. Reported use of prevention strategies and risk of hypothermia at admission to neonatal care. Systematic whenever possible use vs no systematic use. Adjusted for gestational age, birth-weight Z-score, antenatal corticosteroids, preterm prelabour rupture of membranes, preeclampsia/eclampsia/HELLP, caesarean section, Apgar, multiple pregnancy and region.

In further multivariable adjusted logistic regression analyses of hypothermia at admission to NICU, infants born in units reporting use of prevention if infant <28 weeks of gestation or with a birth weight below 1000 g had a twofold increase in the odds for admission hypothermia and infants born in units that reported no systematic (sometimes) use of any prevention strategy had a nine-fold increase in the odds of admission hypothermia, compared with units systematically using exothermic heat/transwarmer mattress, bags/wraps and caps (sometimes). There were no differences in admission temperatures between units having guidelines for hypothermia prevention and units without guidelines (56% vs 58%, p=0.17).

The probability of hypothermia was highest among the infants with lowest gestational ages who had a 60 to 90% probability of being admitted to the NICU with a body temperature below 36.5°C as illustrated in Figure 12.

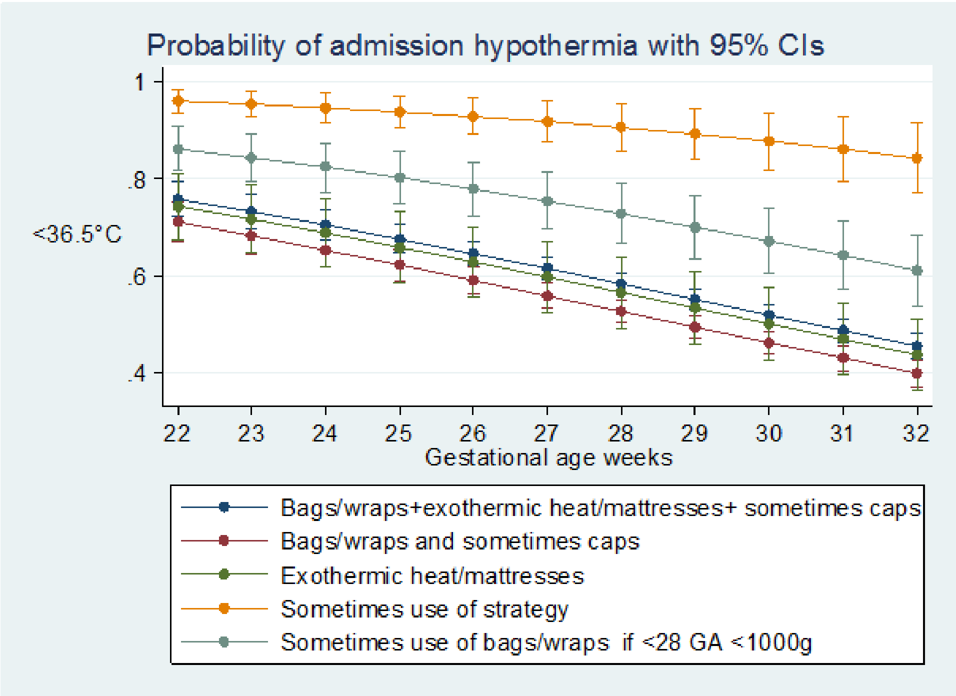

Figure 12. Predicted probability of admission hypothermia by gestational age and hypothermia prevention strategy.

The incidence of hyperthermia was overall low in this cohort 4.8% (282/5861) at admission to neonatal care, but was associated with the no systematic (sometimes use of hypothermia prevention group) that had increased odds (OR 5.07 95% CI (1.01-25.4) of hyperthermia compared with the reference group bags/wrap+exothermic heat/transwarmer mattress and caps.

5.2 BREAST MILK FEEDING AFTER VERY PRETERM BIRTH

Paper III

In the Stockholm region, 80% of the infants received their mother's own milk at 36 weeks PMA, 55% exclusively and 25% partially. Infants born <28 weeks of gestation received mother’s own milk less often at 36 weeks PMA, compared with infants born at 28 to 31 weeks, 46% vs. 54 % (p=0.03).

In infants born between 28-31 weeks of gestation the volume of mother’s own milk provided at postnatal day 3 and 7 was significantly related to breast milk feeding at 36 weeks PMA. There was also a dose-response relationship between mother’s own milk intake at day 7 and exclusive, partial and no breast milk feeding at 36 weeks of PMA in infants born 28-31 weeks of gestation Table 2.

	Breast milk feeding at 36 weeks PMA			
Postnatal day 7 (n=90)	**Exclusive (n=55)**	**Partial (n=20)**	**No (n=15)**	**P value**
Total volume of enteral feeding, median IQR, mL/kg	157 (120-174)	155 (74-168)	130 (90-164)	0.75
Total volume of mother’s own milk, median IQR, mL/kg	121 (81-161)	52 (11-108)	38 (10-51)	<0.001

Enteral intake and intake of mother’s own milk was calculated using the birthweight in the denominator.

Table 2. Enteral intake at postnatal day 7 in relation to exclusive, partial or no breast milk feeding at 36 weeks PMA.

In the adjusted analyses of predictors of exclusive vs partial breast milk feeding at 36 weeks PMA (adjusted for maternal country of birth, parity, onset of delivery and gestational age) being a non-Nordic mother was associated with less exclusive breast milk feeding, OR 0.27, 95% CI (0.10-0.69) compared with Nordic mothers and a gestational age at birth below 28 weeks of gestation was also associated with lower chance of exclusive breast milk feeding, OR 0.29 95% CI (0.11-0.82) compared with infants born between 28 and 31 weeks. Onset of delivery and parity was not associated with the chance of exclusive breast milk feeding.

Among infants born between 28 and 31 weeks of gestation, the adjusted odds ratio for exclusive breast milk feeding compared with partial breast milk feeding at 36 weeks PMA was 1.18 (1.06-1.32) for each 10 ml/kg increase in breast milk at postnatal day 7 after birth.

