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IMMEDIATE SKIN-TO-SKIN CONTACT FOR VERY PRETERM AND LOW BIRTH WEIGHT INFANTS

FROM NEWBORN PHYSIOLOGY TO MORTALITY REDUCTION

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Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-656-0
Cover illustration: Rebecka Lagercrantz

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Agnes Linnér

The thesis will be defended in public at Rehabsalen, Norrbacka, Karolinska University Hospital, June 10 2022 at 9.00 a.m.

https://ki-se.zoom.us/j/67683547260

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"There is no such thing as a baby, there is a baby and someone."

-Donald Winnicott

POPULAR SCIENCE SUMMARY OF THE THESIS

Some babies are born too small or too soon. In this thesis, born too small refers to a birth weight below 2.5 kg and too soon to birth more than two months early. Small babies need special care to survive and thrive, for example external heat to keep a normal body temperature. They need supplementary feeds before they learn how to breastfeed, and some small babies need breathing support. The proportion of babies born too small is low in high-income countries such as Sweden, whereas it is much higher in low- and middle-income countries. There are considerable differences between newborn care and the resources dedicated to this in high- versus low- and middle-income countries. Consequently, the chances of survival are much lower for babies born too small in low- and middle-income countries.

A method of care that has been studied during the past decades is Kangaroo mother care (KMC). KMC is a package of interventions including skin-to-skin contact (SSC) between the small baby and the mother, breast milk feeds and early discharge from the hospital to be followed up at home. KMC and SSC are terms often used synonymously in reports, but SSC refers to the baby placed naked on the parent's chest. Research evaluating the impact of SSC has shown that SSC leads to a better temperature, more breastfeeding, better bonding between the baby and the parent, fewer infections and even better survival. In low- and middle-income countries, SSC is usually not allowed during the first days if the baby needs oxygen, medicines or drips, but is initiated later on when the baby is stable but not yet feeding and growing well enough to be sent home. In Sweden, SSC is often practiced intermittently in the newborn unit.

The aim of my thesis was to find out more about the effects of SSC on babies born too small or too soon when it is started directly after birth instead of after some days or weeks. Especially, we wanted to know if the baby's temperature (study I), heart rate, respiratory rate and oxygen saturation (study II and V) were different during SSC compared to during care in an incubator or bed. We also wanted to find out how soon after birth SSC is started for babies born too soon in Sweden and how many hours per day they spend in SSC (study III). Most importantly, knowing that most small babies who die in low-income settings die within the first days of life, we wanted to find out if even more deaths can be prevented if SSC is started directly after birth in parallel to the medical care (study IV). Studies I-III were done in high-income countries; Norway and Sweden, and studies IV-V were done in low- and lower middle-income countries; Ghana, India, Malawi, Nigeria and Tanzania.

In study I, we found that in Sweden, babies born too soon who are cared for in SSC from birth have somewhat lower temperatures compared to those cared for in incubator. This was the opposite of what we had previously learned about SSC but we concluded that the difference was small and that SSC is safe in this aspect.

In study II, babies in SSC during the first six hours in Sweden had more optimal heart rate and breathing parameters. This was important because if babies are more stable, it is more likely that they can be left undisturbed with their parents and kept from stressful interventions.

SSC is an essential component of the care in Swedish neonatal units. Study III, however, showed that we started SSC after half a day for babies born two to three months early and after more than three days for babies born three to four months early. Further, these first days, babies born too soon only got a couple of hours of SSC.

Study IV showed that earlier KMC could reduce deaths in small babies during the first month in life by a quarter. Considering the number of babies that die worldwide, this could mean a very large number of saved lives.

Study V showed that there was no difference in heart rate, respiratory rate or oxygen saturation between small babies in KMC and control care during the first four days. We concluded that KMC immediately after birth can safely be implemented in small babies.

ABSTRACT

There is a contrast between the incidence of low birth weight and the contents and outcomes of neonatal care in high- versus middle- and low-income countries. Most of the neonatal deaths worldwide are attributed to low birth weight, occur within the first three postnatal days and can be prevented without intensive care.

There are many benefits of skin-to-skin contact when initiated as per today's recommendations, after an infant has become stable. Intermittent skin-to-skin contact is a component of neonatal care in Sweden. There is a knowledge gap concerning the effects of skin-to-skin contact initiated immediately after birth in unstable newborn very preterm and low birth weight infants.

