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Kjell Helenius

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To my lovely wife and children

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ABSTRACT

The care of very preterm infants is demanding, and the outcomes are superior when these infants are delivered in hospitals with the highest standard of care. This often requires transfer of the expectant mother when very preterm delivery is suspected. This process can be time-consuming and is potentially associated with high costs. The alternative approach includes delivering very preterm infants in hospitals that are close to the family and may provide a lower level of care, and transferring the infants to appropriate facilities after birth; this approach has been suggested to increase the risks of unfavourable outcomes.

The aim of this thesis was to evaluate the costs associated with centralisation of very preterm deliveries, to assess factors that precede and facilitate centralisation, to evaluate the effect of extremely preterm birth in lower-level hospitals with and without early postnatal transfer on outcomes and to initiate international collaboration to allow for benchmarking of neonatal care outcomes.

The results presented in this thesis show that centralisation of very preterm deliveries can be effectively achieved at a low cost, and identified crucial elements of the perinatal organisational pathways. The results also show that the advantage of delivering extremely preterm infants in hospitals that provide the highest level of care persists even in a setting with highly specialised neonatal transfer teams. Extremely preterm infants born in lower-level hospitals were at increased risk of adverse outcomes also without being subjected to early postnatal transfer. Within the realms of this study Finnish Medical Birth Register data were included in a multinational benchmarking collaborative, and subsequent analyses of mortality in very preterm infants showed marked variations between high-income countries.

These findings indicate that centralisation of very preterm deliveries cannot be replaced by a system that relies on postnatal transfers without placing infants at severe risk. The findings also highlight the need for continuous benchmarking of neonatal outcomes and sharing of results both nationally and internationally.

KEYWORDS: Very preterm infant, extremely preterm infant, neonatal transfer, health care costs, centralisation, neonatal intensive care, mortality, severe brain injury

TURUN YLIOPISTO
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TIIVISTELMÄ

Pienten keskosten hoito on vaativaa, ja parhaat hoitotulokset saadaan, kun synnytykset keskitetään sairaaloihin, joissa on resursseja kaikkein pienimpien keskosten hoitamiseksi. Keskittäminen edellyttää usein raskaana olevan äidin siirtämistä korkeimman hoitotason sairaalaan ennen synnytystä, mikäli hyvin ennenaikaista synnytystä epäillään. Keskittämisprosessi voi olla haastava ja kallis. Vaihtoehtoinen ratkaisu on synnyttää pienet keskoset sairaaloissa jotka ovat lähempänä perheen kotia ja usein tarjoavat rajallisempia hoitomahdollisuuksia, ja kuljettaa vastasyntyneet keskoset varhain synnytyksen jälkeen sairaalaan jossa on mahdollista tarjota asianmukaista hoitoa; tällä mallilla on aikaisemmin ehdotettu olevan haitallisia vaikutuksia keskosille.

Tämän väitöskirjan tavoitteina oli arvioida pienten keskosten synnytysten keskittämisen kustannuksia, tarkastella tekijöitä jotka edistävät keskittämistä, arvioida miten varhainen siirtokuljetus ja syntyminen alemman hoitotason sairaalassa vaikuttavat hoitotuloksiin sekä liittyä kansainväliseen pienten keskosten hoitotulosten vertailuverkostoon.

Tulosten perusteella todettiin että pienten keskosten synnytysten keskittäminen oli saavutettavissa alhaisilla kustannuksilla, ja tunnistettiin tärkeitä elementtejä hoidon organisaatiossa jotka mahdollistavat keskittämisen. Erittäin pienten keskosten varhaiset siirtokuljetukset olivat yhteydessä kohonneeseen riskiin vakaviin aivoverenvuotoihin, ja syntyminen alemman hoitotason sairaaloissa ilman varhaista siirtokuljetusta kohonneeseen kuolleisuuteen. Kansainväliseen vertailuverkostoon liittymisen myötä osoitettiin, että pienten keskosten kuolleisuudessa oli merkittävää vaihtelua verkoston maiden välillä.

Nämä löydökset osoittavat, että pienten keskosten synnytysten keskittämistä ei voida korvata synnytyksen jälkeisillä sairaalakuljetuksilla ilman että keskoset altistuisivat kuoleman ja vakavien aivoverenvuotojen riskeille. Löydökset korostavat myös kansainvälisen hoitotulosten vertailun ja tiedon jakamisen tärkeyttä sekä kansallisella että kansainvälisellä tasolla.

AVAINSANAT: Pieni keskonen, erittäin pieni keskonen, vastasyntyneen siirtokuljetus, terveydenhoitokulut, keskittäminen, vastasyntyneen tehohoito, kuolleisuus, vakava aivovamma

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Abbreviations

AAP	American Academy of Pediatrics
ANZNN	Australia and New Zealand Neonatal Network
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CNN	Canadian Neonatal Network
CTG	Cardiotocography
DRG	Diagnosis related group
EPICE	Effective Perinatal Intensive Care in Europe
EPIQ	Evidence-based Practice for Improving Quality
FinMBR	Finnish Medical Birth Register
iNeo	International Network for Evaluating Outcomes in Neonates
INN	Israel Neonatal Network
IQR	Interquartile range
IVH	Intraventricular haemorrhage
LNU	Local neonatal unit
MOSAIC	Models of Organising Access to Intensive Care for very preterm births
NDAU	Neonatal data analysis unit
NEC	Necrotising enterocolitis
NHS	National Health Service
NICU	Neonatal intensive care unit
NNRD	National neonatal research database
NRNJ	Neonatal Research Network Japan
OR	Odds ratio
PPROM	Preterm premature rupture of membranes
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SCBU	Special care baby unit
SD	Standard deviation
SEN1500	Spanish Neonatal Network

SNQ	Swedish Neonatal Quality register
SR	Standardised ratio
SwissNeoNet	Swiss Neonatal Network
THL	National Institute for Health and Welfare
TuscanNN	Tuscan Neonatal Network
UK	United Kingdom
UKNC	United Kingdom Neonatal Collaborative
VLBW	Very low birth weight
VON	Vermont Oxford Network
VPT	Very preterm

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Helenius K, Helle E, Lehtonen L. Amount of antenatal care days in a context of effective regionalization of very preterm deliveries. *J Pediatr*, 2016;169:81-6.

II. Helenius K, Mäkikallio K, Valpas A, Lehtonen L. Successful antenatal transfers to level 3 hospitals in cases of threatened very preterm deliveries: a national survey. (Manuscript)

III. Helenius K, Lehtonen L, Longford N, Modi N, Gale C. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. *BMJ,* 2019;367:l5678.

IV. Helenius K, Lehtonen L, Sjörs G, et al. Survival in very preterm infants: An international comparison of 10 national neonatal networks. *Pediatrics*, 2017;140:e20171264.

1 Introduction

Prematurity remains the most common reason for infant mortality worldwide (Liu et al., 2015, Lehtonen et al., 2017), even if advances in research and neonatal care have greatly improved survival (Costeloe et al., 2012; Grisaru-Granovsky et al., 2014; Ancel et al., 2015; Stoll et al., 2015). Improved survival of preterm infants has been listed as one of the greatest achievements in paediatric research in the past decades (Cheng et al., 2016). The care of the most preterm and most vulnerable infants is usually provided in hospitals with the highest level of care, commonly referred to as level 3 hospitals, but the organisation and designation of levels of care differ between countries. Centralisation of the most preterm deliveries to level 3 hospitals is one of the means that has been shown to improve neonatal outcomes (Phibbs et al., 2007; Rautava et al., 2007; Lasswell et al., 2010; Lorch et al., 2012) and the implementation of this centralisation has been successful in several settings (Lui et al., 2006; Binder et al., 2011). However, in some settings centralisation has been difficult to achieve (Gale et al., 2012). When very preterm infants are born in lower-level hospitals, neonatal transfer to a level 3 hospital is often indicated. It has been shown that infants born in lower-level hospitals and transferred after birth to level 3 hospitals have worse outcomes compared to infants born in level 3 hospitals (Kollee et al., 1988; Shlossman et al., 1997; Mohamed & Aly, 2010), but it has been unclear whether this is due to sicker infants being transferred, suboptimal stabilisation in lower-level hospitals, or direct effects of early neonatal transfer (Harding & Morton, 1994; Hauspy et al., 2001; Palmer et al., 2005; Watson et al., 2013). It is also not known whether using neonatal transfer teams specifically trained to carry out high-risk neonatal transfers could diminish the effects of early neonatal transfer and being born in lower-level hospitals.

Large international collaboration networks have the potential to provide large databases for epidemiological research. The International Network for Evaluating Outcomes in Neonates (iNeo) was founded in Toronto, Canada, and has grown to be one of the largest neonatal research collaborative networks worldwide (Shah et al., 2014). The aim of the iNeo collaboration is to collect a large, multinational population-based database containing a wide range of background and outcome data of very preterm infants, compare outcomes between network members,

identify sources of outcome differences, and eventually to implement quality improvement initiatives within the member networks. The iNeo database currently includes 11 national or regional neonatal networks, and serves as a platform for epidemiological neonatal research.

The first aim of this thesis was to assess the organisational costs incurred by centralisation of very preterm deliveries, to evaluate the process behind the decision to centralise mothers with imminent very preterm delivery, and to study the relationship between birth in lower-level hospitals with and without early neonatal transfer and neonatal outcomes. The second aim was to join Finnish population-based neonatal data with the iNeo project, to enable international comparison and benchmarking of neonatal care.

2 Review of the Literature

2.1 Classification of prematurity and low birth weight

The normal duration of pregnancy is 40 weeks after the first day of the last menstrual period, and a pregnancy is referred to as term if the duration is between 37 and 42 weeks. Any pregnancy of duration shorter than 37 weeks is referred to as preterm, and these can be further classified into very preterm (less than 32 weeks) and extremely preterm (less than 28 weeks) (Blencowe et al., 2012). Newborn infants can also be classified according to birth weight, where infants with a birth weight between 2500 and 4500 grams are considered to be of normal birth weight, and any infant weighing less than 2500 grams as being of low birth weight. Low birth weight infants can be further classified as very low birth weight (less than 1500 grams) and extremely low birth weight (less than 1000 grams). These definitions are the ones most commonly used.

2.2 Mortality in very preterm infants

Complications related to preterm birth are the most common causes of mortality worldwide in children under five years of age, representing 15% of all deaths in this age group (Liu et al., 2015). Mortality is an objective endpoint, and is frequently reported in studies on preterm infants. Mortality is defined as the rate of deaths in a specified group, and can be defined as perinatal mortality (risk of stillbirth or death of live-born infants within 7 days after birth), neonatal mortality (risk of death of live-born infants within the first 28 days of life) or infant mortality (risk of death of live-born infants within the first year of life). The definition of stillbirth varies, but is usually defined as fetal demise after a specified gestation, examples range from 20 to 28 completed gestational weeks (Hoyert & Gregory, 2016; Lawn et al., 2016). Mortality definitions vary between studies. Mortality is inversely related to gestational age; infant mortality rates of live born very preterm infants reported in studies vary from approximately 30% to 70% at 24 gestational weeks to over 90% at 31 gestational weeks (Fellman et al., 2009; Ishii et al., 2013; Ancel et al., 2015; Stoll et al., 2015). Survival before 24 gestational weeks is

possible and even quite frequent in some settings, but there are large variations internationally and within countries with regards to at what stage active treatment is initiated. It has been shown that hospitals that are proactive in providing care for infants born at 22 to 23 gestational weeks tend to have higher rates of survival and survival without major morbidities even in more mature infants (Serenius et al., 2014; Rysavy et al., 2015). Limits of viability are arbitrarily defined, and might lead to self-fulfilling prophecies; if no infants are resuscitated, none survives, and if the survival rate is zero, it might lead to conclusions that there is no point in attempting resuscitation. A study from the Netherlands showed that after lowering the limit of active treatment, also infants born at higher gestational ages had better outcomes (Zegers et al., 2016). This might be due to increased experience in caring for infants born at the limit of viability.

Comparison of mortality in very preterm infants is an important part of benchmarking studies, but mortality rates cannot be reliably compared unless the denominator is the same. Frequently reported denominators include all fetuses alive at admission to maternity unit, all live-born and stillborn infants, all live-born infants and all infants admitted to neonatal intensive care. Ideally, comparative studies on mortality should include all fetuses at risk or all fetuses alive at presentation.

2.3 Severe neonatal morbidities in very preterm infants

Very preterm infants are frequently diagnosed with severe morbidities, many of which are specific for preterm infants. These morbidities are often used as endpoints in studies on very preterm infants, and their prevalence increases with decreasing gestational age. Respiratory distress syndrome, RDS, is commonly diagnosed in very preterm infants within hours after birth, and is due to a relative lack of pulmonary surfactant in the neonatal lung. This causes the lung alveoli to remain unaerated after delivery or collapse, and is clinically manifested by signs of respiratory distress, such as increased work of breathing, grunting, respiratory acidosis and need for respiratory support and supplemental oxygen. Radiographic findings on chest x-ray imaging usually include opacity of the lungs and ground-glass appearance. RDS is treated with exogenous surfactant and respiratory support such as nasal continuous positive airway pressure or mechanical ventilation (Subramaniam et al., 2016). Bronchopulmonary dysplasia, BPD, is characterised by inflammation and abnormal development of the immature neonatal lung (Jobe, 2011; Bancalari & Jain, 2018). There are several forms of diagnostic criteria for BPD, but commonly used definitions include prolonged need for respiratory support exceeding the first four weeks of life or up to 36 weeks of corrected

gestational age, depending on the definition. Necrotising enterocolitis, NEC, is one of the most devastating morbidities in very preterm infants, and is characterised by inflammation within the bowel wall, manifested clinically by signs such as abdominal distension, feeding intolerance and intestinal pneumatosis (Battersby et al., 2018). The mortality rate in preterm infants with NEC is as high as 30%. Retinopathy of prematurity, ROP, is commonly associated with toxic effects induced by excess supplementary oxygen on the developing retina, and is diagnosed by ophthalmological examination (Hellström et al., 2013).

The morbidities of particular interest in this thesis are intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). IVH usually originates from haemorrhage in the immature germinal matrix adjacent to the cerebral ventricles, and commonly presents during the first week of life (Papile et al., 1978). IVH is normally detected by using cranial ultrasound scanning, and is categorised into four grades based on severity. In grade I, the haemorrhage is restricted to the germinal matrix, in grade II it extends into the ventricles, and in grade III the haemorrhage is accompanied by ventricular enlargement. Grade 4 is the most severe, and denotes haemorrhage and/or infarction also in the cerebral parenchyma. The grade of IVH severity is related to later outcomes, and very preterm infants diagnosed with grade 3 of 4 IVH, commonly referred to as severe IVH, have up to 60% risk of developing unfavourable neurological outcomes later in life such as motor impairment, cognitive impairment, hearing impairment or visual impairment (Mukerji et al., 2015). IVH can develop into posthaemorrhagic hydrocephalus, which is characterised by disrupted flow of cerebrospinal fluid and subsequent dilatation of the ventricles. The underlying mechanism is thought to be induced by mechanical obstruction or indirect inflammatory responses induced by blood clots in the ventricles (Klebe et al., 2019). PVL is usually associated with hyperventilation, hypoxic/ischemic insult to the brain or inflammatory insults such as chorioamnionitis or neonatal sepsis (Khwaja & Volpe, 2008). PVL is usually diagnosed after the first month of life using either cranial ultrasound or magnetic resonance imaging, and can be seen as cystic lesions or porencephalic cysts in the white brain matter or as diffuse scarring adjacent to the ventricles. PVL is associated with poor neurodevelopmental outcomes such as cognitive impairment and motor impairment, including cerebral palsy (Volpe, 2009). Severe IVH, PVL, posthaemorrhagic hydrocephalus and porencephalic cysts are used together to denote “severe brain injury” in Original Publication III in this thesis.