Between 36 and 40 weeks PMA the proportion of infants receiving breast milk decreased over all. Of the 76 infants who were exclusively breast milk fed at 36 weeks PMA 71 %

(54/76) were still exclusively breast milk fed at 40 weeks, 24% (18/76) received partial breast milk feeding and four infants (5%) received no maternal milk. In the analysis of sustained breast milk feeding between 36 and 40 weeks PMA, neither country of birth, parity, gestational age or early and high intake of mother's own milk was significantly related to the changes seen between 36 and 40 weeks PMA.

Breastfeeding at breast was seen in 76% (44/58) of the infants exclusively fed with mother's own milk at 40 weeks PMA. Gavage at discharge was additionally investigated in the Stockholm region and 70% (96/138) of singleton infants were gavage fed at discharge.

Paper IV

At discharge from neonatal care in the EPICE regions, 58% of the infants received breast milk, exclusive or partial. There were large variations between the regions (Figure 13). The highest rate of breast milk feeding was seen in Denmark, Eastern region (80%) and the lowest in the Northern region of UK, 36%.

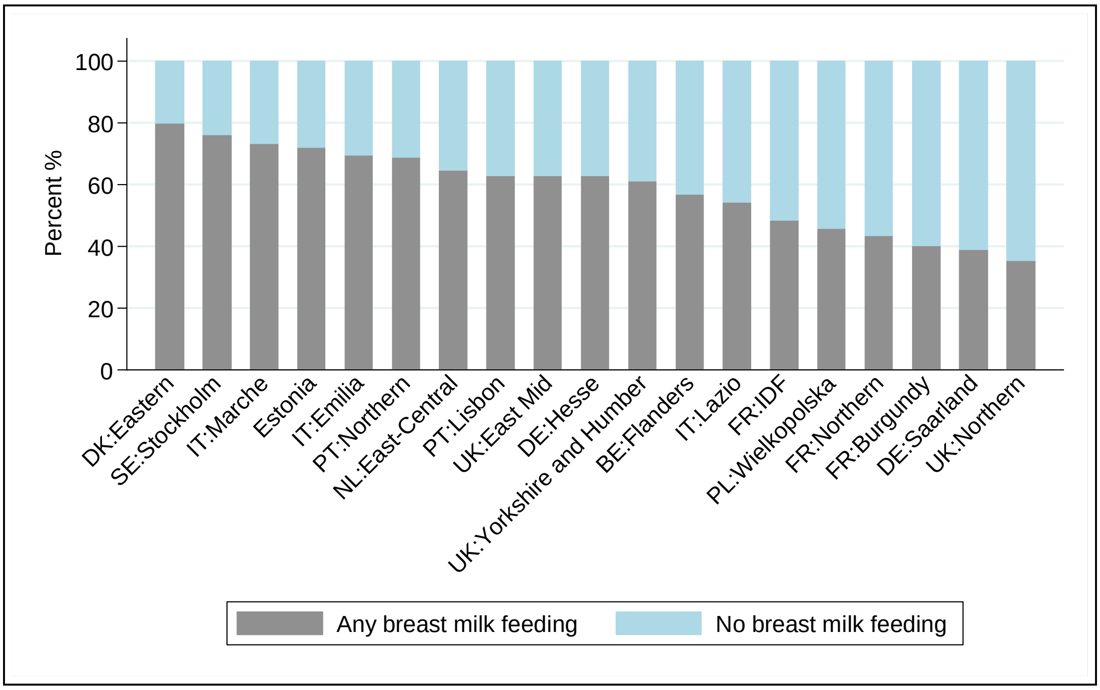

Figure 13. Distribution of any breast milk feeding at discharge from neonatal intensive care in the EPICE regions.

Covariates positively associated with any breast milk feeding at discharge in the adjusted analysis were: primiparity, any course of antenatal corticosteroids, first enteral feed at less than 24 hours after birth, and mother's own milk at first enteral feed. Having a low gestational age, higher PMA at discharge and neonatal morbidity were negatively associated with any breast milk feeding at discharge in the multivariate analysis adjusted for maternal age, country of birth, parity, preeclampsia/eclampsia/HELLP, antenatal corticosteroids, type of delivery, multiple birth, gestational age, Apgar, SGA, congenital anomalies, time of first enteral feed, mother's own milk as first feeding, infant morbidity, and any between hospital transfer.

Exclusive breast milk feeding at discharge was more often seen in native mothers, after vaginal delivery, singleton birth and in infants who received mother's own milk at first enteral feed. Being a younger mother and multiple birth were associated with less chance of exclusive breast milk feeding at discharge. analysis. (Table 3). Infants size, age and morbidity were not associated with the chance of being exclusively breast milk fed at discharge.

	Exclusive vs partial breast milk feeding			
	Exclusive N=1812	**Partial N=2014**	**Gestational age adjusted**	**Multi-variable adjusted[a]**
	Numbers and column percentages		Risk Ratios (95% Confidence Interval)	
Maternal age, years				
– <25	187 (10.3)	264 (13.1)	0.85 (0.75-0.96)	0.82 (0.72-0.95)
– 25-34	1124 (62.0)	1180 (58.6)	1.00 (reference)	1.00 (reference)
– ≥35	496 (27.4)	556 (27.6)	0.99 (0.92-1.07)	0.97 (0.89-1.05)
Country of mother's birth				
– Native	1371 (75.7)	1377 (68.4)	1.00 (reference)	1.00 (reference)
– Other	294 (16.2)	489 (24.3)	0.77 (0.70-0.85)	0.81 (0.73-0.90)
Parity				
– 1	1075 (59.3)	1211 (60.1)	1.00 (reference)	1.00 (reference)
– 2	462 (25.5)	454 (22.5)	1.07 (0.98-1.16)	1.05 (0.96-1.15)
– 3	164 (9.1)	199 (9.9)	0.95 (0.83-1.08)	0.92 (0.79-1.06)
– ≥4	90 (5.0)	140 (7.0)	0.86 (0.72-1.03)	0.82 (0.66-1.01)
Preeclampsia /eclampsia/HELLP,yes	305 (16.8)	313 (15.5)	1.02 (0.93-1.12)	1.05 (0.94-1.17)
Any antenatal corticosteroids, yes	1635 (90.2)	1838 (91.3)	0.92 (0.81-1.04)	0.94 (0.82-1.08)
Type of delivery				
– Vaginal	643 (35.5)	541 (26.9)	1.00 (reference)	1.00 (reference)
– Cesarean	1156 (63.8)	1467 (72.8)	0.83 (0.76-0.89)	0.88 (0.80-0.96)
Type of pregnancy				
– Singleton birth	1320 (72.8)	1236 (61.4)	1.00 (reference)	1.00 (reference)
– Multiple birth	492 (27.2)	778 (38.6)	0.74 (0.67-0.82)	0.71 (0.64-0.80)
Time of first enteral feed				
– <1 day	592 (32.7)	585 (29.0)	1.00 (reference)	1.00 (reference)
– 1-6 days	1103 (60.9)	1285 (63.8)	0.97 (0.87-1.07)	0.93 (0.83-1.03)
– >=7 days	70 (3.9)	100 (5.0)	0.92 (0.75-1.13)	0.84 (0.68-1.05)
Mother's own milk at first enteral feed, yes	784 (43.3)	746 (37.0)	1.27 (1.14-1.42)	1.25 (1.11-1.41)