The overall aim of this thesis was to fill the knowledge gap on the effects of skin-to-skin contact initiated immediately after birth in unstable very preterm and low birth weight infants in high- as well as in low- and middle-income countries. More specifically, the aims were to investigate the cardiorespiratory effects and the effect on mortality.

The five studies in this thesis derive from three randomised clinical trials comparing care in skin-to-skin contact immediately after birth with conventional care for very preterm or low birth weight infants, and from one register study. Studies I and II involved very preterm infants in Scandinavia, where study I (n=55) investigated the effect on infant temperature at one postnatal hour and study II (n=91) infant cardiorespiratory parameters during the first six postnatal hours. Study III (n=1475) reported on skin-to-skin contact initiation time and daily duration as per the Swedish Neonatal Quality Register. Study IV (n=3211) was a trial on the effect on neonatal mortality in low birth weight infants in Ghana, India, Malawi, Nigeria and Tanzania. Study V described the cardiorespiratory parameters during the first four days in the infants enrolled in study IV.

Study I found that infants in skin-to-skin contact had 0.3°C lower temperature at one postnatal hour and study II that they had 0.52 points higher stability on a six-graded scale during the first six postnatal hours. Study III found that currently in Sweden, we initiate skin-to-skin contact for very preterm infants after half a day and daily durations of skin-to-skin contact amount to five hours during the stay in the neonatal unit. Study IV found 25% reduced neonatal mortality in low birth weight infants exposed to immediate and continuous skin-to-skin contact. Study V found similar cardiorespiratory parameters during the first four days of life in the two allocations of the cohort of study IV.

There were benefits of skin-to-skin contact initiated immediately after birth, in terms of cardiorespiratory stabilisation in very preterm infants in high-income countries and mortality reduction in low birth weight infants in low- and middle-income countries. Skin-to-skin contact immediately after birth was not part of the conventional care. Data were collected during different postnatal time periods in the studies and were thus not comparable in detail.

Mother-neonatal intensive care units should be available where low birth weight infants are born and skin-to-skin contact integrated into the neonatal medical care. Future research should focus on risks and scale-up.

LIST OF SCIENTIFIC PAPERS

I. Linner A, Klemming S, Sundberg B, Lilliesköld S, Westrup B, Jonas W, Skiöld B. Immediate skin-to-skin contact is feasible for very preterm infants but thermal control remains a challenge. *Acta Paediatrica 2020;109(4):697-704. doi: 10.1111/apa.15062*

II. Linnér A, Lode Kolz K, Klemming S, Bergman NJ, Lilliesköld S, Markhus Pike H, Rettedal S, Westrup B, Jonas W. Immediate skin-to-skin contact may have beneficial effects on cardiorespiratory stabilisation in very preterm infants. *Acta Paediatrica 2022;00:1-8. doi:10.1111/apa.16371*

III. Linnér A, Lilliesköld S, Jonas W, Skiöld B. Initiation and duration of skin-to-skin contact for extremely and very preterm infants: A register study. *Submitted manuscript*

IV. WHO immediate KMC study group. Immediate "Kangaroo mother care" and survival of infants with low birth weight. *New England Journal of Medicine 2021;384(21):2028–2038. doi:10.1056/NEJMoa2026486*

V. Linnér A, Westrup B, Rettedal S, Kawaza K, Naburi N, Newton S, Morgan B, Chellani H, Arya S, Samuel V, Adejuyigbe E, Wireko Brobby NA, Boakye-Yiadom AP, Gadama L, Assenga E, Ngarina M, Rao S, Bahl R, Bergman NJ. Cardiorespiratory stabilisation in the "Immediate Kangaroo mother care study": Post hoc analyses of a randomised clinical trial. *Manuscript*

ASSOCIATED PROTOCOL PAPERS

A. Linnér A, Westrup B, Lode Kolz K, Klemming S, Lilliesköld S, Markhus Pike H, Morgan B, Bergman NJ, Rettedal S, Jonas W. The Immediate parent-infant skin-to-skin study (IPISTOSS): Study protocol of a randomised controlled trial on very preterm infants cared for in skin-to-skin contact immediately after birth and some physiological, epigenetic, psychological and neurodevelopmental consequences. *BMJ Open 2020;10(7):e038938. doi:10.1136/bmjopen-2020-038938*