2.4 Centralisation of very preterm deliveries

2.4.1 The organisational framework of centralisation

Centralisation of very preterm deliveries entails selectively delivering very preterm infants in hospitals with obstetric and neonatal units providing the highest level of care. Units are usually classified based on the level of expertise, the availability of resources and the care they are expected to deliver, and the classification varies depending on the setting. The most widely used classification in international literature is the American Academy of Pediatrics classification, in which neonatal units are classified into four groups (AAP, 2012). Level 1 units are expected to provide basic care for low-risk infants, have capabilities to provide resuscitation and postnatal care for term (37 to 42 gestational weeks) and late preterm (35 to 37 gestational weeks) infants, and provide continued care for infants transferred back from higher-level units. In addition to level 1 requirements, level 2 units are expected to care for infants born at or after 32 gestational weeks, or with a birth weight of 1500 grams or more, and infants who are moderately ill. Level 2 units are also expected to provide special treatments such as short-term mechanical ventilation, and have 24-hour access to laboratory and radiology services. In addition to level 2 requirements, level 3 units are expected to be able to care for all infants born before 32 gestational weeks or with a birth weight below 1500 grams, and any very ill infants of any gestational age. They are also expected to have staff available with expertise in neonatal intensive care, as well as a wide range of paediatric subspecialists and paediatric surgeons for consulting. Level 3 units should also provide a full range of advanced life support, including a full range of on-going mechanical ventilation, and have capability to perform major neonatal surgery on site. In addition to level 3 requirements, level 4 units should have the capability to perform surgical repair of e.g. complex cardiac anomalies requiring cardiopulmonary bypass.

2.4.1.1 Organisation of neonatal care in the United Kingdom

In the United Kingdom (UK), the classification of neonatal units differs from that of the AAP (NHS Clinical Reference Group). Neonatal units are divided into three groups: Special Care Baby Units (SCBU), Local Neonatal Units (LNU) and Neonatal Intensive Care Units (NICU). Based on this national definition, SCBU are expected to care for newborn infants with a gestational age of 32 weeks or more, and with an anticipated birth weight of 1000 grams or more. SCBU are not expected to provide neonatal intensive care apart from initial care prior to transfer. LNU are expected to care for singleton infants born at 27 gestational weeks or

more with an anticipated birth weight of 800 grams or more, and for twins and higher order multiples born at 28 gestational weeks or more. LNU provide non-invasive respiratory support, but generally only short periods of mechanical ventilation. If prolonged intensive care is anticipated, the infant is transferred to the regional NICU. NICUs are expected to care for infants of all gestational ages, including infants born before 27 gestational weeks and at less than 800 grams, and infants of any gestational age requiring prolonged intensive care.

2.4.1.2 Organisation of neonatal care in Finland

In Finland, neonatal units follow the AAP classification. There are 23 delivery hospitals in the country, all of which are associated with neonatal units. There are five level 3 university hospitals, which serve as perinatal centres, 17 level 2 units and one level 1 unit in the country. The country is divided into five areas according to the provision of specialised health care, with one level 3 hospital and three or four level 2 hospitals per area. Hospitals cater for the basic needs, such as term birth, of their respective populations within their catchment areas, but for situations such as very preterm birth, the care is centralised to the level 3 hospital in each area, complying to national recommendations (Sosiaali- ja terveysministeriö, 2010; Current Care Guidelines, 2018). The national recommendations state that infants born before 32 gestational weeks or with an expected birth weight of <1500 grams should be delivered in level 3 hospital, but no specific guidance is offered for the practical arrangement of antenatal transfers.

2.4.1.3 Organisation of neonatal care in the USA

In the USA, the Committee on Perinatal Health together with the March of Dimes foundation issued the *Toward Improved Outcomes of Pregnancy* recommendation, which stated that very preterm deliveries, that is, deliveries of infants weighing less than 1500 grams or born before 32 completed weeks of gestation, should take place in regional perinatal centres with associated level 3 NICUs (Ryan Jr, 1975; March of Dimes, 1976). The recommendation was close to current centralisation strategies worldwide, with one or few level 3 perinatal centres providing the highest level of care, and several level 2 and level 1 units working in close collaboration to provide adequate care for all newborn infants within a certain region. Level 2 and level 1 units were expected to refer any very preterm infants to one of the regional level 3 perinatal centres. They also recommended 24-hour consultant service and neonatal transfer teams to be provided by the perinatal centres. There are, however, wide variations in centralisation of very preterm deliveries between states and regions (Haberland et

al., 2006; Binder et al., 2011) and the adoption of the AAP recommendations for designating levels of neonatal care is not universal (Bronstein et al., 2011; Kroelinger et al., 2018).

2.4.2 Studies supporting centralisation

The benefit of centralising very preterm deliveries to level 3 hospitals has been confirmed in observational studies also after therapies such as exogenous surfactant and antenatal corticosteroids were established as routine neonatal care (Table 1). The outcome in the listed studies was neonatal or infant mortality in live-born infants. Cifuentes and colleagues studied birth certificates and discharge abstracts of over 16,000 singleton infants born with a birth weight <2000 grams in the state of California in 1992 and 1993 (Cifuentes et al., 2002). They found increased odds of mortality among infants born in lower level hospitals compared to infants born in hospitals with regional NICUs, with odds ratios (OR) ranging from 2.38 in hospitals with no NICU to 1.11 in hospitals with small community NICUs. Johansson and colleagues studied over 2,000 infants born at <32 gestational weeks in 1992 to 1998 in a population-based study in Sweden (Johansson et al., 2004). They found that birth in level 2 hospitals was associated with a two-fold mortality compared to infants born in level 3 hospitals among infants born at 24 to 27 gestational weeks, but no significantly increased mortality among infants born at >27 gestational weeks. In the Cincinnati region in the USA, Warner and colleagues studied 848 infants born in 1996 to 1997 with birth weights from 500 to 1499 grams (Warner et al., 2004). They found that infants born in level 2 hospitals had both increased mortality (OR 1.87) and mortality or severe morbidity (OR 2.64), compared to infants born in level 3 hospitals. In Finland, Rautava and colleagues studied 2,291 very preterm and very low birth weight infants born in 2000 to 2003 (Rautava et al., 2007). They found a two-fold increased mortality among infants born in level 2 hospitals compared to infants born in level 3 hospitals. A systematic review by Lasswell and colleagues found that there was a significant increase in mortality related to birth in level 2 hospitals among both very preterm (OR 1.55) and very low birth weight (OR 1.62) infants, when compared to infants born in level 3 hospitals (Lasswell et al., 2010).

Table 1. Overview of studies supporting centralisation of very preterm and very low birth weight deliveries.

Study	Setting	Population	Exposure	Reference	Outcome	Main findings
Cifuentes et al. 2002	Statewide study, California, USA	16,732 infants with birth weight <2000g	Birth in level 1/2 hospitals	Birth in level 3 hospitals	Infant mortality*	OR 1.11 to 2.38
Johansson et al. 2004	National study, Sweden	2,253 VPT infants	Birth in level 1/2 hospitals	Birth in level 3 hospitals	Infant mortality	OR 2.00**
Warner et al. 2004	Regional study, Cincinnati, USA	848 VLBW infants	Birth in level 1/2 hospitals	Birth in level 3 hospitals	Infant mortality*	OR 1.87
Rautava et al. 2007	National study, Finland	2,291 VPT and VLBW infants	Birth in level 2 hospitals	Birth in level 3 hospitals	Infant mortality	OR 2.1
Lasswell et al. 2010	Systematic review	41 studies including 104,944 VLBW infants (37 studies) and 9,300 VPT infants (4 studies)	Birth in level 1/2 hospitals	Birth in level 3 hospitals	Neonatal or infant mortality***	OR 1.62 (VLBW); OR 1.55 (VPT)

VPT, very preterm; VLBW, very low birth weight; OR, odds ratio
*Mortality up to one year if continuously hospitalized
**Infants born at 24-27 gestational weeks
***Depending on the mortality outcome used in the included studies

Subsequent studies have confirmed these findings, and further associated favourable outcomes with high numbers of very preterm and very low birth weight admissions. In a state-wide study from California that included over 48,000 very low birth weight infants, Phibbs and colleagues found that the odds of infant mortality were significantly increased among infants born in level 1 or level 2 hospitals (OR 1.22 to 2.72) compared to infants born in level 3 hospitals (Phibbs et al., 2007). They also found that mortality was increased among infants born in level 3 hospitals with <100 very low birth weight admissions per year (OR 1.08 to 1.78) when compared to infants born in level 3 hospitals with >100 very low births weight admissions per year. Lorch and colleagues evaluated the effect of birth in high volume level 3 hospitals (level 3 hospitals with >50 very low birth weight admissions per year) in three states in the USA, and found that perinatal mortality was decreased in very low birth weight infants when delivered in high volume level 3 hospitals, compared to other hospitals (Jensen & Lorch, 2015). In the UK,

Marlow and colleagues found that extremely preterm (born between 22 and 27 gestational weeks) infants admitted to hospitals with high activity NICUs (>2,000 intensive care days annually) had lower odds of perinatal mortality (OR 0.68) compared to those born in hospitals with lower activity NICUs (Marlow et al., 2014).

Some studies have shown that mortality of very preterm infants is higher among infants born outside of office hours, such as nights, weekends and holidays. Jensen and Lorch showed that mortality was higher in very low birth weight infants delivered at night in all hospitals in unadjusted analyses, and that after adjusting for confounders, the risk of IVH was increased when compared to infants born during normal working days (Jensen & Lorch, 2017). Lehtonen and colleagues showed that infant mortality was increased among very preterm infants delivered outside of office hours in level 2 hospitals when compared to infants born in level 3 hospitals during office hours (Lehtonen et al., 2011). Interestingly, no mortality disadvantage was seen among infants born during office hours in level 2 hospitals, or among infants born outside office hours in level 3 hospitals. In Sweden, preterm infants who were born at night had higher neonatal and infant mortality rates compared to preterm infants born during daytime (Luo & Karlberg, 2001). Other studies, conducted in level 3 hospitals in Australia and USA, have shown no effect of time of birth on mortality in very preterm or very low birth weight infants, and suggested that staffing in these hospitals was adequate also during nights and weekends (Abdel-Latif et al., 2006; Bell et al., 2010). A study from a level 3 hospital in Canada, where neonatologists were present throughout the 24-hour day in one epoch, and only during daytime in the other, showed no difference in infant mortality among extremely preterm infants between the epochs (Lodha et al., 2017). The findings in these studies highlight the need for continuous expertise on site in the whole neonatal team when caring for very preterm and very low birth weight infants.

2.5 Identification of mothers in need of antenatal transfer

Identifying mothers that need antenatal transfer is crucial for the success of centralisation of very preterm deliveries. If the threshold for antenatal transfer is too low, level 3 hospitals might end up being overcrowded with women who do not deliver preterm. On the other hand, if the threshold is too high, mothers who need antenatal transfer might not be identified in time. This is a very delicate balance, and obstetricians frequently assess pregnant women with signs of possible spontaneous preterm delivery. The difficult task is to determine which women are likely to deliver very preterm, and arrange antenatal transfer to a level 3 hospital.

Several clinical signs are usually assessed, such as the frequency of contractions, ripening of the uterine cervix (softening, shortening, funnelling and dilatation of the cervix) and possible rupture of the fetal membranes (di Renzo et al., 2012; Boots et al., 2014). If the fetal membranes rupture before 37 gestational weeks and prior to the onset of labour, the term preterm premature rupture of membranes (PPROM) is used. Some adjunctive bedside tests can be used to aid in the prediction of preterm delivery (Honest et al., 2012; Conde-Agudelo & Romero, 2016). The problem with tests used for predicting preterm delivery is that most have poor positive predictive values, and are often of little use in identifying mothers needing antenatal transfer (NICE, 2015). Monitoring of fetal wellbeing during labour can be performed using cardiotocograhpy (CTG). CTG is recorded by placing an ultrasound transducer on the mother's abdomen, and shows the fetal heart rate in relation to uterine contractions (Shy et al., 1990; Alfirevic et al., 2017).

In addition to spontaneous preterm delivery, maternal conditions such as chorioamnionitis and pre-eclampsia might necessitate preterm delivery and hence be an indication for antenatal transfer. Chorioamnionitis is a bacterial infection involving the fetal membranes and placenta, which might have severe detrimental effects on both mother and fetus (Tita & Andrews, 2010). Pre-eclampsia is a condition that is characterised by signs such as elevated blood pressure, proteinuria, nausea, generalised oedema, hyperreflexia, and it can eventually lead to life-threatening convulsions (Lain & Roberts, 2002). Prompt identification and appropriate care of mothers presenting with these conditions has the potential to save both mother and fetus. Mothers developing pre-eclampsia or chorioamnionitis are usually under close surveillance, and thus can often be transferred to level 3 hospitals for delivery when necessary. Mothers delivering precipitously or developing acute conditions such as placental abruption often cannot be transferred, and are thus not necessarily eligible for antenatal transfer.

2.6 Neonatal transfer of very preterm infants

If the pregnant mother is not transferred to a level 3 hospital prior to delivery, the very preterm infant is delivered in a lower-level unit. In such cases, it is common for infants to be transferred to a level 3 unit shortly after birth.

2.6.1 Neonatal transfer versus antenatal transfer

Several studies in various settings have performed comparisons between very preterm infants transferred prior to delivery (antenatal transfer), infants transferred shortly after delivery (early postnatal transfer), infants born and cared for in low-

level hospitals and infants born and cared for in level 3 hospitals (Table 2). In a national study from the Netherlands, Kollee and colleagues analysed the associations of mortality and morbidity with antenatal transfer, early postnatal transfer and on-going care in low-level hospitals (Kollee et al., 1988). They associated antenatal transfer with decreased neonatal mortality when compared to infants born and cared for in low-level hospitals (OR 0.40). Shlossman and colleagues compared early postnatal transfer to antenatal transfer in a regional cohort of preterm infants, and found significantly increased neonatal mortality and morbidities among postnatally transferred infants (Shlossman et al., 1997). In California, Towers and colleagues showed that early postnatal transfer of very low birth weight infants after delivery in level 1 hospitals was associated with increased rates of grade 3 and 4 IVH (Towers et al., 2000). The largest study to date on early postnatal transfer was published in 2010, and was based on a nationwide sample from the USA, comprising over 67,000 very low birth weight infants (Mohamed & Aly, 2010). The findings indicated a significantly increased risk of both any IVH and severe IVH among postnatally transferred infants.

The causal impact of neonatal transfer on neonatal outcomes has, however, not been established because of the inherent difficulties in comparing cohorts of very preterm infants with marked differences in background factors such as gestational age, sex, exposure to antenatal corticosteroids and severity of illness. Infants who are born precipitously in lower-level hospitals are less likely to be exposed to antenatal steroids, and might have a higher risk of poor outcomes compared to peers exposed to antenatal corticosteroids and born in level 3 hospitals. Infants who are critically ill might be deemed unfit for postnatal transfer, and mothers with obstetrical complications tend to gravitate to level 3 hospitals. These factors, among others, make the analysis of any causal effects of postnatal transfer difficult.