Table 3. Regression analysis of exclusive vs partial breast milk feeding at discharge. Risk ratios and 95% confidence interval of exclusive vs partial breast milk feeding. Adjusted for maternal age, country of birth, parity, preeclampsia/eclampsia/HELLP, antenatal corticosteroids, type of delivery, multiple birth, gestational age, Apgar, SGA, congenital anomalies, time of first enteral feed, mother's own milk as first feeding, infant morbidity, and any between hospital transfer.

Most of the units had written breast milk feeding policies (66%). Unit policies that were positively associated with breast milk feeding at discharge were having a breast milk feeding protocol RR 1.49 (1.07-2.10) and availability of donor milk 1.25 (1.00-1.57), p=0.048,after adjustment for maternal age, country of mother's birth, parity, preeclampsia/eclampsia/HELLP, antenatal corticosteroids, type of delivery, multiple birth, gestational age, Apgar, SGA, congenital anomalies, infant morbidity and any between hospital transfers

Among those 3826 infants receiving any breast milk feeding at discharge, 2593 (68%) were breastfeeding at breast. Breastfeeding at breast at discharge varied between the regions with the highest rates in Sweden, 93%; Denmark, 85%; and lowest in Marche, Italy, 16%; and Saarland, Germany, 22%.

6 EPIDEMIOLOGICAL TERMINOLOGY

The WHO defines epidemiology as “the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems”. Epidemiological studies include both descriptive and analytical studies to study determinants of health and disease.

When performing or evaluating a study there are several considerations.

6.1.1 Validity

The validity is looked at from an internal and external perspective. Internal validity means that in the absence of systematic or random errors, the study measures what it was set to do. External validity means that the findings are generalisable to other similar populations. A study cannot have good external validity in the absence of sufficient internal validity.

6.1.2 Systematic and random errors

Selection bias
Selection bias encompasses bias resulting from pre-existing differences between the groups being studied with respect to the outcome. It is the most challenging menace to the internal validity in studies with observational design.

Information bias
Information bias results from incorrect collection of information concerning the exposure and/or the outcome and may introduce systematic error. Non-differential misclassification is the result from inaccuracies of similar magnitude or frequency in both the exposed and unexposed part of the cohort

Random errors
The impact of random error is imprecision. Random error has no preferred direction and the estimate may be imprecise but not inaccurate usually reducing the possibility to find associations, even when they exist. The impact of the imprecision caused by the random error can be minimised with large sample sizes

6.1.3 Confounding

Bias by confounding is a major concern in epidemiological studies. Confounding is a third variable (not the exposure or outcome variable of interest) that distorts the observed relationship between the exposure and outcome, as it is related to both the exposure and outcome (Figure 14). A variable that is an intermediate variable between the exposure and outcome is NOT a confounder. The confounding variable can produce an estimate that is more extreme (positive or negative) than the true association, or an underestimation of the true association or produce an association that does not exist.

Methods that can be used to control for confounding in the design of the study are randomisation, restriction and matching (also in analysis). In analysis, stratification can be used, investigating the association between exposure and the outcome within homogeneous categories or strata of the confounding variable. Multivariate analysis control for confounding and statistically takes a number of variables into account simultaneously. When the model is correctly specified it efficiently describes the association between exposure and outcome, as well as other variables that may confound the effect of exposure.

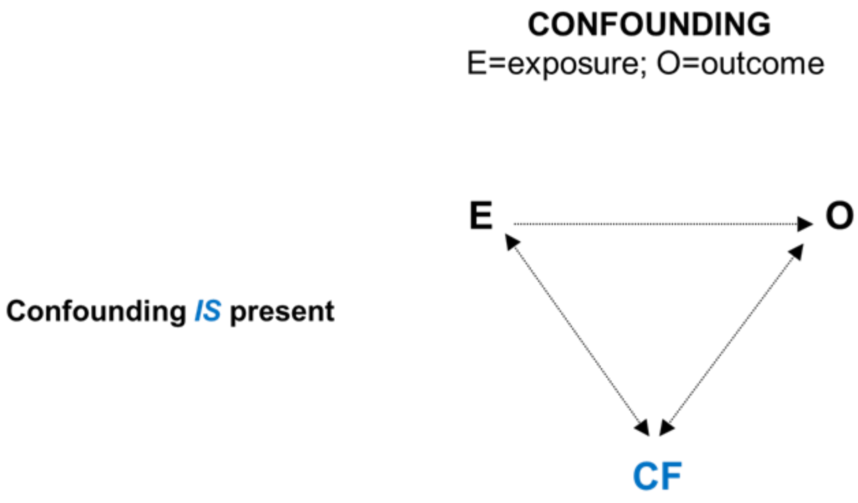

Figure 14. Confounding.