B. WHO immediate KMC study group. Impact of continuous Kangaroo mother care initiated immediately after birth (iKMC) on survival of newborns with birth weight between 1.0 to < 1.8 kg: study protocol for a randomized controlled trial. *Trials. 2020;21(1):280. doi:10.1186/s13063-020-4101-1*

CONTENTS

LIST OF ABBREVIATIONS

BW	birth weight
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPAP	continuous positive airway pressure
DAG	direct acyclic graph
DSMB	data safety and monitoring board
EPT	extremely preterm infant
FiO2	fraction of inspired oxygen
GA	gestational age
GCP	Good Clinical Practice
HFNC	high flow nasal cannula
HIC	high-income country
IFCDC	infant- and family-centred developmental care
iKMC	immediate Kangaroo mother care
iSSC	immediate skin-to-skin contact
IQR	interquartile range
KMC	Kangaroo mother care
LBW	low birth weight
LMIC	low- and middle-income countries
MIC	middle-income country
MNCC	mother-newborn couplet care
M-NICU	mother-neonatal intensive care unit
MV	mechanical ventilation
NICU	neonatal intensive care unit
NIDCAP	Newborn Individualized Developmental Care and Assessment Program
PT	preterm
RCT	randomised clinical trial
SCRIP	Stability of the cardiorespiratory system in the preterm
SD	standard deviation
SE	standard error
SNQ	Swedish Neonatal Quality Register
SSC	skin-to-skin contact

SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TIDieR	Template for Intervention Description and Replication
UNICEF	United Nations International Child Emergency Fund
VLBW	very low birth weight
VPT	very preterm
WHO	World Health Organization

1 BACKGROUND

1.1 PREMATURITY AND LOW BIRTH WEIGHT

1.1.1 Definitions and epidemiology

The definition of preterm birth is birth before 37 completed weeks of gestation. Birth before 28 gestational weeks is classified as extremely preterm (EPT), before 32 weeks as very preterm (VPT) and before 37 weeks as moderately preterm. Low birth weight (LBW) refers to birth weight below 2.5 kg and very low birth weight (VLBW) is birth weight below 1.5 kg. LBW can be attributed to prematurity but also to intra-uterine growth restriction in term infants, which is more common in low- and middle-income countries (LMIC).

About 20 million children are born LBW yearly, which amounts to 15% of all births (1). Global preterm birth rates vary between 6% in Sweden (2) and the United Kingdom (3), 10% in the United States (4) and with the highest rate at 18% in Malawi (5). Preterm births are thus unevenly distributed with the 60% occurring in South Asia and Sub-Saharan Africa (6). In all, 80% of preterm births are moderately preterm (6).

1.1.2 Causes

Preterm birth can be induced or spontaneous (7). Conditions leading to induction of preterm birth can be maternal, foetal or a combination of both. When a woman has preeclampsia, the pregnancy may need to be ended for the safety of the mother but preeclampsia can also lead to foetal risks related to placental insufficiency and consequently intra-uterine growth restriction or foetal hypoxia. Spontaneous onset of preterm labour may be caused by a maternal infection, such as chorioamnionitis, by cervical insufficiency or by the more or less emergent complete or partial abruptio placentae. Hence, the mechanisms behind preterm birth can be inflammatory, mechanical, vascular or neuroendocrine. Genetic and socioeconomic factors also affect the risk of preterm birth.

1.1.3 Mortality and morbidity

In 2020, 2.4 million infants died during the neonatal period, defined as the first 28 days of life (8). This translates to a global neonatal mortality rate of 17 per 1000 live born and half of all under-five child deaths. Of these deaths, a third is attributed to preterm birth (9) and 80% to LBW (10). The denominator in these calculations is facility-based births and it should be acknowledged that some infants are born and die at home.