Several studies have questioned the causality between neonatal transfer and poor outcomes such as mortality and intraventricular haemorrhage. In Belgium, Hauspy and colleagues studied a regional cohort of preterm infants born at 24 to 34 gestational weeks, and found that exposure to antenatal corticosteroids, infant sex, birth weight and maternal hypertension, but not early postnatal transfer, were significantly associated with neonatal mortality (Hauspy et al., 2001). A secondary analysis of infants participating in a multi-centre randomised controlled study on the effects of morphine analgesia in ventilated very preterm infants (the NEOPAIN trial) evaluated the relationship between early postnatal transfer and short-term outcomes (Palmer et al., 2005). These analyses showed that transferred infants were more likely than non-transferred infants to have IVH after adjusting for gestational age and infants' severity of illness, but after adjusting for antenatal corticosteroid exposure the difference was no longer

significant. Watson and colleagues studied a regional cohort of very low birth weight infants based on transfer status by 48 hours of age (Watson et al., 2013). Their findings were similar to those of Palmer et al. in showing that transferred infants did have an increased risk of IVH, but that the differences became statistically insignificant after multivariate adjusting. Factors that were significantly associated with IVH in their study were RDS, PDA, vaginal delivery, Apgar scores at 5 minutes of age and exposure to antenatal corticosteroids. Their conclusion was that early postnatal transfer is not an independent risk factor for IVH, and that the increased risk of IVH was attributed to the overall clinical status of the infant and other risk factors.

2.6.2 Postnatal transfer between level 3 hospitals

Studying the effects of postnatal transfer of very preterm infants is complicated because there is no ethically sound way to conduct a randomised controlled trial on the subject. In some settings, due to unfortunate closure or overcrowding of level 3 NICUs, scientists have been able to conduct small-scale studies on transfers between level 3 hospitals. Such studies have the potential to limit confounding caused by birth in facilities not designed to care for very preterm infants. In 1988, Bowman and colleagues published a study on 34 very preterm infants transferred between level 3 hospitals in Melbourne, Australia, and 111 non-transferred controls. Transfer was necessitated shortly after birth because of limited NICU capacity (Bowman et al., 1988). They found a significant increase in mortality among postnatally transferred infants compared to those that were not transferred. Harding and Morton published a similar study from Auckland, New Zealand, comparing 40 postnatally transferred preterm infants to two matched non-transferred controls each (Harding & Morton, 1993). They found no difference in mortality, but significant disadvantage regarding IVH and neurodevelopmental outcome in postnatally transferred infants. The most recent study on postnatal transfers between level 3 hospitals was conducted by Longhini and colleagues, and it compared 75 postnatally transferred preterm infants to 75 non-transferred controls (Longhini et al., 2015). They found no differences in any of the studied outcomes, including mortality and IVH. The problems inherent in these three studies are the limited sample sizes, and that two studies were performed in an era when therapies such as antenatal corticosteroids for fetal lung maturation and exogenous surfactant were not routine neonatal care. The study by Longhini et al was elegantly performed, but suffered a weakness in low numbers of the smallest infants; only half of the infants were very low birth weight, and only eleven were extremely preterm.

Table 2. Studies on antenatal and neonatal transfer

Study and year	Setting	Population	Exposures	Reference	Outcome	Main findings
Kollee et al. 1988	National study, the Netherlands	365 VPT and VLBW infants	Antenatal transfer to level 3 hospitals	Infants born and cared for in low-level hospitals	Mortality*	OR 0.40
Bowman et al. 1988	Level 3 hospital in Melbourne, Australia	143 VPT infants	Postnatal transfer between level 3 hospitals	Infants born in level 3 hospitals	Mortality**	OR 5.2
Harding & Morton 1993	Level 3 hospital in Auckland, New Zealand	40 transferred infants; 80 inborn controls	Postnatal transfer between level 3 hospitals	Infants born in level 3 hospitals	IVH (any grade)	OR 1.74
Shlossman et al. 1997	Level 3 hospital in Delaware, USA	150 VPT infants***	Postnatal transfer	Antenatal transfer	Mortality**	Effect size 15%
Towers et al. 2000	Level 3 hospital in California, USA	329 VLBW infants with birth weight 500-1200 g	Postnatal transfer from level 1 hospitals	Infants born in level 3 hospitals	Severe IVH	OR 2.8
Mohamed & Aly 2010	National study, USA	67,596 VLBW infants	Postnatal transfer	Infants not transferred	IVH (any grade)	OR 1.75

VPT, very preterm; VLBW, very low birth weight; OR, odds ratio; IVH, intraventricular haemorrhage
*Neonatal and pre-discharge mortality
**Mortality not specified
***Gestational age 24 to 34 weeks

2.6.3 Potential mechanisms of transfer-induced brain injury

Risk factors for IVH in preterm infants include factors such as early sepsis, hyper- and hypoventilation and hemodynamic instability, while exposure to antenatal corticosteroids have been shown to decrease the risk (Linder et al., 2003). The risk for developing IVH, as most other complications of prematurity, is inversely related to gestational age. The immature germinal matrix is susceptible to haemorrhage especially during the first few days of life, and IVH is typically diagnosed by cranial ultrasound scanning within the first week of life (Papile et al., 1978).

Because early postnatal transfer typically takes place during these first days of high vulnerability, and has been associated with IVH in epidemiological studies, it would seem plausible that transfer has an independent role contributing to the increased risk of brain injury. A causal relationship has not, however, been established. A recent study evaluated the magnitude of vibration preterm infants and preterm-like manikins were exposed to during ambulance transfer (Blaxter et al., 2017). They found that vibration exposure exceeded 20% of the recommended values applied to adults in all twelve transferred preterm infants, and up to 70% in two infants. They also noted that vibration caused more potentially damaging insult than acceleration or deceleration. Co-existing factors that have been suggested to influence the previously noted increased risk of brain injuries in transferred very preterm infants include lack of exposure to antenatal corticosteroids, sicker and smaller infants being transferred and vaginal delivery (Watson et al., 2013). In order to determine the potential causal effect of early postnatal transfer on brain injuries, the potential confounding effect of such factors should be addressed.

2.7 International benchmarking initiatives

Several national and international collaboration networks have been established to allow for comparison and benchmarking of neonatal outcomes. These networks vary in size, aims, and methods of recruitment. Some are established for relatively short periods of time for a selected research goal, while others are designed as continuous benchmarking initiatives.

2.7.1 The Vermont Oxford Network

The Vermont Oxford Network (VON) is a non-profit benchmarking initiative that has been collecting data from neonatal units in the USA and worldwide since 1989 (Horbar et al., 2010; Profit & Soll, 2015). The network has grown from the initial handful of units to over 1200 units currently, and the VON database has served as a platform for numerous scientific publications. The VON is open for any neonatal unit to join for an annual fee, and the VON very low birth weight database includes data for very low birth weight or very preterm live born infants who are admitted to participating units within 28 days from birth. The units included in VON are mostly from the US, but there are several other countries in which most or all level 3 units belong to VON, such as Italy and Finland. The benchmarking data provided by VON can be evaluated at each participating neonatal unit by comparing local data to the aggregated data of all other neonatal units, and different outcomes can be evaluated separately; thus individual neonatal units can identify potential areas that need improvement.

2.7.2 European collaboratives

Several European neonatal research collaboratives have been established over the past few decades. The Euro-Peristat collaboration currently includes 31 European countries. Studies from this collaboration have evaluated important epidemiological factors including the effect of terminations of pregnancy and stillbirth on mortality rates, and provided vital benchmarking data (Zeitlin et al., 2016; Blondel et al., 2018; Delnord et al., 2018; Smith et al., 2018). The collaboration has published European health reports in 2008, 2013 and 2018 (EURO-PERISTAT, 2018).

The Models of Organising Access to Intensive Care for very preterm births (MOSAIC) project started out as a detailed comparison of perinatal and neonatal care pathways for very preterm infants in 10 regions in Europe, and included all stillborn and live born very preterm infants in the participating regions (Mosaic Research Group, 2019). Publications from the MOSAIC group include topics such as characteristics of obstetric and neonatal units (van Reempts et al., 2007; Blondel et al., 2009), differences in mortality and other short-term outcomes (Zeitlin et al., 2008; Draper et al., 2009; Field et al., 2009) and differences in rates of breastfeeding and BPD (Bonet et al., 2011; Gortner et al., 2011). This multinational collaboration subsequently led to the formation of the Effective Perinatal Intensive Care in Europe (EPICE) cohort study, which included stillborn and live born very preterm infants from 19 regions in 11 European countries. Publications from the EPICE cohort have addressed topics such as the impact of evidence based practices and perinatal care strategies on outcomes (Wilson et al., 2016; Zeitlin et al., 2016; Edstedt Bonamy et al., 2017; Norman et al., 2017; Nuytten et al., 2017) and variability in hospital stay and severe morbidities in very preterm infants (Maier et al., 2018; Edstedt Bonamy et al., 2019). The MOSAIC and EPICE cohorts relied on prospective data collection, while the Euro-Peristat project utilises routinely collected data from national registers. The children in the EPICE cohort are currently being evaluated for outcomes at five years of age.

2.7.3 The International Network for Evaluating Outcomes in Neonates

Many countries and regions have established national neonatal networks in order to benchmark unit performance and collect databases for research. Over the past decade, some of these networks have started to expand benchmarking across national borders. The International Network for Evaluating Outcomes in Neonates (iNeo) is one of these, and has proven to be a highly functional research platform for neonatal epidemiological studies (Shah et al., 2014). The iNeo currently includes 10 national neonatal or regional networks, spanning 11 countries: Australia and New Zealand

Neonatal Network, Canadian Neonatal Network, Finnish Medical Birth Register, Israel Neonatal Network, Neonatal Research Network Japan, Spanish Neonatal Network, Swedish Neonatal Quality Register, Swiss Neonatal Network, Tuscan Neonatal Network and the United Kingdom Neonatal Collaborative (Figure 1). The coverage of these networks compared to national birth statistics range from approximately 60% to a full 100% of live born very preterm infants. The inclusion criteria in the participating networks vary from all stillborn and live born infants in some networks, to only live born infants admitted to neonatal care in others, hence comparisons that include all networks are limited to live born infants admitted to neonatal care.

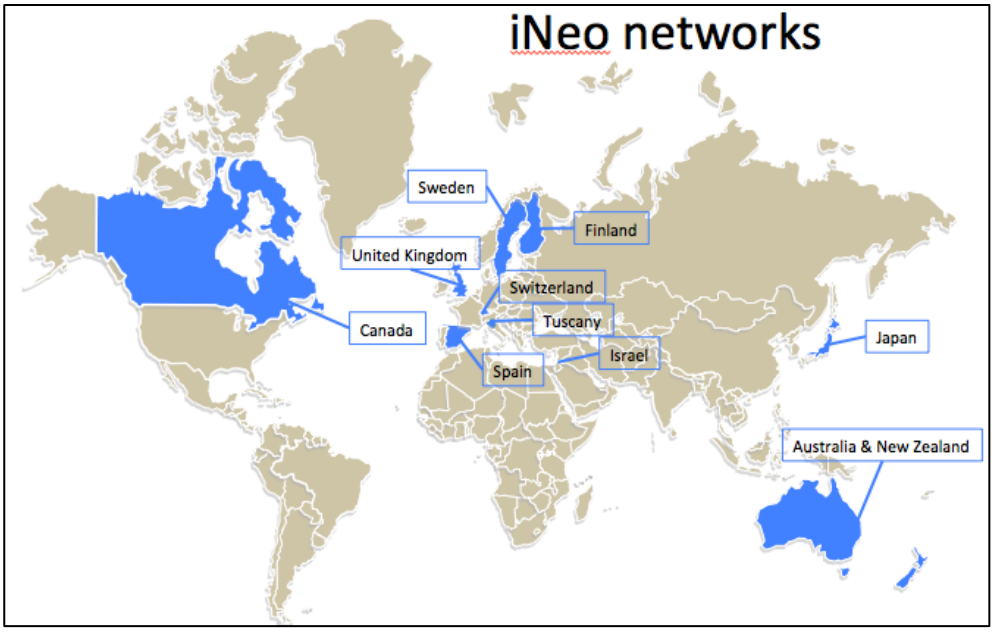

Figure 1. Member networks of the iNeo.

Neonatal networks participating in the iNeo collaboration are committed to provide a standard common dataset for very preterm infants included in their respective network databases. Each variable in the dataset is defined, and every effort is made to harmonise the data to be comparable between networks. The common iNeo dataset comprises variables in the following domains: demographic and birth details (e.g. gestational age, sex, birth weight, birth place, multiplicity and mode of delivery), antenatal details (e.g. antenatal corticosteroids, maternal diseases, rupture of membranes), admission and neonatal course details (e.g. resuscitation, surfactant, admission temperature, severity of illness score), diagnoses (e.g. RDS,

NEC, ROP, BPD, IVH, PVL) and discharge details (e.g. age at discharge or death, transfer, supplemental oxygen at discharge).

The iNeo collaboration has so far produced 15 publications, including a comparison of short-term neonatal outcomes (Shah et al., 2016), a comparison of country-specific birth weight references and their relation to common birth weight references and to neonatal outcomes (Martin et al., 2016), a comparison of differences in the management and identification of ROP (Darlow et al., 2017), a comparison of ventilation strategies in very preterm infants (Beltempo et al., 2018), a comparison of end-of-life strategies in the member networks (Helenius et al., 2019) and a comparison of preventive measures for severe NEC between the member networks (Adams et al., 2019). The iNeo collaboration continuously produces new studies utilising the large multinational database of very preterm infants.

3 Aims

This thesis was an epidemiological study aiming to evaluate the effects and execution of different models of centralisation of care for very preterm infants, and to integrate anonymised neonatal data from the Finnish Medical Birth Register into an international research network to allow for benchmarking of neonatal care. The study had four specific aims, listed below.

1. To estimate the antenatal costs of centralisation of very preterm deliveries in Finland (Original publication I)
2. To survey Finnish obstetricians on indications, contraindications and possible problems related to antenatal transfer of mothers with threatened very preterm delivery to level 3 perinatal centres (Original publication II)
3. To evaluate the effects of birth in non-tertiary hospitals with and without early postnatal transfer in extremely preterm infants born in England (Original publication III)
4. To join the iNeo network (Figure 1) and compare survival of very preterm infants within the network (Original publication IV)

4 Materials and Methods

This thesis is based on four original publications (Original publications I-IV). Each publication is based on a different dataset, and the applied methods also differ between the publications. This chapter will give an overview of these materials and methods.

4.1 Original publication I

4.1.1 Setting

We acquired data on all children born in Finland during 2004 to 2006, irrespective of gestational age, and their mothers; data were obtained from the Medical Birth Register to identify all born children and their mothers, and from the Hospital Discharge Register to identify all hospitalisations of the mothers up to one year prior to delivery in order to catch all hospitalisations during pregnancy. The study was approved by the regional ethics committee of the Hospital District of Southwest Finland.

4.1.2 Data management

Infant-mother dyads were cross-linked to the mothers' hospitalisations occurring up to one year prior to the delivery. Each pregnancy was analysed separately, and the mothers had up to three pregnancies within the study period. Only hospitalisations coded under obstetrics and gynaecology were considered. Gestational age at the beginning and end of each hospitalisation was calculated based on the admission date, delivery date, and gestational age at delivery. The mothers' place of residence was determined by zip codes included in the registers. Mothers were divided into those living within level 3 hospital catchment areas and those living outside those areas. Mothers living outside level 3 hospital areas normally deliver in a level 1 or level 2 hospital, and were thus candidates for centralisation.