7 DISCUSSION

7.1 GENERAL DISCUSSION

The overall objective of this thesis was to study thermal care and breastfeeding after very preterm birth. The general research question was to investigate if and how, thermal and breastfeeding interventions are implemented in the care of the very preterm infant in European neonatal intensive care units.

The main findings of this thesis are that more than half of the infants, born <32 weeks of gestation in the EPICE-regions, were hypothermic at admission to neonatal care. A body temperature <35.5° at NICU admission was strongly associated with mortality throughout the first month after birth. Systematic use of hypothermia prevention in the delivery room was associated with higher admission temperatures and lower risk of hypothermia at admission to the NICU, in contrast to sometimes use, for which both hypo- and hyperthermia were seen more often.

There were large variations in breast milk feeding rates at discharge across European NICUs. Early breast milk feeding support is of importance to achieve higher rates of breast milk feeding at discharge. There is still room for improvement in the care of the very preterm infant across European settings, in regard to both thermal care and breast milk feeding.

The objective of the EPICE project was to build an empirical knowledge base, investigating if and how evidence-based interventions are translated into practice in the care of the very preterm infant in maternity and neonatal units across Europe. I was given the opportunity to investigate two factors with a solid evidence base: thermal care and breast milk feeding, which had previously been shown to be associated with beneficial outcomes for the very preterm infant, but still vary across Europe. In the following section, the results from the different studies will be discussed and methodological limitations, as well as ethical considerations will be addressed. First, the two studies about hypothermia and thermal care will be discussed, followed by the breastfeeding studies.

7.2 HYPOTHERMIA AND THERMAL CARE

The large number of infants who had a temperature below 36.5°C at admission to the NICU was unexpected, but in line with other studies reporting similar proportions of hypothermic infants after our data collection ended (99, 100) The improvements in perinatal intensive care during the last decades and the advanced technology involved might have contributed to the belief that hypothermia is no longer problem in high-resource settings. In addition, considerably lower temperatures than 36.5°C were common, 13% of the infants had an admission temperature below 35.5°C and the risk of mortality was doubled in this group. The risk of mortality remained significantly elevated throughout the first month after birth, among those that survived to 24 hours.

The finding that admission temperature is associated with mortality after very preterm birth is consistent with other studies from high-income settings (99-102). For more than a century, it has been known that exposure to cold after birth is associated with neonatal mortality and morbidity. In the 1950's, an RCT investigating different incubator temperatures concluded that a colder environment contributed to mortality, especially in the lower gestational ages (98).

In a recent RCT of occlusive wrapping of infants born <28 weeks of gestation, that was powered to investigate the effects of hypothermia on mortality, the authors concluded that occlusive wrapping did not have an effect on mortality, although it improved admission temperatures. This study was stopped at interim analysis, since the mortality was so similar between the groups that continuing the study would not detect any difference in mortality between the intervention and control group (106). However, their study showed that mortality was highest among infants with a temperature <34.5°C and with increasing temperatures mortality decreased. Another study by de Almeida et al. concluded that the infant body temperature drop in the delivery room, resulting in hypothermia (temperature measured 5 minutes after birth) was the main factor behind admission hypothermia (99).

This rapid temperature fall (95, 96) after birth has been shown previously and stresses the importance of immediate hypothermia prevention in the delivery room. Our study showed no association between age at admission and admission temperature, which could further support this. The incidence of admission hypothermia was high, 41-70%, regardless of which hypothermia prevention method that was used in the unit where the baby was born. As we have shown that there is an association between hypothermia and mortality in this cohort, it would have been interesting to explore how the different strategies related to mortality, but we did not have sufficient power to do this.

The physiological process that may underlie the association between hypothermia and neonatal mortality has not been clarified, but the causal risk factors for hypothermia in very preterm infants have been well described and have contributed to the improvement of hypothermia preventing strategies tested in several RCTs. Placing infants born below 28 weeks of gestation in bags/wraps without drying has proved to be an effective way of lowering the incidence of hypothermia (106, 159). The observational design of our study, and the exposure measure on unit rather than the individual level, did not allow us to make inference about the causality between hypothermia prevention strategy and risk of hypothermia. Nevertheless, it gives estimates about the possible effectiveness of hypothermia prevention derived from the real world. One could speculate that interventions tested in clinical trials are effective as long as the trial is ongoing, but outside the controlled setting, the effect size may decrease.

Infants born in units reporting no systematic use of hypothermia prevention had increased odds of both hypothermia and hyperthermia at admission to the NICU, compared to infants born in units reporting systematic use of prevention. This finding could imply that systematic use contributes to a more effective use, in terms of keeping the infant in the range of normothermia (160).

There was no difference in risk of hypothermia or hyperthermia at admission between units having guidelines for hypothermia prevention or not. This could mean that units that have guidelines have difficulties with the staff adherence, or that the guideline is of lower quality or not implemented. Guyatt et al. stresses the importance of evaluating the quality of evidence before implementation of a guideline, as it otherwise could lead to improper recommendations (15). The GRADE evaluation system has developed tools that support the assessment of the quality of evidence before creating clinical guidelines and recommendations (161). Unfortunately, we did not have the capacity to collect and analyse the content of the guidelines in the different units and regions participating in the EPICE study.

In contrast to other studies, we did not find an association between admission hypothermia and major neonatal morbidity. Miller et al. reported greater odds of IVH in infants with admission temperatures between 32.0 and 35.9°C (born at 24 to <32 weeks of gestation and with a birth weight <1500g) (101). We can, however, not exclude that there was an association with IVH in our study, as there could be undiagnosed IVH among infants who died early in the first week of life. Laptook et al. showed an increase of late-onset sepsis with decreasing admission temperatures (102). Unfortunately, we did not have comparable data.

When comparing results from observational studies on neonatal hypothermia, a recurring problem is the different definitions used to define hypothermia, making the interpretation between studies less straight forward. The rationale for choosing the WHO definition of hypo-, normo- and hyperthermia was that it defines a temperature where the infant body is in the thermoneutral normal range, 36.5-37.5°C. A cohort study by Lyu et al., investigating the association between admission temperature and mortality or major morbidity in infants born at <33 weeks of gestation, showed that temperatures between 36.5-37.2°C were associated with the lowest mortality and morbidity (100). Their finding supports that the WHO definition of normothermia is applicable also to very preterm infants.