Globally, the cut-off for when a birth is considered a miscarriage or a preterm birth varies between 22 and 28 gestational weeks. The chance of survival at birth before 28 weeks of gestation varies greatly from 10% in LMICs to 90% in high-income countries (HIC) (6). An infant born at 34 weeks has a 50% chance of survival in a LMIC whereas an infant born at 24 weeks in a HIC has a 50% chance of survival with neonatal intensive care (6). Of prematurity related neonatal deaths, 47% occur during the first day of life and 70% during the first three days (11). The main contributors to prematurity related deaths are hypothermia, hypoglycaemia and sepsis (9).

In addition to the increased risk of mortality, LBW and preterm infants are also at risk of acute and chronic morbidity and contribute to the burden of non-communicable diseases such as cardiovascular disease (5). The risk of neurodevelopmental delay is higher in children and adolescents born preterm or LBW (12, 13).

1.2 NEWBORN PHYSIOLOGY

1.2.1 Transitioning from foetal to extra-uterine life: The Golden Hour

The first minutes and hours after birth is a dynamic period when the newborn infant needs to transition from intra-uterine life with oxygenation via the placenta and a high pulmonary vascular resistance to extra-uterine life with lung aeration and a decreasing pulmonary resistance (14). The concept the "Golden Hour" derives from emergency medicine (15) and is applied to a wide range of specialities including neonatology (16, 17). It stresses the importance of planning and delivering the right care early, to improve short- and long-term outcomes. During the Golden Hour, it is important that the newborn infant has the optimal environment for doing the transition (16). The preterm infant faces an increased risk of disturbances of the transition, because the lungs and other organs are immature. In addition, labour prepares the infant for birth under normal circumstances and a higher proportion of preterm infants are born by Caesarean section.

Management of the preterm infant immediately after birth includes respiratory support, thermal support and measures to maintain normoglycaemia (16). It has been emphasised that supporting the transition is a more appropriate terminology than performing resuscitation (18), because preterm infants do have resources to adapt to the new environment, if given the right conditions.

The Apgar score is a composite score taking into account the heart rate, respiratory effort, tone, reflex irritability and skin colour of the infant. Each parameter is graded zero to two and the newborn infant is assessed at one, five and ten minutes after birth. The score is used to aid in decision making in terms of continued observation, support and treatment (19). The role of the Apgar score in assessing preterm infants has been questioned owing to their lower muscle tone and other breathing pattern, explained by immaturity rather than illness (20). Low Apgar scores, however, predicted death across gestational ages (GA) in a study based on the Swedish Medical Birth Register (21). Hence, the Apgar score is used to describe the cardiorespiratory and neurological state of the infant during the first ten minutes after birth.

1.2.2 Oxygen saturation

The foetus has an oxygen saturation of 60% or even lower during labour (22). Preterm infants reach an oxygen saturation of 90% at eight postnatal minutes on average, which is slightly later than their term equivalents, according to a report by Dawson et al. (22). Guidelines state that the newborn infant, independent of GA, should reach an oxygen saturation over 90% at ten minutes after birth (23, 24). Hypoxia is associated with a vicious circle involving persistent pulmonary hypertension. A target range of 90-94% for newborn infants with supplementary oxygen and 90-100% with no respiratory support is recommended as a compromise between the negative effects of hypoxia in terms of increased mortality and risk of necrotising enterocolitis, versus the toxic effects of oxygen contributing to the

development of retinopathy of prematurity (25). Recommendations are to support the preterm infant with continuous positive airway pressure (CPAP) in order to recruit the lung volumes, which will lead to a decrease in pulmonary vascular resistance and improved oxygenation (18). Room air or 30% oxygen should be used initially, titrated to reach the above target ranges. Most infants with mild respiratory distress syndrome adapt with non-invasive respiratory support, but those with increased work of breathing and/or high fraction of inspired oxygen (FiO2) may need intra-tracheal instillation of surfactant followed by either extubation or continued invasive ventilation. Criteria for surfactant administration vary across GAs.

1.2.3 Heart rate

Paediatric reference values for heart rates have been presented in a systemic review where prematurity was an exclusion criterion (26). The normal range for heart rate was 123 to 164 beats per minute in term infants. Common features of preterm infants are that they display bradycardias as a sign of their immature central breathing control, that they may have a higher heart rate at rest and that heart rate varies greatly with the state and condition of the infant. Heart rate variability refers to the variance in inter-beat intervals and is under the influence of the parasympathetic nervous system and circulating hormones (27). Newborn infants have greater heart rate variability than older children and adults, owing to a different autonomic regulation.