Antenatal hospitalisations occurring for obstetrical reasons were further limited to those occurring between 22 and 32 weeks of gestation. Any hospitalisation in level 3 hospitals within this gestational age range among mothers residing outside level 3 hospital catchment areas were expected to be due to centralisation. The antenatal length of stay was determined by counting all inpatient care days occurring before the day of delivery; the day of delivery was regarded as day 0, which meant that only complete calendar days before the day of delivery were counted.

4.1.3 Outcomes and statistical analyses

The studied outcome was antenatal length of stay caused by centralisation of very preterm deliveries. Differences between groups were assessed using Mann-Whitney U-test, independent samples t test or χ^2 test, as appropriate. P-values <0.05 were considered significant. Data management and statistical operations were performed using SPSS version 22.0 statistical software (IBM Corporation, Armonk, NY).

4.2 Original publication II

This study was conducted as an internet-based nationwide survey on obstetrical referral practices in Finland in cases of threatening very preterm delivery (Appendix I). The survey was distributed to obstetricians in all level 2 hospitals in Finland. The geographical distribution and approximate number of annual deliveries in Finnish delivery hospitals is shown in Figure 1 in Original publication II. The data was collected utilising the REDCap program. The survey included 45 questions in the following domains: indications for antenatal transfer, contraindications for antenatal transfer, general questions on practical issues related to arranging transfers, and five fictive patient scenarios. Specific clinical signs and conditions included in the survey were frequency of uterine contractions, cervical length, cervical funnelling, cervical dilatation, pre-eclampsia, PPROM and vaginal bleeding. The results were presented in a descriptive manner.

4.3 Original publication III

4.3.1 Setting

This study was conducted in collaboration with the Neonatal Data Analysis Unit (NDAU) at Imperial College London, which maintains the National Neonatal Research Database (NNRD) in the UK. The database contains data on all neonatal

admissions to NHS neonatal units. The NNRD has full coverage of NHS neonatal units in England from 2011 onwards, and very high coverage from 2008 to 2011. The coverage of NHS units in Scotland and Wales is not complete, and there are high numbers of missing infants due to transfers to neonatal units not participating in the NNRD. Based on these coverage issues we chose to limit the sample to extremely preterm infants born at less than 28 gestational weeks who were admitted to NHS units in England between January 1st 2008 and December 31st 2015. The classification and requirements of UK neonatal units is explained in section 2.1.2 above; for the purpose of this thesis, UK neonatal units are referred to as level 2 (Local Neonatal Units, LNU) and level 3 (Neonatal Intensive Care Units, NICU). It should be noted that UK neonatal level 2 units are equipped and expected to care for smaller and sicker infants than level 2 units in the AAP classification.

4.3.2 Data management

We excluded infants who had missing data on gestational age, birth weight or sex because these variables are essential for the analysis. We also excluded infants with severe congenital malformations, trisomy 13, 18 or 21, and infants who were transferred for surgical or cardiac care, because such infants are more likely to have a different transfer pattern and a higher risk of adverse outcomes than otherwise healthy extremely preterm infants. We also excluded infants with improbable birth weight (z-score less than -4 or above 4 compared to national UK birth weight charts). Stillborn infants and infants who die in the delivery room are not routinely captured in the NNRD and were hence also excluded from the analyses.

The infants were divided into groups based on their hospital of birth and their transfer status at 48 hours: the control group, who were born in level 3 hospitals and not transferred; the upward transfer group, who were born in level 2 hospitals and transferred to level 3 hospitals within 48 hours from birth; the non-tertiary care group, who were born in level 2 hospitals and not transferred within 48 hours from birth; and the horizontal transfer group, who were born in level 3 hospitals and transferred to another level 3 hospital within 48 hours from birth. Horizontal transfers in the UK are usually carried out because of lack of capacity in level 3 hospitals. The horizontal transfer group was much smaller than the other three, and was analysed separately.

4.3.3 Statistical analyses: propensity score matching

Propensity score matching was performed before assessing outcomes. The infants in the three largest groups (controls, upward transfer and non-tertiary care) were

matched using propensity score matching and the potential outcomes framework for multiple treatments, namely being assigned to control, upward transfer of non-tertiary care. This included assigning a propensity for each infant for receiving any of the studied treatments, and was achieved by applying a logistic regression model using all available covariates. The model was then supplemented by adding interactions of covariates one at a time, until a model with superior balance was achieved. Extreme propensities were trimmed to minimise residual confounding. Infants were matched on the logit (log-odds) of the propensity score, with a caliper width of 0.1. The caliper was selected based on a sensitivity analysis using different caliper widths (0.05, 0.1, 0.15 and 0.2), where the caliper width of 0.1 yielded the best overall match. In addition to the propensity score matching, matched infants were also matched on what we regarded as principal covariates, namely gestational age, sex and receipt of antenatal steroids. Infants in the control group, upward transfer group and non-tertiary care group were matched based on propensity score and principal covariates 1:1:1, thus forming triplets, each triplet containing one infant from the control group, one infant from the upward transfer group and one infant from the non-tertiary care group. The success of the matching process was assessed by analysing standardised differences (SD) for the covariates across all three matched groups. Data were managed with SPSS version 24.0 (IBM Corporation, Armonk, NY) and statistical analyses conducted using R version 3.2.5.

4.3.4 Outcomes

The three main treatment groups were compared with regards to outcomes, which were death before discharge, severe brain injury (defined as a diagnosis of any of the following: grade 3 or 4 IVH, PVL, or posthaemorrhagic hydrocephalus) and survival without severe brain injury. The outcome rates were compared using the two-tailed t-test. Infants in the horizontal transfer group were separately matched to control infants in a similar manner.

4.4 Original publication IV

4.4.1 Setting

The first prerequisite for this study was to acquire permission from the Finnish National Institute for Health and Welfare (THL) to merge anonymous patient level data from the Medical Birth Register with the iNeo database managed in Toronto, Canada, which contained similar data from all other iNeo networks. The Finnish data contained all very preterm infants born in Finland from 2007 to 2013

(n=1728), and was successfully joined with the iNeo database in early 2016. This included ethical approval from the regional ethics committee at the Hospital District of Southwest Finland. In addition, all participating networks hold ethical approvals from their respective ethics committees. The regional ethics committee at Mount Sinai Hospital in Toronto, Canada, holds ethical approval for the whole iNeo collaboration.

4.4.2 Data management

The most important methodological challenge with this study was to account for differences in study populations. The two main reasons for these differences were incomplete population coverage and differing inclusion criteria in networks. We chose to include infants born before 30+0 weeks of gestation and weighing less than 1500 grams because some iNeo networks include only infants that are born before 32 gestational weeks *and* weigh less than 1500 grams at birth, while others include infants who are born before 32 gestational weeks *or* weigh less than 1500 grams at birth. We set the lower limit of inclusion to 24+0 gestational weeks, because in some networks infants born before 24 gestational weeks are actively resuscitated, while in others they are not; for infants born at 24 gestational weeks onwards almost all units in all networks provide active care. In some networks data are separately collected for infants who are admitted to neonatal care after 36 weeks of corrected age; such infants were also excluded. We also excluded infants who were stillborn or died in the delivery room, because not all networks collected data on stillbirths, and some networks collected data only on infants who were admitted to neonatal intensive care. Infants with severe congenital malformations were excluded due to differences between networks in pregnancy termination practices.

4.4.3 Outcomes and statistical analyses

The primary outcome was survival to discharge among infants born alive and admitted to neonatal care, and the secondary outcome was age at death among nonsurvivors. The standardised ratios of survival in each network were calculated using the indirect standardisation approach, and compared to the pooled estimate of survival in the whole population. The statistical analysis included accounting for confounders through adjusting for gestational age, birth weight z score, multiple births and sex. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc, Cary, NC) or R version 2.2.

5 Results

5.1 The cost of centralisation of very preterm deliveries (Original publication I)

5.1.1 Overview of the study population

The study population included 171,997 pregnancies and 153,703 mothers over three years. Mothers had up to three pregnancies during the studied time interval; all were included. Term delivery (at or after 37 completed gestational weeks) occurred in 94,5% (162,470) of the pregnancies. A total of 5,2% (8,898) of pregnancies resulted in preterm delivery (before 37+0 completed gestational weeks); 4,3% (7,458) were late preterm (32+0 to 36+6 completed gestational weeks) and 0,8% (1,440) were very preterm (before 32 gestational weeks). In 0,4% (629) of pregnancies the gestational age was unknown.

When cross-linking the Medical Birth Register and Hospital Discharge Register we found that of the 153,703 mothers identified in the Medical Birth Register, 153,208 had hospitalisations registered in the Hospital Discharge Register, meaning that for 495 mothers (0,3%) the hospitalisation records were missing; these mothers were excluded from the analysis. Mothers were excluded also if the gestational age at delivery, maternal admission or discharge dates, hospital identification code or birth date of the infant were missing. After exclusions, a total of 170,648 pregnancies and 152,549 mothers remained eligible for analysis.

5.1.2 Deliveries per hospital level

Of very preterm deliveries, 79% occurred in level 3 hospitals (85% of live born very preterm infants), compared to 49% of late preterm deliveries and 34% of term deliveries. In 69,987 pregnancies (41%) the mothers resided within level 3 hospital catchment areas.

5.1.3 Antenatal hospitalisations

The total number of hospitalisation days in all mothers between gestational weeks 22 and 32 was 54,464 days, of which 33,633 (62%) were in level 3 hospitals. Antenatal care days per mother ranged from 1 to 62 in mothers who delivered <32 gestational weeks, from 1 to 77 in mothers who delivered between 32 and 36+6 gestational weeks and from 1 to 90 in mothers who delivered at term. The distribution of the care days in different hospitals according to gestational age is shown in Table 3.

Table 3. Antenatal care days in Finnish hospitals between gestational weeks 22 and 32 in mothers delivering in 2004 to 2006. From Original publication I.

Gestational age group	Hospital level	Pregnancies with hospitalisations n(%)	Antenatal LOS, median (IQR) [range]	Total antenatal care days
<32 weeks N=1,422	Level 1&2 Level 3	521 (37) 1,101 (77)	2 (1-5) [1-39] 4 (2-10) [1-62]	2,174 8,730
32+0 to 36+6 weeks N=7,420	Level 1&2 Level 3	692 (9) 892 (12)	4 (2-9) [1-82] 7 (3-17) [1-77]	5,874 10,996
≥37 weeks N=161,806	Level 1&2 Level 3	3,609 (2) 3,274 (2)	2 (2-3) [1-88] 2 (2-4) [1-90]	12,783 13,907
All N=170,648	Level 1&2 Level 3	4,822 (3) 5,267 (3)	2 (2-4) [1-88] 3 (2-7) [1-90]	20,831 33,633

We looked closer at the 33,633 antenatal care days that occurred in level 3 hospitals to determine the amount of antenatal care received by mothers residing outside level 3 hospital catchment areas. The day of delivery was not counted as an antenatal care day, which means that even if the mother did not receive antenatal care in a level 3 hospital, the delivery might have taken place in a level 3 hospital on the day of admission. Among mothers who delivered very preterm, there was no statistically significant difference in the antenatal length of stay between those mothers who resided in the level 3 catchment area and those who resided outside (and hence were subjected to centralisation due to threatened very preterm delivery); the median antenatal length of stay was 4 days in both groups (p=0.81). Among mothers who delivered late preterm there was a statistically significant difference; centralised mothers had a median of 9 antenatal care days in level 3 hospitals, while those who resided in the level 3 hospital catchment area had a median of 7 antenatal care days (p=0.001). Overall, only in 1,4% of pregnancies in mothers residing outside level 3 catchment areas were hospitalised in level 3 hospitals between gestational weeks 22 and 32, compared to 5,5% of pregnancies

among mothers residing inside level 3 catchment areas. A detailed description of these care days is shown in Table 4.

Table 4. Antenatal care days in Finnish level 3 hospitals between 22 and 32 gestational weeks during 2004 to 2006. Modified from Original publication I.

Gestational age group	Pregnancies	Pregnancies with hospitalisations*	Antenatal LOS, median (IQR) [range]	*p*	Total antenatal care days
<32 weeks	Non-level 3 catchment ** n=833	532 (64)	4 (2-10) [1-62]	0.81	4,412
	Level 3 catchment *** n=595	569 (96)	2 (2-9) [1-54]		4,318
32+0 to 36+6 weeks	Non-level 3 catchment n=4,332	292 (7)	9 (4-19) [1-69]	0.001	4,085
	Level 3 catchment n=3,111	600 (19)	7 (3-15) [1-77]		6,911
≥37 weeks	Non-level 3 catchment n=95,731	584 (1)	3 (2-6) [1-90]	<0.001	3,857
	Level 3 catchment n=66,281	2,690 (4)	2 (2-4) [1-70]		10,050
Total	Non-level 3 catchment n=100,896	1,408 (1)	4 (2-10) [1-90]	<0.001	12,354
	Level 3 catchment n=69,987	3,859 (6)	3 (2-5) [1-77]		21,279

*Percentage of all pregnancies in the specified group
**Mothers residing outside the level 3 hospital catchment area
***Mothers residing inside the level 3 hospital catchment area

We further analysed the pregnancies of mothers who delivered very preterm and resided outside level 3 hospital catchment areas. As shown in Table 4, in 64% of these pregnancies the mother received antenatal care in a level 3 hospital between gestational weeks 22 and 32. The background variables of these pregnancies compared to those where the mother did not receive antenatal care in a level 3 hospital are presented in Table 5. The gestational age was higher, the birth weight was higher, the delivery occurred more frequently on admission day, and there were more stillbirths in pregnancies where the mother did not receive antenatal care in level 3 hospitals, compared to those that did. It should be noted that Table 5 does not list pregnancies according to actual place of delivery, but by where the antenatal care took place. However, the vast majority of pregnancies where

antenatal care was not given in a level 3 hospital resulted in delivery in a level 2 hospital.

Table 5. Comparison of 833 pregnancies resulting in very preterm delivery; mothers receiving antenatal care in level 3 hospitals versus mothers not receiving antenatal care in level 3 hospitals. Modified from Original publication I.

	Antenatal care in level 3 hospital n=532	No antenatal care in level 3 hospital n=301	*p*
Median gestational age	28+6	28+6	0.22
Live births only	29+1	30+3	<0.001
Delivery on admission day, %	22	42	<0.001
Live births only	20	43	<0.001
Mean birth weight, grams	1,153	1,200	0.163
Live births only	1,440	1,568	0.01
Mean maternal age, years	30,7	29,5	0.013
Multiple gestation, %	17	7	<0.001
Live births only	26	9	<0.001
Delivery by caesarean section, %	63	42	<0.001
Live births only	67	58	0.093
Stillbirth, %	6	32	<0.001
Gestational age 30-32 weeks, %	41	47	0.07
Live births only	42	62	<0.001

The total number of antenatal care days between gestational weeks 22 and 32 attributed to centralisation of very preterm deliveries was 12,354 over three years, amounting to 4,118 antenatal care days per year. To achieve this level of centralisation, 12 antenatal beds in level 3 hospitals were needed in the whole country with approximately 60,000 deliveries per year (12,354 divided by 365). The total number of antenatal care days in level 3 hospitals among all pregnancies was 33,633 days, which equates to a need for 31 antenatal beds in level 3 hospitals.

5.2 Obstetrical referral practices for threatening very preterm deliveries in Finland (Original publication II)

5.2.1 Overview of the study participation

All 16 level 2 delivery hospitals in Finland were invited to participate in the electronic survey on obstetrical referral practices for threatened very preterm

delivery. Invitations were sent personally to the obstetricians in charge of the gynaecology and obstetrics department at each level 2 hospital, and to the head of delivery wards where contact details were available. Invitations were sent via e-mail, and followed up by telephone if no reply was received. Representatives from 14 units agreed to fill in the questionnaire, and 12 (75%) provided a full set of replies. Non-replying hospital representatives were approached up to three times for missing replies; two did not respond to e-mail queries and hospital representatives could not be reached by telephone. Respondents were advised to fill in the questionnaire according to hospital protocol and/or general practice in the year 2017. The approached obstetricians were encouraged to invite the whole obstetrics staff to generate the survey replies, in order to get a comprehensive overview of the practices at each hospital.