As hyperthermia is an adverse outcome, the focus should be on maintaining normothermia. Some studies have shown that it is possible to eradicate hypothermia without increasing the risk of hyperthermia (110, 111), while other studies have shown an increased number of hyperthermic infants when applying hypothermia prevention (106, 113). Preventing hypothermia by combining a bundle of temperature preserving strategies will better cover all aspects of thermal care, and also acknowledges the importance of the multidisciplinary team involved in the care of the very preterm infant.

The rationale behind stratifying mortality by the time of death was to be able to investigate if the association was driven only by the critically ill infants at birth, with an inevitable early neonatal death and therefore hypothermic. As the association persisted during the first 27 days and independently of the Apgar score, shown to be an indicator of neonatal mortality

(162), we concluded that we were not studying a reverse association between hypothermia and risk of death. We conclude that infants are likely to benefit from interventions in the first minutes after birth aiming at reducing hypothermia in the delivery room.

This way of stratifying death by time has an implication when exploring determinants of mortality in research. For the parents of a deceased very preterm infant, the timing of death is subordinate knowledge, which has to be remembered when presenting results in forums with parent representatives.

7.2.1 Internal and external validity paper I and II

Limitations of the two studies addressing hypothermia are that we allowed for a two-hour span from birth to registration of NICU admission temperature, and that we did not register the site of temperature measurement, which might influence the precision of the studies. Another limitation is that we did not have hypothermia prevention data on the individual level. The units responding *sometimes* or *never use* of prevention may have had an evidence-based individual approach to hypothermia prevention, although not captured by the questions in the questionnaire.

Another bias is residual confounding, caused by variables that we were not able to control for. For example, we did not register whether the infant received heated humidified gas, shown to improve the chance of being normothermic at admission in an RCT comparing heated vs. cold dry gas (Meyer et al. 2015). However, that intervention was not related to differences in mortality or morbidity between the groups. The rewarming rate of hypothermic infants could also have been considered, although observational studies have not shown any association between rewarming rate and mortality or morbidity (adverse respiratory outcome, IVH, NEC, BPD, ROP) (Rech et al. 2015).

The strengths of the studies include the population-based design, that data was collected using a pretested standardised data collection form in all regions. and that we investigated both individual and unit data in a large cohort. In the mortality analysis, we were able to stratify the analysis on time of death. Although not capturing the individual hypothermia prevention used, we were able to present results from intended use of hypothermia prevention in every-day clinical work. The results from these studies are judged to be generalisable to neonatal units across Europe and other countries/settings with similar resources.

7.3 BREAST MILK FEEDING AFTER VERY PRETERM BIRTH

These two studies; one from Sweden and one from the European cohort, show that it is possible to achieve high rates of breast milk feeding at discharge from the NICU and that early breastfeeding support is associated with higher proportions of infants receiving breast milk after very preterm birth.

There were large variations in any breast milk feeding at discharge between the regions (36-80%). Breastfeeding at the breast, among infants receiving breast milk, also varied widely between the regions (16-93%). These variations were seen both across and within countries and could potentially be explained by the national variations in the overall breastfeeding culture, the differences in paid maternity leave or on a hospital level (163-165), due to differences in the possibility for the parents to spend time in hospital between. (90).

In the EPICE cohort study, we saw that infants who received their own mother’s milk at first enteral feed were more likely to receive any breast milk feeding at discharge. In the Stockholm cohort, where we collected additional information on intake of mother’s own milk, higher provision of mother’s own milk at postnatal day 7 was associated with exclusive breast milk feeding at discharge, one to three months after later.

The results from the unit questionnaires in EPICE did not show an association between unit policy of early breast milk expression and breast milk feeding at discharge. The interpretation of this finding is, however, limited by the fact that the time when the mother started to express is unknown. Expressing within one hour after birth might be a guideline that is hard to implement, although evidence about the importance of early expression exists (133, 166). Other factors associated with the decision to express milk, and with milk volumes, are grief after very preterm birth and the stress that a NICU hospitalisation may entail (167-170).

Our finding that units that provide donor milk had higher rates of exclusive breast milk feeding at discharge is in line with a recent US study (171). A systematic review (172) showed that donor milk had a positive effect on any breast milk feeding, but not on exclusive breast milk feeding which is in line with our results from the EPICE cohort. One of the studies in the review by Williams et al. showed socio-economic and racial differences with decreasing rates of own milk among low-income black mothers when introducing donor milk. In both the Stockholm cohort and the EPICE cohort, being non-Nordic/non-native was associated with less chance of exclusive breast milk feeding at discharge. Many studies, including the EPICE cohort, do not differentiate between mother’s own milk and donor milk. This is a potential problem, especially when conducting quality improvement work trying to improve breast milk feeding rates, and when investigating the association with morbidities such as NEC known to have beneficial effects from own mother’s milk. In addition, the strategies used to promote and to achieve high volumes of mother’s own milk during NICU hospitalisation differ between the acquisition and use of donor milk. Meier (2017) has raised the question about how resources should be prioritised when aiming to achieve the quality initiative of improved breast milk feeding rates (145).

A BFHI accreditation was not associated with improved breast milk feeding at discharge, which is in contrast to the large cluster randomised promotion of breastfeeding intervention trial (PROBIT) in term infants (173). This may illustrate that the BFHI does not sufficiently focus on factors that are key to obtain exclusive breastfeeding after very preterm birth, such as skin-to-skin care/kangaroo-mother care (149, 174) and addressing the establishment of a sufficiently high breast milk production within the first weeks after delivery to maintain exclusive breast milk feeding, when the infant is growing and in need of higher volumes (121, 175). An expanded version of the BFHI dedicated for neonatal care has been developed and is a tool raising awareness and gives support to health care professionals involved in breastfeeding and the care of the very preterm infant and their family (176, 177).