5.2.2 Indications for referral to level 3 hospitals

The survey results regarding indications for antenatal transfer are shown in Table 1 in Original publication II. All hospitals indicated referring mothers from 23+0 gestational weeks onwards; two hospitals from 22+0 weeks onwards and seven hospitals from 22+5 weeks onwards. Five hospitals indicated that the lower gestational age limit is strictly adhered to, while the other seven reported negotiating borderline cases with staff at the level 3 hospital. The upper gestational age limit for referral was 31+6 weeks in ten hospitals, with two reporting upper limits of 33+6 and 34+6 weeks based on local agreements with the level 3 hospital.

All hospitals indicated that premature rupture of membranes at 23 to 28 gestational weeks and severe pre-eclampsia were indications for antenatal referral. The replies for other clinical signs and conditions were variable. Regarding uterine contractions, five hospitals considered a contraction interval of 10 to 15 minutes as an indication, while three hospitals did not regard contractions as an indication for referral, and three considered the presence of any contractions as a contraindication for referral. Cervical length of less than 20 mm was considered an indication for referral in five hospitals, and less than 25 mm in another two hospitals, but was not considered to be an indication for referral in four hospitals. Similar variability was noted for cervical funnelling and cervical dilatation. Eight hospitals would refer a mother with chorioamnionitis and normal CTG tracing, while the remaining four would refer the mother if the CTG was non-reassuring.

5.2.3 Contraindications for referral to level 3 hospitals

The survey results regarding contraindications for antenatal transfer are shown in Table 2 in Original publication II. Suspicion of placental abruption was considered

to be a contraindication for antenatal transfer in ten hospitals, and the remaining two indicated that the amount of haemorrhage, gestational weeks and measures of fetal wellbeing had a major influence on the decision. Vaginal bleeding of unknown origin was not considered a contraindication in any of the hospitals. Maternal sepsis was reported as contraindication in nine hospitals; in seven hospitals with normal CTG tracing, and in the two remaining hospitals if the CTG tracing was non-reassuring. Non-reassuring CTG alone was considered to be a contraindication in seven hospitals, and pathological CTG in the other five hospitals. Decreased fetal movements were considered to be a contraindication in two hospitals, in the remaining ten hospitals antenatal transfer would be undertaken.

Contractions occurring at less than five-minute intervals were considered to be contraindications for antenatal transfer in four hospitals. One hospital reported the presence of any contractions as contraindication, while five indicated that contractions are not a contraindication for antenatal transfer. One hospital did not provide an answer. Regarding the threshold for cervical dilatation as contraindication for antenatal transfer the replies ranged between 3-4 cm in two hospitals to 9-10 cm in two hospitals; one hospital indicated that cervical dilatation was not a contraindication.

5.2.4 Practical issues regarding the arranging of maternal transfer

Few hospitals reported difficulties in arranging in utero transfers. Eleven hospitals reported that antenatal transfer was unsuccessful in 0 to 10% of cases, and one hospital in 11 to 40% of cases. All reported durations of less than 2 hours from the decision to transfer until the ambulance was ready to leave the referring hospital with mother and midwife on board; six hospitals indicated durations of less than one hour. The most frequently reported reasons for unsuccessful transfers were imminent delivery in all twelve hospitals, acute condition of the mother in five hospitals and suspicion of acute fetal compromise in eight hospitals. Only one hospital out of twelve reported that occupancy in the admitting level 3 hospital was a potential reason for unsuccessful antenatal transfer.

Antenatal corticosteroids were routinely (91-100% of cases) initiated before transfer in eleven hospitals, and often (61-90% of cases) in one hospital. Ten hospitals reported routinely and two reported often starting antibiotics when indicated. Ten hospitals indicated starting a mother with contractions on atosiban routinely, one hospital reported sometimes (41-60%) starting atosiban and one quite rarely (11-40%). In mothers with pre-eclampsia, initiating magnesium sulphate prior to transfer occurred routinely in six hospitals, often in three hospitals and rarely or

never (0 to 10%) in three hospitals. In seven hospitals magnesium sulphate would be given for neuroprotection if delivery was expected to take place within 24 hours, in five hospitals this would be left to the discretion of the admitting hospital. The use of nifedipine was variable across hospitals, and the use of sympathomimetics was rare.

5.3 Early postnatal transfer of extremely preterm infants (Original publication III)

5.3.1 Study participants

The study population consisted of 18,213 extremely preterm infants. 365 infants were excluded due to congenital anomalies, 227 for missing data on gestational age, birth weight, z score or sex and 44 due to transfer for cardiac or surgical care. Because UK growth charts extend only to infants born at 23 weeks of gestation or more, 74 infants who were born at less than 23 weeks of gestation were separately matched based on sex, birth weight (30 gram increments) and exposure to antenatal steroids, and were included in the study. After exclusions, 17,577 extremely preterm infants remained in the data. A total of 3,550 (20%) infants were transferred within 48 hours from birth, 14,027 (80%) were not transferred. The flow chart in Figure 2 shows how the final study sample was arrived at. The flow chart also shows that 11,172 infants (64%) were born in level 3 hospitals, and that 1,037 infants (6%) were born in level 1 hospitals or non-hospital maternity units.

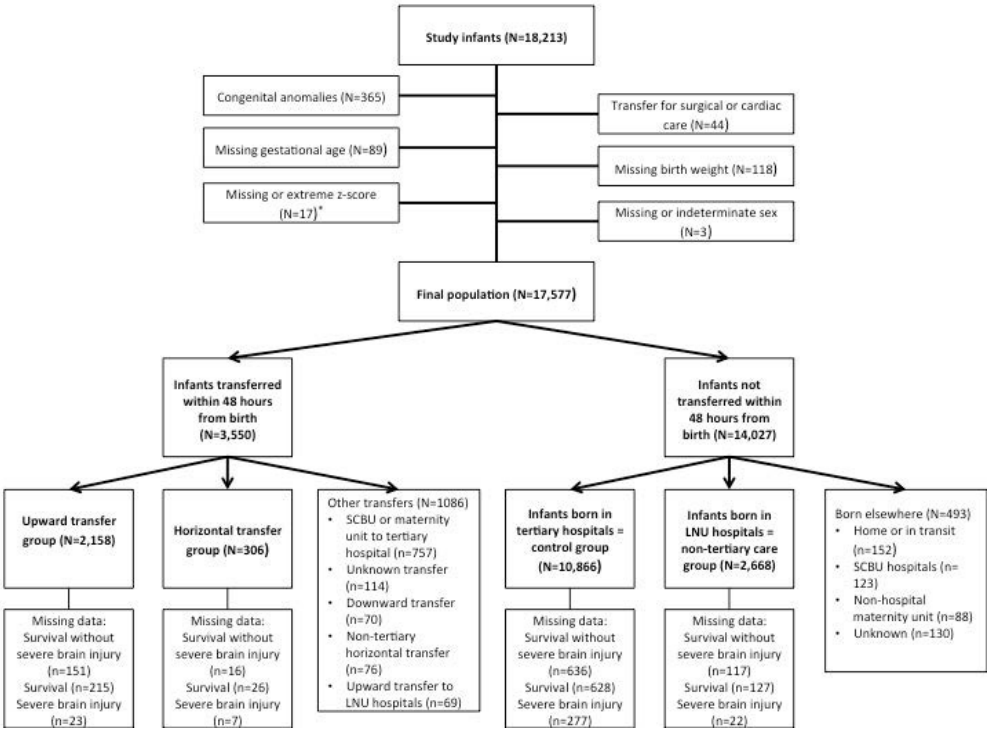

Figure 2. Flow chart illustrating the selection process of infants born at less than 28 weeks of gestation in England in 2008 to 2015. From Original publication III.

*74 infants were born at less than 23 gestational weeks and were separately matched on sex, birth weight and exposure to antenatal steroids, and were included in the analysis

5.3.2 Grouping of infants based on delivery hospital and transfer

A total of 11,172 infants (64%) were born in level 3 hospitals. The control group included 10,866 infants who were born in a level 3 hospital and were not transferred. The upward transfer group included 2,158 infants who were born in level 2 hospitals and transferred to level 3 hospitals within 48 hours from birth. The non-tertiary care group included 2,668 infants who were born in level 2 hospitals and were not transferred within 48 hours from birth. The horizontal transfer group included 306 infants who were born in level 3 hospitals and transferred to another level 3 unit within 48 hours from birth.

5.3.3 Results of propensity score matching

5.3.3.1 Main analysis

Propensity score matching resulted in 727 triplets containing one infant each from the control group, upward transfer group and the non-tertiary care group. The standardised differences of the background variables were compared both before and after the matching process, thus illustrating the success of the match. Table 6 shows the standardised differences before matching; they range from 0.01 to 0.7. A general principle for evaluating these standardised differences is that values below 0.2 are acceptable, and for large samples, values below 0.1.

The standardised differences after matching is shown in Table 7, and shows much lower numbers than before matching, indicating a good match (standardised differences ranging from 0 to 0.068).

Table 6. Background characteristics before matching of extremely preterm infants (<28 gestational weeks) born in England in 2008 to 2015 grouped by hospital of birth and transfer status at 48 hours of age. From Original publication III.

	Control (N=10,866)	Upward transfer (N=2,158)	Standardised difference*	Non-tertiary care (N=2,668)	Standardised difference**	Standardised difference***
Gestational weeks, median (IQR)	26.0 (24.9 to 27.0)	25.6 (24.6 to 26.4)	-0.21	27.0 (26.3 to 27.6)	0.51	-0.70
Mean birth weight, grams, (SD)	807 (188)	797 (172)	0.06	931 (193)	0.50	-0.50
Birth weight z-score, mean (SD)	-0.20 (0.89)	-0.03 (0.82)	0.22	0.02 (0.89)	0.25	-0.05
Male sex (%)	5,799 (53.4)	1,207 (55.9)	-0.03	1,463 (54.8)	-0.03	-0.02
Multiple birth (%)	2,995 (27.6)	497 (23.1)	-0.09	556 (20.8)	-0.15	0.03
Missing values (%)	2 (0)	2 (0)		0 (0)		
Smoking in pregnancy (%)	1,733 (19.5)	418 (22.1)	0.08	503 (21.7)	0.04	-0.02
Missing values (%)	1,998 (18.4)	263 (12.2)		349 (13.1)		
Caesarean delivery (%)	4,028 (40.1)	680 (32.9)	0.16	1,208 (48.5)	0.21	0.23
Missing values (%)	819 (7.5)	93 (4.3)		177 (6.6)		
Surfactant during resuscitation (%)	9,780 (94.0)	2,035 (97.3)	0.08	2,446 (93.7)	0.01	0.11
Missing values (%)	466 (4.3)	66 (3.1)		58 (2.2)		
Antenatal steroids (%)	9,897 (92.4)	1,714 (80,3)	-0.25	2,255 (86.5)	-0.12	-0.11
Missing values (%)	153 (1.4)	24 (1.1)		60 (2.2)		
Apgar 1 min <3 (%)	1,847 (19.5)	467 (23.7)	-0.10	409 (17.1)	-0.06	0.12
Missing values (%)	1,392 (12.8)	186 (8.6)		275 (10.3)		
Apgar 5 min <3 (%)	385 (4.1)	101 (5.2)	-0.02	80 (3.4)	-0.02	0.05
Missing values (%)	1,426 (13.1)	215 (10.0)		331 (12.4)		

Upward transfer, infants born in hospitals with local neonatal units and transferred to level 3 hospitals within 48 hours from birth; non-tertiary care, infants born in hospitals with local neonatal units and not transferred within 48 hours from birth; control, infants born in level 3 hospitals and not transferred within 48 hours from birth; IQR, Interquartile range; SD, Standard deviation.

*Controls vs. upward transfer group

**Controls vs. non-tertiary care group

***Upward transfer group vs. non-tertiary care group

Table 7. Background characteristics after propensity score matching of extremely preterm infants (<28 gestational weeks) born in England in 2008 to 2015 grouped by hospital of birth and transfer status at 48 hours of age. From Original publication III.

	Control (N=727)	Upward transfer (N=727)	Standardised difference (matched)*	Non-tertiary care (N=727)	Standardised difference (matched)**	Standardised difference (matched)***
Gestational weeks, median (IQR)	26.0 (25.0 to 27.0)	26.0 (25.0 to 27.0)	0.000	26.0 (25.0 to 27.0)	0.000	0.000
Mean birth weight, grams, (SD)	900 (56)	900 (69)	-0.012	888 (65),	0.015	0.027
Birth weight z-score, mean (SD)	0.099 (0.24)	0.103 (0.26)	-0.024	0.099 (0.25)	0.030	0.054
Male sex (%)	298 (41.0)	298 (41.0)	0.000	298 (41.0)	0.000	0.000
Multiple birth (%)	158 (21.7)	162 (22.3)	-0.009	172 (23.7)	-0.033	-0.024
Missing values (%)	0	0		1		
Smoking in pregnancy (%)	129 (20.1)	157 (24.1)	-0.068	146 (23.7)	-0.056	0.012
Missing values (%)	86 (11.8)	76 (10.5)		103 (14.2)		
Caesarean delivery (%)	416 (57.2)	405 (55.7)	0.010	398 (54.7)	0.046	0.036
Missing values (%)	0	0		0		
Surfactant during resuscitation (%)	701 (97.9)	695 (98.0)	-0.006	683 (97.1)	0.022	0.025
Missing values (%)	11 (1.5)	18 (2.5)		15 (2.1)		
Antenatal steroids (%)	565 (77.7)	565 (77.7)	0.000	565 (77.7)	0.000	0.000
Missing values (%)	25 (3.4)	11 (1.5)		31 (4.3)		
Apgar 1 min <3 (%)	144 (19.8)	144 (19.8)	-0.014	139 (19.1)	-0.016	-0.017
Missing values (%)	64 (8.8)	67 (9.2)		62 (8.5)		
Apgar 5 min <3 (%)	34 (4.7)	34 (4.7)	-0.050	25 (3.4)	-0.049	0.005
Missing values (%)	84 (11.6)	82 (11.3)		74 (10.2)		

Upward transfer, infants born in hospitals with local neonatal units and transferred to level 3 hospitals within 48 hours from birth; non-tertiary care, infants born in hospitals with local neonatal units and not transferred within 48 hours from birth; control, infants born in level 3 hospitals and not transferred within 48 hours from birth; IQR, Interquartile range; SD, Standard deviation.

*Controls vs. upward transfer group

**Controls vs. non-tertiary care group

***Upward transfer group vs. non-tertiary care group

5.3.3.2 Horizontal transfer vs. controls

Due to the small size of the horizontal transfer group (306 infants) they could not be incorporated into the three-way matched analysis without substantial loss of infants and statistical power. Therefore, we matched the infants in the horizontal transfer group separately to controls, utilising the relative abundance of controls by matching each infant in the horizontal transfer group to 5 controls. This yielded 305 horizontally transferred infants matched to 1,525 controls in the same way as above (propensity score and principal variables). The match was good, which is indicated by standardised differences ranging from 0 to 0.02 (Table 8).

Table 8. Background characteristics before and after pairwise matching extremely preterm infants transferred between level 3 units within 48 hours of postnatal age (horizontal transfer group) to non-transferred infants born in level 3 units (control group). From Original publication III.

	Control (N=10,866)	Horizontal transfer (N=306)	Standardised difference (unmatched)	Standardised difference (matched)
Gestational weeks, median (IQR[d])	26.0 (24.9, 27.0)	26.3 (25.1, 27.1)	0.16	0.00
Mean birth weight, grams, (SD[e])	807 (188)	858 (189)	0.20	0.02
Birth weight z-score, mean (SD)	-0.20 (0.89)	-0.04 (0.80)	0.19	0.01
Male sex (%)	5,799 (53.4)	174 (56.9)	-0.07	0.00
Multiple birth (%)	2,995 (27.6)	115 (37.7)	-0.19	0.00
Missing values (%)	2 (0)	1 (0.3)		
Smoking in pregnancy (%)	1,733 (19.5)	43 (19.1)	-0.04	0.00
Missing values (%)	1,998 (18.4)	81 (26.5)		
Caesarean delivery (%)	4,028 (40.1)	125 (45.0)	-0.10	0.00
Missing values (%)	819 (7.5)	28 (9.2)		
Surfactant during resuscitation (%)	9,780 (94.0)	283 (97.6)	0.06	0.00
Missing values (%)	466 (4.3)	16 (5.2)		
Antenatal steroids (%)	9,897 (92.4)	276 (90.5)	-0.02	0.00
Missing values (%)	153 (1.4)	1 (0.3)		
Apgar 1 min <3 (%)	1,847 (19.5)	29 (11.6)	-0.04	0.00
Missing values (%)	1,392 (12.8)	57 (18.6)		
Apgar 5 min <3 (%)	385 (4.1)	7 (2.9)	-0.04	0.00
Missing values (%)	1,426 (13.1)	65 (21.2)		

IQR, Interquartile range; SD, Standard deviation.

5.3.4 Outcomes

5.3.4.1 Death before discharge

There were 571 triplets in the main three-way analysis where all infants had outcome data available for death before discharge. The results of the main analysis are presented in Table 9. The results showed that infants in the upward transfer group did not have a significantly higher risk of death before discharge compared to controls (OR 1.22, 95% CI 0.92 to 1.61, p=0.16) or the infants in the non-tertiary care group (OR 1.10, 95% CI 0.84 to 1.44, p=0.50). Infants in the non-tertiary care group had a significantly higher risk of death before discharge compared to controls (OR 1.34, 95% CI 1.02 to 1.77, p=0.04). Results from the pairwise comparison of infants in the horizontal transfer group and controls are presented in Table 10. Infants in the horizontal transfer group did not have a significant difference in the odds of death before discharge compared to controls (OR 1.09, 95% CI 0.80 to 1.42, p=0.55).

Table 9. Comparison of outcomes between propensity score matched extremely preterm infants (<28 gestational weeks) born in England in 2008 to 2015 grouped by hospital of birth and transfer status at 48 hours of age. From Original publication III.

	Upward transfer n(%) [95% CI]	**Non-tertiary care n(%) [95% CI]**	**Control n(%) [95% CI]**	**OR (95% CI)**		
				Upward transfer vs. Controls	Non-tertiary care vs. Controls	Non-tertiary care vs. Upward transfer
Death before discharge (N=571)	140 (24.5) [20.9 to 28.1]	150 (26.3) [22.6 to 30.0]	120 (21.0) [17.6 to 24.4]	1.22 (0.92 to 1.61) *p*=0.16	1.34 (1.02 to 1.77) *p*=0.04	1.10 (0.84 to 1.44) *p*=0.50
Severe brain injury (N=705)	194 (27.5) [24.2 to 30.9]	95 (13.5) [10.9 to 16.1]	99 (14.0) [11.4 to 16.7]	2.32 (1.78 to 3.06) *p*<0.001	0.95 (0.70 to 1.30) *p*=0.76	0.41 (0.31 to 0.53) *p*<0.001
Survival without severe brain injury (N=593)	338 (57.0) [42.9 to 61.1]	382 (64.4) [60.5 to 68.4]	408 (68.8) [65.0 to 72.6]	0.60 (0.47 to 0.76) *p*<0.001	0.82 (0.64 to 1.05) *p*=0.11	1.37 (1.09 to 1.73) *p*=0.009

Upward transfer, infants born in hospitals with local neonatal units and transferred to level 3 hospitals within 48 hours from birth; non-tertiary care, infants born in hospitals with local neonatal units and not transferred within 48 hours from birth; control, infants born in level 3 hospitals and not transferred within 48 hours from birth; CI; Confidence interval OR, Odds ratio.

5.3.4.2 Severe brain injury

There were 705 triplets in the main three-way analysis with complete outcome data for severe brain injury. The analysis showed that infants in the upward transfer group had a statistically significantly higher risk of severe brain injury both compared to controls (OR 2.32, 95% CI 1.78 to 3.06, p<0.001) and compared to the non-tertiary care group (OR 2.44, 95% CI 1.89 to 3.23, p<0.001). Infants in the non-tertiary care group did not have a statistically significant difference in the risk of severe brain injury compared to controls (OR 0.95, 95% CI 0.70 to 1.30, p=0.76). Infants in the horizontal transfer group did not have a statistically significant difference in the risk for severe brain injury compared to controls (OR 1.16, 95% CI 0.83 to 1.54, p=0.36).

5.3.4.3 Survival without severe brain injury

A total of 593 triplets in the main analysis had complete outcome data for the analysis of survival without severe brain injury. The results showed that infants in the upward transfer group had a significantly lower chance of survival without severe brain injury both compared to controls (OR 0.60, 95% CI 0.47 to 0.76, p<0.001) and compared to infants in the non-tertiary care group (OR 0.73, 95% CI 0.58 to 0.92, p=0.009). Infants in the non-tertiary care group did not have a statistically significant difference in the chance of survival without severe brain injury compared to controls (OR 0.82, 95% CI 0.64 to 1.05, p=0.11). Infants in the horizontal transfer group did not have a statistically significant difference in the chance of survival without severe brain injury compared to controls (OR 0.91, 95% CI 0.71 to 1.15, p=0.43).

Table 10. Comparison of outcomes after pairwise matching extremely preterm infants transferred between level 3 hospitals within 48 hours of postnatal age (horizontal transfer group) to non-transferred infants born in level 3 hospitals (control group). From Original publication III.

	Horizontal transfer N=305 n(%) [95% CI]	**Controls N=1,525 n(%) [95% CI]**	**OR (95% CI)**
Death before discharge	64 (21.0) [15.4 to 26.8]	299 (19.6) [14.0 to 25.4]	1.09 (0.80 to 1.42) p=0.55
Severe brain injury	52 (17.0) [12.1 to 22.1]	230 (15.1) [10.1 to 20.1]	1.16 (0.83 to 1.54) p=0.36
Survival without severe brain injury	199 (65.2) [58.6 to 71.8]	1028 (67.4) [60.8 to 74.0]	0.91 (0.71 to 1.15) p=0.43

CI; Confidence interval OR, Odds ratio.

5.4 International comparison of survival in very preterm infants (Original publication IV)

5.4.1 Study participants

The iNeo database included a total of 91,835 very preterm infants born between 24+0 and 29+6 gestational weeks and registered in the 10 participating neonatal networks. After excluding 3,070 infants with a birth weight of over 1500 grams and 438 infants who were admitted at >36+0 gestational weeks, the final study sample consisted of 88,327 infants. An overview of the participating networks and the characteristics of the included infants are presented in Table 1 and Table 2 in Original Publication IV.

5.4.2 Survival

Of the 88,327 included infants, 77,172 (87%) survived to discharge. Survival rates differed between networks; the highest survival rate was 93% in Japan, and the lowest 78% in Spain. When analysed by gestational weeks, the greatest difference between networks was noted at 24 weeks, where the survival rate was 84% in Japan and 35% in Israel. The difference in survival rates between networks gradually decreased with increasing gestational age, but the inter-network rank in survival rates was largely unchanged. This is illustrated in Figure 3.

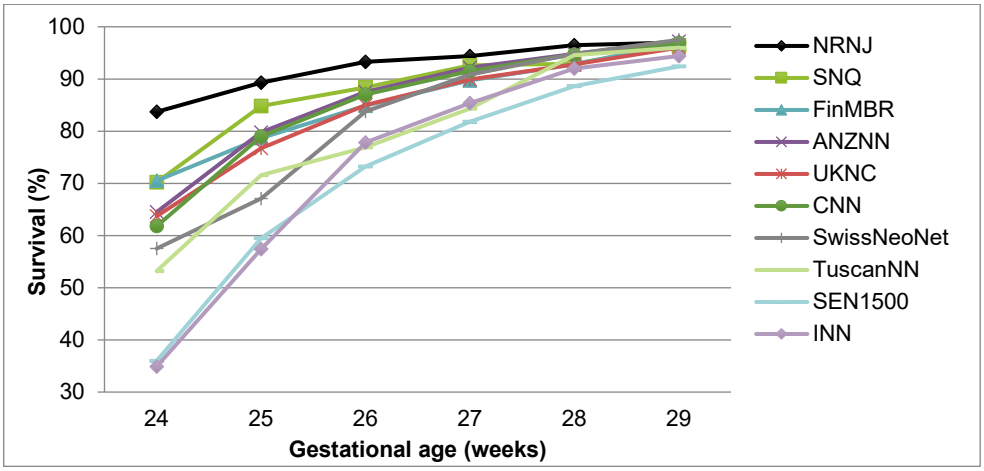

Figure 3. Gestational age-specific survival for very preterm and very low birth weight infants (GA 24+0 – 29+6, birth weight <1500g) born between 2007 and 2013 and admitted to neonatal care in the iNeo networks. From Original publication IV. ANZNN = Australian and New Zealand Neonatal Network, CNN = Canadian Neonatal Network, FinMBR = Finnish Medical Birth Register, INN = Israel Neonatal Network, NRNJ = Neonatal Research Network of Japan, SEN1500 = Spanish Neonatal Network, SNQ = Swedish Neonatal Quality Register, SwissNeoNet = Swiss Neonatal Network, TuscanNN = Tuscan Neonatal Network, UKNC = United Kingdom Neonatal Collaborative

The survival rates in each network were compared to the 99% confidence interval of expected survival based on the whole study population by comparing standardised ratios. The standardised ratios are shown in a funnel plot in Figure 4, where the thin green funnel lines represent the 99% confidence interval of the whole study population, and the vertical bars represent the 99% confidence intervals of the standardised ratio for each network. Any network whose vertical bar fall within or overlap the green funnel has a survival rate that is within the 99% confidence interval of the expected survival rate of the whole population. If the vertical bar is entirely above the green funnel the observed survival rate is above expected, and if it falls below the funnel, it is below expected. The standardised ratio was higher than expected in Japan, and lower than expected in Israel and Spain.

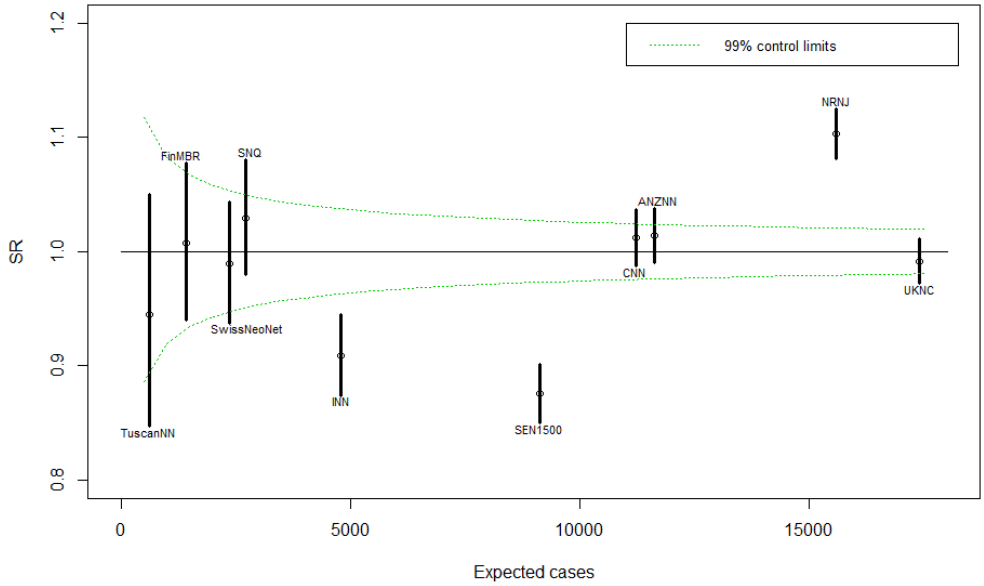

Figure 4. Standardised ratios* of survival for very preterm and very low birth weight infants (GA 24+0 – 29+6 weeks, birth weight <1500g) born during the study period (2007-2013) and admitted to neonatal care in each iNeo network. From Original publication IV. Abbreviations: ANZNN = Australian and New Zealand Neonatal Network, CNN = Canadian Neonatal Network, FinMBR = Finnish Medical Birth Register, INN = Israel Neonatal Network, NRNJ = Neonatal Research Network of Japan, SEN1500 = Spanish Neonatal Network, SNQ = Swedish Neonatal Quality Register, SwissNeoNet = Swiss Neonatal Network, TuscanNN = Tuscan Neonatal Network, UKNC = United Kingdom Neonatal Collaborative. *Standardised ratios (SR) comparing the survival in each network to all other networks combined. Vertical bars are the estimated 99% confidence intervals of the SR. The dotted curves represent the 99% control limits expected under the null hypothesis of similar outcome rates (SR = 1).

5.4.3 Age at death

The secondary aim of this study was to determine the age of death among nonsurvivors in the participating networks. The median age at death was 8 days in the whole study population. The extreme outliers were Finland, where the median age at death was 4 days, and Japan, where the median age at death was 13 days. 122 infants of 194 (63%) in Finland died before 7 days of age, compared to 442 infants of 1,206 (37%) in Japan.

6 Discussion

This thesis evaluates the requisites and effects of centralisation of very preterm deliveries, first by estimating costs incurred by and resources needed for effective centralisation, second by exploring the obstetrical referral practices that enable effective centralisation, and third by evaluating the effect of the alternative to centralisation; care in level 2 hospitals with or without postnatal transfer. Through initiating collaboration with an international research network, the iNeo, this thesis also paves the way for future international benchmarking of neonatal care results and quality improvement in the field of neonatal care, using population-based data.

6.1 The costs and benefits of centralising very preterm deliveries

The fact that centralising very preterm deliveries to level 3 hospitals decreases mortality has been shown in several high quality publications (Johansson et al., 2004; Phibbs et al., 2007; Rautava et al., 2007; Lasswell et al., 2010; Lorch et al., 2012). In most countries, the majority of the population lives outside the catchment of level 3 hospitals, thus identifying mothers in need of antenatal transfer due to impending very preterm delivery is essential. This requires vigilance among obstetricians in lower-level hospitals, and timely arrangement of antenatal transfer to a tertiary hospital. Centralisation often includes a reorganisation of the healthcare system and reallocation of recourses, and is often a time-consuming process inherent with difficulties.