The likelihood of receiving any breast milk feeding at discharge was lower among infants born at a lower gestational ages and in infants with neonatal morbidities, which is consistent with findings from previous studies (150, 178, 179). The likelihood of exclusive breast milk feeding compared to partial breast milk feeding was, however, not associated with gestational age and infant morbidity. When speculating, this finding could mean that providing exclusive breast milk is more of a maternal decision and motivation while any breast milk feeding is more operated by the infant's clinical condition, maternal complications and medication, or unit policies and staff attitudes. In study III, we chose not to include infant morbidity in the analysis as we investigated breast milk feeding regardless of route and were limited in power, but with the results from study IV it would have been interesting to investigate the impact of infant morbidity in a setting with a high percentage (80%) of breast milk feeding at discharge.

Multiples were also treated differently in the present studies. In study III we chose to exclude multiples because difficulties in comparing milk yield data for mothers who started to express breast milk for 2 or 3 children, but where only one of the twins/triplets survived until 36 weeks PMA. In addition, the emotional effect on milk supply when losing a child needs to be kept in mind. The group of multiples was not sufficiently large to analyse separately. In study IV, we chose not to exclude multiples. The results showed that multiple birth was associated with a lower chance of exclusive breast milk feeding. This finding is in line with a study from Maastrup et al. (2014), and needs to be considered when giving breast feeding support to mothers of these already more vulnerable infants.

A study about routine feeding decision in the NICU showed that breast milk feeding support was influenced by staff preferences and unit norms, resulting in inconsistent and not always effective feeding strategies in the NICU. McInnes et al. suggested the development of clear guidelines to be able to have unified information and support in the feeding decisions in the NICU (180). There is also a need for increased parental involvement in the decisions about feeding. In addition, higher rates of mother's own milk at discharge have been reported in units where a multidisciplinary lactation and nutrition team engages in the implementation of protocols (121).

Factors associated with successful breast milk feeding from a parental perspective in the NICU were knowledge about breastfeeding, strengthening mothers' motivation and concordance between parental needs, not to be separated from their baby, need of privacy and NICU routines (181).

Breastfeeding at breast was seen in 76% of the exclusively breast milk fed infants in the Stockholm region. In paper IV, there were large variations in breastfeeding at breast rates between the regions at discharge (13-93%). This illustrates the room for improvement across regions. Strategies known to be effective are skin to skin as the first step to breastfeeding at breast and KMC contributes to increased breastfeeding at breast rates in VLBW infants (148, 149, 174). One of the regions in the EPICE study that had the highest rates of breastfeeding at breast, apart from the Stockholm region (93%) was Eastern region in Denmark (85%). These regions are in countries with unrestricted parental visiting in the NICU (163).

The benefits of breast milk and breastfeeding for the very preterm infant and the mother are well established. (2, 57, 68, 69, 124, 126-130, 132, 182). It would therefore be unethical, and not in line with best practice, not to provide the parents with evidence-based information enabling them to make an informed choice about provision of mother's own milk and breastfeeding. In addition, as health care professionals, we need to acknowledge and help realising their breastfeeding goal, i.e. provide knowledge and necessary tools known to improve breast milk feeding after very preterm birth.

7.3.1 Internal and external validity paper III and IV

The precision in the breastfeeding studies was high, as both the exposure and outcome were measured in a consistent way on the individual level, using a well-defined data collection instrument and unit questionnaire when retrieving data from medical records and information about unit policies.

A limitation is that we did not differentiate between mother's own milk and donor milk at discharge in the unit questionnaire in study III. However, given the general scarcity of donor milk and the volumes needed for an infant at near-term equivalent age, it is most unlikely that infants would receive donor milk rather than formula at discharge, but we cannot exclude that this occurred in a few cases. Another aspect that needs to be addressed is the varying definitions used in breastfeeding research, leading to difficulties when comparing results between studies. Differences can be found in the route of administration (at breast, gavage, cup/bottle) and type (mother's own milk/donor milk) and in the distinction between exclusive and partial breast milk feeding. The breastfeeding definitions used are in line with the definition by the WHO (183).

The results may have suffered from residual socioeconomic-confounding in the association between the individuals' characteristics, unit policies and breast milk feeding, as we were not able to consider several factors previously shown to be associated with breast milk feeding; mother's intention to breastfeed, medication use, socioeconomic status and smoking (151, 184, 185). Study III is generalisable to settings with a high rate of infants receiving breast milk at discharge, settings where donor milk is routinely available and where the parents have the possibility to stay with their baby in the NICU during hospitalisation. Study IV is generalisable to other European settings caring for very preterm infants, but probably also to other high-income settings.

7.4 THE GLOBAL PERSPECTIVE

Although the focus of this thesis is on infants born in European high-resource settings, the importance of thermal care and breastfeeding should be mentioned in a global perspective. Thermal care, e.g. skin-to skin/KMC and breastfeeding are two life-saving interventions among infants that are born outside settings with intensive care, defined as availability of surfactant and ventilation (Lawn et al. 2013). Focusing on improving newborn thermal care and breastfeeding both locally and globally could be a way to contribute towards fulfilling several of the Sustainable Development Goals (186).

7.5 ETHICAL CONSIDERATIONS

One of the main aspects of research ethics is informing patients, in this case parents, about the purpose and how the study will be conducted and that it at any time is possible to withdraw from the study without the feeling that the care would be affected. For each participating region in the EPICE project, ethical approval has been obtained as required by national legislation (from regional or hospital ethics committees). Parental consent was obtained according to regional and hospital ethics committee requirements (an active written consent or passive consent, meaning that the parents have received information about the study, and are assumed to have consented if not stated otherwise).

For the Stockholm region, the studies were approved by the Regional Ethical Review Board, situated in Stockholm: Approval number (2011/209-31/1). The Board waived active parental consent to the data collection. The nurses gave written information about the data collection to the parents, as soon as possible after admission to the neonatal intensive care unit. At the EPICE meetings, ethics has often been on the agenda. We have discussed the differences between the countries/regions. We have also had discussions about how to handle the data, from the time when the data collection instrument/questionnaires are filled at the departments and how to safely share and store the database of the research team without jeopardising the anonymity and integrity of the study participants.