6.1.1 Costs of centralisation

Costs of hospital care are calculated differently depending on the health care system. In the US, insurance coverage varies, and in many studies hospital cost estimates are derived from insurance databases, and thus represent charges instead of actual costs. Hospital billing systems differ also within countries, and the costs can be based on diagnoses (Diagnosis Related Groups, DRG), length of stay, administered treatments, or insurance reimbursement. Comparing health care costs across different settings reliably is therefore very difficult, if not impossible. The

only consistent factor that is common to most studies on costs of care of very preterm infants is that costs increase with decreasing gestational age. In Original publication I we chose the amount of antenatal care days as proxy for costs to solve the problem with non-comparable costs, because care days are comparable between countries regardless of billing or insurance systems. Our finding that mothers delivering very preterm and referred to level 3 hospitals for delivery did not have significantly more antenatal care days in level 3 hospitals than non-referred mothers, is an indicator that the costs of centralisation is acceptable when compared to the costs associated with the alternatives, delivery in lower-level hospitals and early postnatal transfer. We showed in Original publication III that by delivering eight extremely preterm infants in level 3 hospitals instead of lower-level hospitals and subjecting infants to early postnatal transfer, would avoid one case of severe brain injury. It has been shown that severe brain injuries frequently lead to neurodevelopmental impairment such as cerebral palsy, which is accompanied by an up to six-fold increase in cumulative health care costs during early childhood compared to prematurity without comorbidities (Centers for Disease Control and Prevention, 2004; Korvenranta et al., 2010; Mukerji et al., 2015).

6.1.2 Improving neonatal outcomes by increasing centralisation

Historical studies conducted over four decades ago increased the awareness of the need for centralisation of very preterm deliveries (McCormick, 1985; Ryan Jr, 1975). Neonatal care has advanced over those decades; examples include the near universal availability of antenatal steroids and exogenous surfactant (Liggins & Howie, 1972; Hallman et al., 1985). Several studies have shown the benefit of centralising very preterm deliveries to level 3 hospitals, and these findings are collated in the systematic review by Lasswell and colleagues (Lasswell et al., 2010). Infants born even at 22 and 23 gestational weeks now have chances of survival (Ishii et al., 2013), and reassuringly, studies show that increased survival is not necessarily accompanied by higher rates of severe morbidities. A study from the USA showed that the rates of survival without impairment of infants born at 22 to 24 weeks increased from 16% to 20% between epochs 2000-2003 and 2007-2011 (Younge et al., 2017). In Sweden, Serenius et al. showed that increased survival of the smallest preterm infants did not lead to higher rates of survivors with disabilities (Serenius et al., 2015). A recent Swedish national study utilising national data from 1973 to 1997 showed that the rates of adults born extremely preterm and very preterm surviving to adulthood without morbidities have increased significantly over time, and showed the inverse association between

gestational age and survival free of morbidities (Crump et al., 2019). Increased chances of survival at such low gestational ages further increases the number of infants that could be saved by centralising deliveries. Some studies suggest that lowering the threshold for active resuscitation might improve outcomes also for infants who are born at higher gestational ages (Zegers et al., 2016). Successfully providing active care for infants born at less than 24 gestational weeks increases the need for centralisation, as such infants are even more rare than more mature preterm infants, and their care requires the highest possible level of medical expertise and experience.

6.1.3 Factors influencing the success of centralisation

Difficulties might arise when the organisational framework does not support centralisation. One example of such difficulties can be seen in the UK, where newborn care was restructured into managed clinical networks beginning in 2003, with the aim to deliver extremely preterm infants in level 3 hospitals. One effect of this restructuring was that the rate of centralisation of extremely preterm deliveries in selected gestational age categories did increase from 18% to 49%, but an unwanted increase in early postnatal transfers ensued (Gale et al., 2012). This can also be due to the fact that several highly specialised neonatal transfer teams have been established across the UK; the availability of such a team can be seen as a tempting alternative to the time-consuming and potentially frustrating process of arranging antenatal transfer (Kempley et al., 2007; Gale et al. 2012).

Caring for very preterm infants is associated with high costs, and might lead to high profit for hospitals delivering that care in certain settings. This might increase preference to keep these sick infants in facilities with sub-standard care possibilities. In California, where care centralisation has been implemented and studied well, new neonatal units proliferated in the 1990s and subsequently the proportion of very preterm infants born in level 3 hospitals decreased (Haberland et al., 2006; Phibbs et al., 2007). Another example from the past decade of potential financial interests influencing centralisation could be seen in Germany, where a study by Bartels and colleagues showed that among very low birth weight infants (birth weight below 1500 grams), mortality was significantly increased when delivery took place in neonatal units with <36 such deliveries annually, as compared to birth in larger units (Bartels et al., 2006). The subsequent re-organisation efforts issued by a governmental body were overturned in court, possibly due partly to financial incentives and partly historical traditions of providing care in small units (Poets, 2014).

6.2 Postnatal transfer and severe brain injury – it's the ride, after all?

Studies estimating the possible causal effects of early neonatal transfer on neonatal outcomes are limited because of the ethical constraints on performing randomised controlled trials. Studies focusing on early postnatal transfer have been restricted to retrospective studies, which usually are at high risk of bias, and the estimating of causal effects is problematic. This could be an explanation for why previous studies show conflicting results (Mohamed & Aly, 2010; Watson et al., 2013).

6.2.1 Statistical issues

A frequently encountered source of bias is the different composition of groups of transferred and non-transferred infants; transferred infants tend to have more risk factors than the non-transferred counterparts. Adjusting for covariates is standard in retrospective studies, and methods normally include formation of regression models to account for differences in background variables. Regression modelling utilising e.g. logistic regression is, however, accompanied by statistical pitfalls, such as the assumption of a linear relationship of predictor variables and log-odds of the outcome, and the temptation to select a statistical model that yields the most promising results. In Original publication III, we avoided most of these pitfalls by using propensity score matching and the potential outcomes framework. Propensity score matching is frequently mentioned in statistical literature as a tool to draw causal inferences from retrospective data (Stuart, 2010; Mccaffrey et al., 2013). The potential outcomes framework approach requires all matching procedures be done without evaluating outcomes, which strengthens the reliability of the modelling. We were fortunate enough to have a rich set of background variables available for determining the propensity scores, which is a further strength of this approach. As stated in the Discussion in Original publication III, the main limitation is that without instrumental variables, it is impossible to account for unmeasured confounding. An instrumental variable is by definition a variable that influences the probability of receiving an intervention, but does not influence directly on the outcome (Baiocchi et al., 2014). Adding an instrumental variable approach would have underlined the causal relationships suggested by our study, but on the other hand, a study by Lorch and colleagues, which compared propensity score matching and an instrumental variable approach, showed that propensity score matching underestimated the beneficial effect of being born in a level 3 hospital, rather than overestimating it (Lorch et al., 2012).

6.2.2 Arranging maternal versus neonatal transfer

Avoiding early postnatal transfers and deliveries of very preterm infants in low-level hospitals is possible only by delivering very preterm infants in tertiary hospitals. This means that in most cases, mothers need to be identified and transferred before delivery is imminent. The identification of mothers in need of antenatal transfer is difficult and multifactorial, but it is a task obstetricians in level 2 hospitals encounter frequently. Spontaneous preterm birth is difficult to predict, and most adjunctive tools have very low positive predictive values (NICE, 2015; Kyozuka et al., 2019; Vivanti et al., 2019). The results in Original publication II indicated agreement between Finnish level 2 obstetricians regarding indications for antenatal transfer in cases of chorioamnionitis, PPROM and pre-eclampsia, but for clinical signs of spontaneous preterm delivery there were large variations. Contraindications for antenatal transfer that reached high agreement in our study were placental abruption and pathological CTG tracing, but no obvious consensus emerged for other clinical signs.

The most frequently encountered contraindication for antenatal transfer in non-tertiary hospitals in Finland was imminent delivery; very few units reported difficulties in arranging the referral itself, such as delay in locating an admitting tertiary hospital or arranging an ambulance or escorting personnel for transfer. Even if the obstetrician makes the decision that antenatal transfer is urgently needed, it is not always possible to achieve. This is highlighted e.g. in a study by Gale and colleagues in London, UK, where almost half of requests for antenatal transfer failed (Gale et al., 2012). They further reported that the median duration of successful antenatal transfers was over 5 hours, and that in some cases where antenatal transfer was not successful, the mother had been hospitalised for more than 12 hours, and that a median of 7 tertiary units had been contacted in trying to find an admitting hospital for both infant and mother. In another study from the UK by Kempley and colleagues, the introduction of a specialised neonatal transfer service was followed by improved response times, but also by a decrease in antenatal transfers, when compared to the years before introducing the transfer service (Kempley & Sinha, 2004; Kempley et al., 2007). These findings suggest that arranging antenatal transfer in the UK can be very time-consuming, and that availability of specialised neonatal transfer teams might lead to reluctance to undertake the task of arranging antenatal transfer.

6.2.3 Possible detrimental effects of early postnatal transfer

It has been well established that extremely preterm infants are at high risk of severe brain injury. There are several plausible explanations for a direct physiological link between early postnatal transfer and severe brain injury. Transferred infants are

commonly exposed to hypothermia and noxious stimuli such as noise and vibration (Arora et al., 2014; Gupta et al., 2019). It has also been shown that postnatal transfers of infants are commonly complicated with adverse events such as equipment malfunction and critical handover shortfalls (Lim & Ratnavel, 2008). A recent study showed that neonates are exposed to high levels of vibration when measured by sophisticated equipment that registered vibration and acceleration in the head and torso region (Blaxter et al., 2017). Innovative animal models have been investigated, exposing rat pups to vibration levels similar to those measured during ambulance transfer. Preliminary, yet unpublished results suggest that rat pups exposed to vibration at an age equivalent to 35 gestational weeks in human infants show marked brain damage, and the effects are even more severe in rat pups equivalent to 28 gestational weeks (Personal communication; Dr Don Sharkey, University of Nottingham, UK). These findings are very interesting, and might identify a biologically plausible link between early postnatal transfer and brain injury.

6.3 Benchmarking of neonatal care

Learning by sharing results has become more and more important in the modern era of neonatal care. Regional and national research databases can be successfully merged into multinational research platforms, which have the ability to serve as bases for large epidemiological studies. As part of this thesis, the national population based data from the Finnish Medical Birth Register were merged with the international iNeo collaboration database.

6.3.1 Why are collaborative databases important in benchmarking?

Important outcomes such as neonatal mortality are frequently reported in scientific studies on very preterm infants. Pertaining to differences in study methodology, direct comparison of outcomes from different studies can be difficult. Defining the denominator is especially important regarding mortality, as the denominator can be any of the following: all fetuses at risk (Smith et al., 2018), all fetuses alive at hospital admission (Fellman et al., 2009; Costeloe et al., 2012), all live- or stillborn infants (Zeitlin et al., 2016), all live born infants (Stoll et al., 2015) or most commonly, all infants surviving to admission to neonatal care excluding delivery room deaths (Zeitlin et al., 2016). Compilation of a common dataset with well-defined variables used in multiple settings enables reliable comparison between neonatal units, geographical regions and countries. Only by comparing outcomes assessed by similar standards can we directly compare the performance of different

units. The iNeo database used in Original publication IV has clear definitions for each of the included variables, and allows for comparison between the member networks. The aim of the collaboration is to identify differences in care strategies and outcomes, and ultimately to initiate quality improvement projects based on the results.

6.3.2 How can international benchmarking improve neonatal outcomes?

One of the first goals of benchmarking is to identify differences in outcomes and make stakeholders aware of them. This enables focused quality improvement initiatives both within and between neonatal units, and also on a larger, national scale. The Vermont Oxford Network has been leading the way for such quality improvement initiatives since the 1990s (Horbar et al., 2010). A good example of a recent national quality improvement initiative ignited by the perceived need for improvement and care quality ascertainment is the Evidence-based Practice for Improving Quality (EPIQ) collaboration in Canada. This collaboration has been able to invite all level 3 neonatal units in Canada to join forces in comparing outcomes, care practices and potential improvement targets. This collaboration includes focus group discussions on how to improve outcomes, and site visits, where units can learn from each other in real life in a professional community committed to open knowledge sharing. The application of EPIQ in Canada has been accompanied by significant improvements in neonatal outcomes (Lee et al., 2014). The methodology adopted in Canada has also been successfully implemented in China (Cao et al., 2019). Such data transparency and unrestricted knowledge exchange initiatives can be used as a model for quality improvement.

6.4 Limitations

The main limitations of this thesis are related to the retrospective nature of the studies. The data in Original publications I, III and IV were collected from large research databases, which were not specifically designed for these particular studies. The aim of the iNeo network is to contain population-based data for all countries, but for the time being networks in some countries, such as Japan and Spain, fall short of this goal. On the other hand, most of the other networks have complete or close to complete national coverage, such as Sweden, Finland, the UK, Switzerland, Israel and Tuscany. A problem inherent in routinely collected datasets is that the quality and completeness of the data relies on the input of data. In such datasets, either nurses or physicians usually enter data manually based on medical journal notes or discharge summaries after the infant is discharged. Up until 2018,

data in the Finnish Medical Birth Register were collected on paper sheets. This introduces a risk of false entries and misinterpretation of the data. Routinely collected datasets should also be validated regularly for accuracy of the data (Gissler et al., 1995; Battersby et al., 2018).

The data sources used in Original publications III and IV had limitations inherent in their design. Some of the iNeo networks routinely collect data on stillborn infants and delivery room deaths, but because some did not, we had to exclude such infants from all datasets in order to reliably compare mortality rates between networks. The NNRD data also lacks data on stillborn and delivery room deaths. This can be a significant limitation, because previous studies have shown that up to 30% of very preterm infants die before admission to neonatal care, either before delivery or shortly thereafter (Rautava et al., 2007; Fellman et al., 2009; Ancel et al., 2015). The provision of active care at the low end of the gestational age range is highly variable, and directly affects mortality rates (Rysavy et al., 2015). By excluding stillbirths and delivery room deaths the survival rates in study IV cannot be used for counselling parents, but can be compared to other studies using the same denominator. In Original publication III the potential influence of this limitation is that some fetuses delivered stillborn in level 2 hospitals could potentially have been saved if the mother first presented to a level 3 hospital. The extent of this potential limitation in Original publication III remains unknown because the data are not available.

Large datasets should be analysed with caution, because as the number of included infants grows, the likelihood of small differences reaching statistical significance also grows. Therefore it is imperative to evaluate the clinical significance of all findings derived from these large datasets. The studies in this thesis have aimed to apply robust analytical methods and restrict analyses to clinically important outcomes to avoid the risk of overanalysing the data or drawing false conclusions. Recently it has been proposed that the traditionally used levels of significance should be changed from p-values <0.05 and 95% CI to more stringent $p<0.005$ and 99,5% CI, which would be especially relevant in large studies (Ioannidis, 2018). In Original publication IV we used 99% CI to denote statistical significance as predefined prior to analysis, but in study III we defined the level of significance at 95% in the protocol. We did not deviate from the prespecified level of significance, although most of our findings remained significant also when applying a more stringent level of significance.

Original publication II was performed as a questionnaire, and replies to such a study might not reflect actual care decisions. A prospective study collecting data on measurable clinical variables such as cervical shortening, contraction intervals and time of arranging transfers would have been more accurate. However, the aim of the study was to explore the different variables that are considered relevant to

clinicians in making referral decisions, identify perceived problems in arranging transfers, and serve as base for future prospective studies.

6.5 Prospects for the future

The studies in this thesis show that centralisation of very preterm deliveries is feasible at a reasonably low cost in Finland, and that the organisation of perinatal services allows for transfer of mothers at risk of very preterm delivery. This highlights the need for reorganisation of perinatal services in countries such as the UK, where centralisation is difficult and time-consuming. The UK health care system suffers from barriers both in perinatal and neonatal care, and needs to be re-evaluated on a national level in order to decrease mortality and severe brain injuries in the most vulnerable infants. Establishing a causal biological link between early postnatal transfer and brain injury could enforce initiatives to minimise postnatal transfers. Benchmarking via international collaboratives such as the iNeo provides valuable information for neonatal professionals, and should provoke open communication and knowledge exchange between neonatal units, in order to improve neonatal outcomes even further. Benchmarking could also be improved by extending data to also include follow-up of very preterm infants, following the example of e.g. the Canadian Neonatal Follow-Up Network (Synnes et al., 2014). Future neonatal research should also focus on outcomes beyond the neonatal period and outcomes that are perceived relevant by parents and preterm survivors, as suggested by recent research (Webbe et al., 2019). The use of long-term outcomes for benchmarking is justified also because the goal of neonatal intensive care is to help vulnerable premature infants grow to become healthy adults.

7 Conclusions

I. The costs of centralising very preterm deliveries in Finland are low, as measured by antenatal care days in level 3 hospitals among centralised mothers.

II. Thresholds of clinical signs for indications and contraindications for antenatal transfer in Finnish level 2 hospitals were variable between hospitals, but arranging transfers in Finland is usually neither time-consuming nor difficult.

III. Among extremely preterm infants in England, birth in non-tertiary hospitals with early postnatal transfer is related to increased odds of severe brain injury, and birth and care in level 2 hospitals without early postnatal transfer is associated with increased odds of mortality.

IV. Mortality and age at death in very preterm infants varies considerably between high-income countries participating in the iNeo network.

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Kjell Helenius

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Appendix

Survey form for Original publication II: Successful antenatal transfers to level 3 hospitals in cases of threatened very preterm deliveries: a national survey.

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Survey of referral practices for mothers with threatened very preterm delivery

Please complete the survey below.

Thank you!

1. Hospital ID number	_____
2. How many cases of threatened preterm delivery < 32 gestational weeks potentially needing antenatal transfer do you normally encounter in your unit?	◯ < 1/month ◯ 1-2/month ◯ 2-5/month ◯ 6-10/month ◯ >10/month
3. How many women did you refer to level 3 hospitals at < 32 gestational weeks due to threatening preterm delivery in 2017?	_____
4. How many very preterm infants (< 32 gestational weeks) were born in your hospital in 2017?	_____
5. How many of the women you referred in 2017 delivered before 32 gestational weeks in a level 3 hospital?	_____
6. What is the lower gestational age threshold in your hospital for considering antenatal transfer to a level 3 hospital?	_____
7. What is the upper gestational age threshold in your hospital for considering antenatal transfer to a level 3 hospital?	_____
8. Is the lower threshold strictly adhered to?	◯ Yes ◯ No ◯ We negotiate with the level 3 hospital
9. If the lower threshold is not strictly adhered to, what factors influence the decision?	☐ Referring hospitals obstetricians' attitude to active care ☐ Referring hospital paediatricians'/neonatologists' attitude to active care ☐ Level 3 hospital obstetricians' attitude to active care ☐ Level 3 hospital paediatricians' attitude to active care ☐ Parents' attitude to active care ☐ Other
Other	_____

10. If the upper threshold is not strictly adhered to, what factors influence the decision towards delivering the infant in the level 2 hospital even in antenatal transfer is feasible?	☐ Availability of obstetrician in level 2 hospital ☐ Availability of paediatrician/neonatologist in level 2 hospital ☐ Availability of obstetrician in level 3 hospital ☐ Availability of paediatrician/neonatologist in level 3 hospital ☐ Availability of nursing staff in level 2 hospital ☐ Availability of nursing staff in level 3 hospital ☐ Patient load in level 2 neonatal ward ☐ Patient load in level 3 NICU ☐ Time of day ☐ Day of week ☐ Time of year ☐ Multiple pregnancy ☐ Maternal disease, which? ☐ Pregnancy complication, which? ☐ IUGR ☐ Macrosomia ☐ Other
What maternal diseases?	_____
What pregnancy complications?	_____
Other	_____

Indications for antenatal transfer to a level 3 hospital < 32 gestational weeks

We appreciate that the indications for antenatal transfer and decision process is always individual. We kindly ask you to describe your evaluation of each clinical sign as if the sign is presenting alone, irrespective of other findings.

Fill out all scenarios where you would proceed to antenatal transfer to a level 3 hospital.

11. Uterine contractions (excluding Braxton-Hicks-type)	◯ < 5 minute intervals ◯ 10-15 minut intervals ◯ Regular, 1-2 contractions per hour ◯ Irregular, over 1 hour intervals ◯ Not an indication ◯ Women with contractions are not referred
12. Cervical length on ultrasound, no funnelling	◯ < 20 mm ◯ 20-25 mm ◯ 25-30 mm ◯ > 30 mm ◯ Not an indication
13. Cervical funnelling on ultrasound	◯ Pointed, small funnel ◯ Narrow funnel, about 1/3 of the cervix ◯ Narrow funnel, about 2/3 of the cervix ◯ Wide funnel, about 1/3 of the cervix ◯ Wide funnel, about 2/3 of the cervix ◯ Deep, very wide funnel comprising the whole cervix ◯ Not an indication

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14. Cervical opening	◯ 0-2 cm ◯ 3-4 cm ◯ 5-6 cm ◯ 7-8 cm ◯ 9-10cm ◯ Not an indication
15. Actim Partus®-testi (or similar test)	◯ If positive ◯ If negative ◯ Not an indication ◯ Not in use
Actim Partus: comments	_____
16. Fetal fibronectin	◯ If positive ◯ If negative ◯ Not an indication ◯ Not in use
17. Other test to identify preterm labour	◯ If positive ◯ If negative
Which test?	_____
18. PPROM	☐ "High" PROM < 32 weeks, no contractions ☐ PROM < 22 weeks, no contractions ☐ PROM < 23 weeks, no contractions ☐ PROM < 24 weeks, no contractions ☐ PROM < 25 weeks, no contractions ☐ PROM < 26 weeks, no contractions ☐ PROM < 27 weeks, no contractions ☐ PROM < 28 weeks, no contractions ☐ PROM 28+0-31+6 weeks, no contractions ☐ Not an indication
19. Vaginal bleeding, aetiology unknown, mother stable	◯ Yes ◯ No
20. Maternal infection other than chorioamnionitis	☐ CTG normal ☐ CTG non-reassuring ☐ CTG pathological ☐ Maternal sepsis ☐ Not an indication
21. Chorioamnionitis	☐ CTG normal ☐ CTG non-reassuring ☐ CTG pathological
22. Mild pre-eclampsia	◯ Yes ◯ No

23. Severe pre-eclampsia	◯ Yes ◯ No
24. If the mother is in severe pre-eclampsia/HELLP, we proceed to antenatal transfer	◯ Immediately ◯ After lowering the BP to below 200/120 ◯ After lowering the BP to below 180/110 ◯ After lowering the BP to below 160/100 ◯ Other
Other	_____
25. Severe pre-eclampsia/HELLP - we wait for lab results before antenatal transfer	◯ Yes ◯ No
26. Severe pre-eclampsia/ HELLP and MgSO4	◯ We start MgSO4 to prevent eclampsia during transfer, if needed ◯ We don't start MgSO4 during transfer in fear of side effects
27. Tocolytics dyring transfer	☐ We start atosiban during transfer if needed ☐ We give peroral nifedipine during transfer if needed ☐ We start betamimetics during transfer if needed ☐ We don't give tocolytics during transfer
28. Antenatal corticosteroids	◯ We administer antenatal corticosteroids before transfer ◯ We leave antenatal corticosteroids to the discretion of the level 3 obstetricians
29. MgSO4 and neuroprotection	◯ We start MgSO4 for neuroprotection of the infant during transfer, if we estimate delivery will take place within 24 hours ◯ We don't start MgSO4 for neuroprotection of the infant during transfer, even if we estimate delivery will take place within 24 hours
30. We contact the following personnel upon referring a patient in risk of delivery < 32 weeks	☐ Labour and delivery midwife in level 3 hospital ☐ Obstetrician in level 3 hospital ☐ Neonatologist in level 3 hospital
31. Means of antenatal transfer	☐ Taxi in selected cases ☐ Always ambulance ☐ Midwife to escort, if there is a clear risk of imminent preterm delivery ☐ Mother has iv access ☐ CTG available during transfer
Comments regarding indications for antenatal transfer	_____

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Contraindictions for antenatal transfer	
32. Cervical opening	◯ 0-2 cm ◯ 3-4 cm ◯ 5-6 cm ◯ 7-8 cm ◯ 9-10 cm ◯ Not a contraindication
33. Frequency of contractions (excluding Braxton-Hicks-type)	◯ < 5min ◯ About 10min ◯ About 15min ◯ Other ◯ Not a contraindication ◯ Mothers with contractions are not referred
Other	_____
34. Fetal distress	☐ Decreased movements ☐ Abnormal CTG ☐ Other
Other signs of fetal distress	_____
35. Maternal infection	☐ Poor maternal condition/sepsis and normal CTG ☐ Poor maternal condition/sepsis and non-reassuring CTG ☐ Non-reassuring CTG while mother well-appearing
36. Vaginal bleeding	☐ Unclear aetiology ☐ Suspicion of placental abruption ☐ Not a contraindication
Comments on contraindications	_____

Arrangement of antenatal transfer	
37. How frequently are antenatal transfers unsuccessful?	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
38. If antenatal transfer is unsuccessful, what is normally the reason(s)	☐ Maternal condition ☐ Imminent delivery ☐ Poor fetal condition ☐ Availability of ambulance ☐ Availability of escorting personnel (midwife, nurse) ☐ Level 3 Labour & delivery cannot accept patient ☐ Level 3 NICU cannot accept patient

39. How long does it normally take to arrange antenatal transfer (from transfer decision to ambulance leaving for level 3 hospital with mother on board)?	◯ < 1h ◯ 1-2h ◯ 2-3h ◯ >3h

What interventions are done in the level 2 hospital before transfer?

40. Antenatal corticosteroids	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
41. Antibiotics (when indicated)	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
42. Atosiban (in mothers with contractions)	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
43. Sympatomimetics (in mothers with contractions)	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
44. Nifedipine (all mothers)	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
45. MgSO4 (in mothers with pre-eclampsia/HELLP)	◯ Rarely or never (0-10%) ◯ Quite rarely (11-40%) ◯ Sometimes (41-60%) ◯ Often (61-90%) ◯ Routinely (91-100%)
46. Who are involved in the decision to transfer?	☐ Level 2 on-call obstetrics/gynaecology physician ☐ Level 2 obstetrics/gynaecology consultant ☐ Level 2 on-call paediatrician/neonatologist ☐ Level 3 obstetrician ☐ Level 3 neonatologist
Comments	_____

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Patient cases

Case 1: preterm labour
30-year woman, < 32 weeks gestation. PROM 1 hour ago at home. Cervix is soft and the patient is having contractions. Beds and staff available at both level 2 and level 3 hospital (150km away). Ambulance and escorting staff are arranged within 30 minutes. Mother is well and CTG normal.

Case 1. Gestational week limits for antenatal transfer, e.g. 22+5 to 31+6	_____
Case 1. Does the decision change in case of a twin pregnancy; if so, how?	_____

Case 1. At what thresholds of the following clinical signs would you consider antenatal transfer contraindicated?

Case 1. Cervical opening	◯ 0-2 cm ◯ 3-4 cm ◯ 5-6 cm ◯ 7-8 cm ◯ 9-10 cm ◯ Not a contraindication
Case 1. Frequency of contractions (excluding Braxton-Hicks-type)	◯ < 5min ◯ About 10min ◯ About 15min ◯ Other ◯ Not a contraindication ◯ A mother with contractions is not referred
Case 1: Other	_____
Case 1: Comments	_____

Case 2: preterm labour, long distance
30-year woman, < 32 weeks gestation. PROM 1 hour ago at home. Cervix is soft and the patient is having contractions. Beds and staff available at both level 2 and level 3 hospital (300km away). Ambulance and escorting staff are arranged within 30 minutes. Mother is well and CTG normal.

Case 2. Gestational week limits for antenatal transfer, e.g. 22+5 to 31+6	_____
Case 2. Does the decision change in case of a twin pregnancy; if so, how?	_____

Case 2. At what thresholds of the following clinical signs would you consider antenatal transfer contraindicated?	
Case 2. Cervical opening	◯ 0-2 cm ◯ 3-4 cm ◯ 5-6 cm ◯ 7-8 cm ◯ 9-10 cm ◯ Not a contraindiaction
Case 2. Frequency of contractions (excluding Braxton-Hicks-type)	◯ < 5min ◯ About 10min ◯ About 15min ◯ Other ◯ Not a contraindication ◯ A mother with contractions is not referred
Case 2: Other	_____
Case 2: Comments	_____

Case 3: Pre-eclampsia **30-year mother, < 32 weeks. Membranes intact, cervix normal. Developing signs of pre-eclampsia, elevated BP, lab tests show developing HELLP and mother suffers from headache, nausea and has clonic patellar reflexes. Mother cannot get up from bed even with help. No contractions. Very little fetal growth over the past month, but fetus otherwise well. Mother has received betamethasone twice during the past 48 hours. Both level 2 and level 3 hospital can admit baby and mother. Ambulance and escorting personnel are available within 30 minutes.**	
Case 3. Gestational week limits for antenatal transfer, e.g. 22+5 to 31+6	_____
Case 3. Does the decision change in case of a twin pregnancy; if so, how?	_____
Case 3. Comments	_____

Case 4. Preterm labour, cervical insuficciency **30-year old mother, < 32 weeks. Previously precipitate delivery at 28 weeks. Cervical cerclage applied for cervical insufficiency. Cervix is softened, cerclage in place, mother has contractions. Fetal status reassuring. Both level 2 and level 3 hospital can admit baby and mother. Ambulance and escorting personnel are available within 30 minutes.**	
Case 4. Gestational week limits for antenatal transfer, e.g. 22+5 to 31+6	_____

Case 4. Does the decision change in case of a twin pregnancy; if so, how?	_____

Case 4. At what thresholds of the following clinical signs would you consider antenatal transfer contraindicated?

Case 4. Frequency of contractions (excluding Braxton-Hicks-type)	◯ < 5min ◯ About 10min ◯ About 15min ◯ Other ◯ Not a contraindication ◯ A mother with contractions is not referred
Case 4. Other	_____
Case 4. Comments	_____

Case 5. Preterm labour, PPROM, chorioamnionitis

30-year old mother, < 32 weeks. PPROM 3 weeks earlier. GBS positive, mother has received antibiotics and full antenatal corticosteroid course. Mother is otherwise well, but has a fever of 38,6C, CRP is 80. Cervix is softened and she has contractions. Both level 2 and level 3 hospital can admit baby and mother. Ambulance and escorting personnel are available within 30 minutes.

Not relevant; mother has been referred already 3 weeks ago due to PPROM	◯
Case 5. Gestational week limits for antenatal transfer, e.g. 22+5 to 31+6	_____
Case 5. Does the decision change in case of a twin pregnancy; if so, how?	_____

Case 5. At what thresholds of the following clinical signs would you consider antenatal transfer contraindicated?

Case 5. CTG	☐ Normal ☐ Tachycardic ☐ Monotonous ☐ Pathological
Case 5. Cervical opening	◯ 0-2 cm ◯ 3-4 cm ◯ 5-6 cm ◯ 7-8 cm ◯ 9-10 cm ◯ Not a contraindication

Case 5. Frequency of contractions (excluding Braxton-Hicks-type)	◯ < 5min ◯ About 10min ◯ About 15min ◯ Other ◯ Not a contraindication ◯ A mother with contractions is not referred
Case 5. Other	_____
Case 5. Comments	_____

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