7.6 CLINICAL IMPLICATIONS AND FURTHER PERSPECTIVES

Optimal thermal care and breast milk feeding are important factors in reducing morbidity and mortality after very preterm birth. Neither the importance of thermal care, nor the importance of breast milk for the very preterm infant is new knowledge, but results from this thesis show that these areas need repeated attention.

Very preterm birth is a common condition, affecting 1 to 2 % of all births, and the gains of improved outcomes are multifactorial, both at the individual level for the infant and the family, and for the society. Implementing evidence-based guidelines would improve outcomes (Zeitlin et al. 2016) and reduce ineffective treatments for the infant. In turn, this would improve the cost-effectiveness of the care of the very preterm infant.

Implementation of new guidelines and staff adherence to these are complex matters (Berenholtz et al. 2009; Grol et al: 2003; Cabana et al. 1999). Involving a multidisciplinary team (121) with expertise in several areas to be able to encompass all the aspects involved in thermal care and breastfeeding after very preterm birth could be a facilitator working with implementation, as well as focusing on involving all health care personnel in the work in improving thermal care and breast milk feeding.

The European resuscitation council (103) suggests that admission temperature should be registered as a predictor of outcomes and as a quality indicator. In addition, measuring infant temperature more frequently in the first 10-20 minutes after birth would provide information about if and when the drop in temperature occurs, and how pronounced it is. This could also be beneficial in terms of evaluating the hypothermia preventing strategy, aiming at keeping infants normothermic. Thermal care is not an isolated phenomenon only involving the first hours after birth, but is ongoing through all stages in the NICU hospitalisation.

Every care aspect that can facilitate and help mothers who wish to provide their infant with their own milk and later breastfeeding at breast should be emphasised. Breastfeeding would probably also benefit of being acknowledged as a quality indicator in neonatal care.

To be able to evaluate implemented strategies and interventions in daily clinical work, a quality register is of great importance. In Sweden, there is a neonatal quality register (Svenskt Neonatalt Kvalitetsregister (SNQ) since 2001. A register can be used to get an understanding of the effect of an intervention or to detect improvement areas (187). Furthermore, it is a tool when providing feedback and when benchmarking.

In conclusion, low gestational age and birth weight are both strongly associated with the risk of mortality. To optimise disease free survival after very preterm birth, effective thermal care and provision of mother’s own milk are two areas that need continuous attention.

8 CONCLUSIONS

- Admission hypothermia after very preterm birth is a significant problem in neonatal units in Europe. More than half of the infants had a temperature below 36.5°C at admission to the neonatal intensive care unit.

- A body temperature <35.5°C measured at admission to neonatal care, was associated with a twofold risk of mortality in the neonatal period.

- Infants born in units reporting systematic use of hypothermia prevention strategies had significantly higher admission temperatures and lower risk of hypothermia at admission to neonatal care.

- The proportion of infants that were *hyperthermic* at admission was overall low in this cohort. Nevertheless, *hyperthermia* is a potentially adverse outcome when preventing hypothermia.

- Infant body temperature should be measured already in the delivery room and admission temperature should be acknowledged as a quality indicator in neonatal care.

- High intake of mother's own milk in the early postnatal period is strongly related to exclusive breast milk feeding at near term age in infants born very preterm.

- Most infants received breast milk at discharge from neonatal care in European units, but there were large variations between units (36-80%). Breastfeeding at the breast also varied widely between regions (16-93%).

- Infants who received mother's own milk at first enteral feed were more likely to receive breast milk at discharge from NICU after very preterm birth. Units that used donor milk had higher rates of exclusive breast milk feeding at discharge.

- The overall results from this thesis conclude that there is room for improvement in thermal care and breastfeeding after very preterm birth across neonatal units in Europe.

9 SVENSK SAMMANFATTNING

Av alla barn som föds i Europa, föds ca 1.5% mycket för tidigt (före 32 fullgångna graviditetsveckor, dvs. minst två månader för tidigt). Under de senaste åren har det skett en snabb utveckling inom obstetriken och neonatalvården vilket har bidragit till en ökad överlevnad hos de mycket för tidigt födda barnen. Sjukligheten i denna grupp av barn är dock fortsatt hög och innebär ofta flera veckors till flera månaders vård på neonatalavdelning. Sjukligheten samvarierar med graden av prematuritet, dvs. kortare graviditetslängd ökar risken för död och sjuklighet. Både den tidiga värmemiljön som möter barnet efter förlossningen och tillgången till bröstmjölk och amning under vårdtiden är två områden av stor påverkan på sjuklighet och dödlighet för det för tidigt födda barnet.

Det övergripande syftet med denna avhandling är att studera den tidiga värmemiljön och tillgången till bröstmjölk och amning efter mycket för tidig födsel i Europa.

Studierna är en del av ett europeiskt samarbetsprojekt, Effective Perinatal Intensive Care in Europe (EPICE, www.epiceproject.eu) vars syfte är att undersöka om evidensbaserad medicin/vård omsätts i vården av det mycket för tidigt födda barnet på förlossnings- och neonatalenheter. Under perioden 2011-2012 samlades data in på barn födda före 32 veckors gestationsålder i 19 regioner i 11 länder i Europa varav Stockholm utgör en av regionerna. Uppgifter om graviditet, förlossning och neonatalvård både på individ- och enhetsnivå samlades in med hjälp av strukturerade frågeformulär.

Avhandlingen omfattar fyra delarbeten. Delarbete I undersöker associationen mellan kroppstemperatur vid inläggning och svår neonatal sjuklighet samt risken för död under vårdtiden. Delarbete II omfattar både individ- och enhetsdata och beskrev värmebesparande strategier, visade att vara effektiva i att minska andelen kalla barn i randomiserade kontrollerade studier. Vidare studerades även associationen mellan användning av värmebesparande strategier och risken för hypotermi (kroppstemperaturer under 36.5°C) vid ankomst till neonatalavdelningen hos barn födda mycket för tidigt. Vidare undersöktes även risken för hypertermi (kroppstemperatur över 37.5°C) vid ankomst till neonatalavdelningen.

Delarbete III omfattar Stockholmsregionen och undersöker om tidigt (inom första levnadsveckan) och högt intag hos barnet av mammans egen mjölk var positivt relaterat till helamning, intag av mammans bröstmjölk oavsett tillvägagagångssätt (från bröstet, sondmatning, kopp eller flaska) i fullgången tid efter mycket för tidig födelse. Delarbete IV omfattar både individ- och enhetsdata och beskriver amningsutfall vid utskrivning från neonatalvården efter mycket för tidig födelse samt undersökte vilka amningsfrämjande faktorer som kan bidra till att fler barn får bröstmjölk vid utskrivning från neonatalavdelningen.

Delarbete I visar att 53% av alla mycket för tidigt födda barn hade hypotermi vid inläggning på neonatalavdelning. Temperaturer under 35.5°C förekom hos 13% av barnen och var förenade med en 140% riskökning för död dag 1-7 och en 80% riskökning för dag 7-28. Ingen association med neonatal sjuklighet sågs.

I delarbete II var andelen barn som hade hypotermi vid ankomst till neonatalavdelningen hög i alla grupper av värmebesparande åtgärder (41-77%). Oddsen att vara hypoterm vid ankomst till neonatalavdelningen ökade niofalt i gruppen av barn som var födda på enheter som uppgav att de inte hade systematisk användning av strategi i jämförelse med enheter som uppgav systematisk användning av värmebesparande strategi. Andelen barn som var hyperterma var relativt låg (2-8%) i de olika värmebesparande grupperna men är ett oönskat utfall vid arbetet med att förhindra barn som blir kalla efter förlossningen.

Delarbete III visar att 80% av barnen fick bröstmjölk vid 36 veckors postmenstruell ålder (55% helt och 25% delvis) från neonatalavdelningarna i Stockholmregionen. Ett högt intag av mammas egen mjölk vid en postnatal ålder av 7 dagar ökade chansen av att vara helammad vid 36 veckors postmenstruell ålder för varje 10 ml/kg ökning av bröstmjölk [Odds Ratio 1.18; 95% konfidens intervall (1.06-1.32)]. Av de kvinnor som uppnått helamning i vecka 36 helammade fortfarande 71% i vecka 40. Av de barn som vid 40 veckors postmenstruell ålder enbart fick mammans bröst mjölk, ammade 76% direkt från bröstet.

Delarbete IV visar att 58% av barnen fick bröstmjölk (helt eller delvis) vid utskrivning från neonatalavdelningarna i de inkluderade regionerna i Europa. Det var stora variationer mellan regionerna i bröstmjölksutfall/amningsutfall, 80% i den regionen med högst andel och 36% i den regionen med lägst andel. Även detta delarbete visade att tidigt intag av mammans bröstmjölk ökade chansen till att få bröstmjölk vid utskrivning från neonatalavdelningen. Enheter som använde sig av donatormjölk hade en högre andel barn som enbart fick bröstmjölk vid utskrivning. Andelen barn som ammade direkt från bröstet varierade stort mellan regionerna (16-93%).

Etiskt övervägande: Alla delarbeten är observationella och därmed är det liten risk för påverkan på barnen. Persondata har presenterats på ett sådant sätt som gör att det inte går att identifiera enskilda individer. Projektet är godkänt i den regionala etikprövningsnämnden i Stockholm (Dnr 2011/209-31/1) och enligt deltagande regioners regler för etikprövning för forskning.

Sammanfattningsvis är mycket för tidig födelse förenat med hög risk för sjuklighet och dödlighet. Även i europeiska högteknologiska länder som ur ett internationellt perspektiv är världsledande inom neonatalvård uppnås inte optimala resultat inom den tidiga värmemiljön efter förlossningen och tillgången till bröstmjölk och amning under vårdtiden.

Detta avhandlingsarbete bidrar till att belysa och aktualisera att dessa två områden är i regelbundet behov av att uppmärksammas. Det är inte acceptabelt att barn blir oavsiktligt kalla efter förlossningen. Att öka medvetenheten om både förekomst och eventuella risker med hypotermi kan i förlängningen förhoppningsvis bidra till att förbättra klinisk praxis så att andelen barn som blir kalla efter mycket för tidig födelse kan minimeras. Avhandlingsarbetet visar även vikten av tidig urmjölkning efter förlossningen för senare gynnsamt amningsutfall efter mycket för tidig födelse.

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When Anna-Karin and Mikael asked me if I wanted to be part of a European collaboration project (EPICE) about evidence-based care after very preterm birth they gave me an opportunity to investigate a clinically important question by doing research. Being part of the EPICE collaboration has been a tremendous experience. It has involved meetings with dedicated clinicians and researchers from 11 European countries to formulate research questions, discuss ethical and methodological problems and to write and review publications. The EPICE-project has also a strong focus on dissemination of the research findings. When hearing about a large European project, some people warned me about the hierarchical structures and protectionism often involved in large collaborations, but it turned out to be the opposite in this research group.

During the data collection period, I visited all the neonatal units in the Stockholm area, which together with the experience of data collection and database work reminded me of that clinical research would not be possible without the work of the staff in the units measuring variables and then registering them. Collecting the data for my studies gave me a broader understanding of the cohort, as reading medical charts and entering data in the dataset I later used when I performed statistical analysis.

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During my research education, I have also had the opportunity to combine the work of my studies with clinically addressed questions when working with the Swedish neonatal quality register (SNQ) and value based care where admission temperature is one of the investigated determinants of health. When I was invited to participate in the “Normothermia group” at the neonatal unit at Karolinska University Hospital I had the opportunity to combine research and quality work in a clinical setting and hope to continue so.

Vi kan inte skänka barnen framtiden men vi kan ge dem nuet
Kathleen Norris

Elias, Lea och Benjamin

Es jūs dikti mīlu

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