1.2.4 Respiratory rate

Breathing may be a challenge for EPT and VPT infants due to surfactant deficiency, impaired lung liquid clearance at birth and poor respiratory drive (28). The normal range for respiratory rate in term infants was 34 to 57 breaths per minute according to a systematic review (26). This range is frequently approximated to 40 to 60 breaths per minute and used as reference values also for preterm infants. Preterm infants are at risk of respiratory distress syndrome where a common symptom is tachypnoea. They may also experience apnoeas of prematurity consequently presenting as bradypnoea. Hence, the respiratory rate in the preterm infant is a sensitive marker of instability or underlying morbidity.

1.2.5 Temperature

Normothermia is defined by the World Health Organization (WHO) as temperature 36.5°C to 37.5°C (29) and this is the target temperature according to European resuscitation guidelines (24). However, there is a grey-zone at the lower boundary and hypothermia is often defined as temperature under 36.0°C, because of the relation between low temperature and adverse outcome (30). The newborn infant, especially if preterm, is dependent on the ambient temperature and will quickly drop in body temperature by means of evaporation, radiation, convection and conduction (31). Preterm and LBW infants are at risk of hypothermia because of their body composition with a high body surface-to-weight ratio, their thin skin with little subcutaneous fat and no brown fat stores. Moreover, the immature nervous system and consequently the immature, extended posture leads to exposure of large surfaces of the body, unless supported. VLBW infants can be placed in a plastic wrapper initially for conservation of heat and humidity and are placed in an incubator for thermal support, with SSC as an

alternative for example where incubators are not available (32). Temperature and humidity settings of the incubator depend on the infant's GA and are usually weaned during the first postnatal days to weeks before transferring the infant from the incubator to a cot (33).

Hypothermia is associated with some of the transitional disturbances that are commonly seen in the neonatal intensive care unit (NICU); transient tachypnoea, persistent pulmonary hypertension and hypoglycaemia (34), with later morbidities and even mortality (35-37). Hypothermia in the newborn infant at admission to the NICU is associated with 28% increased odds of mortality before discharge and 11% increased risk of late sepsis for every 1°C decrease in admission temperature (30). This emphasises the importance of maintaining normothermia in the newborn infant, even if reversed causality may be involved in the above associations.

Temperature can be measured intermittently or continuously. Rectal temperatures reflect the core temperature well, but axillary temperature is less invasive and is considered a good enough estimate of the infant's core temperature. A skin probe placed on the trunk is an alternative to continuous measurement (32).

1.3 STRATEGIES TO IMPROVE NEWBORN HEALTH AND SURVIVAL

The third of the United Nations 17 Sustainable Development Goals is to ensure healthy lives and promote wellbeing for all at all ages (38). Target 3.2 is to end all preventable deaths, aiming at fewer than 25 under-five deaths per 1000 live born and fewer than 12 neonatal deaths per 1000 live borns by the year 2030. Neonatal mortality has decreased by 50% during the past two decades, but it has been estimated that the future decrease will be slower and that it will take another two decades to reach Sustainable Development Goal 3.2 in some regions of the world.

1.3.1 Obstetric care

Causes of preterm birth involve chronic diseases and infections in the mother and pregnancy related conditions such as preeclampsia (39). Nutritional status contributes to the overall health of the pregnant woman (40). Maternal and infant health are closely correlated and poor maternal health contributes to a large proportion of induced and spontaneous preterm births. Neonatal mortality can therefore to a large extent be prevented by actions to improve maternal health. Such actions may be the prevention and treatment of infections, diabetes and high blood pressure and improved nutrition; pre-conception and throughout pregnancy. Family planning; postponing the first pregnancy and birth spacing, also plays an important part in maternal and infant health.

A challenge in maternal and infant health was previously poor *access* to healthcare whereas there has now been a shift in focus to the poor *quality of care,* including lack of trained staff and material resources. An example is the proportion of women giving birth in a hospital versus the proportion of births attended by skilled birth attendants (41). Limited and unpredictable access to medication and equipment is also a main issue (42).

1.3.2 Antenatal corticosteroids

Antenatal corticosteroids prepare the preterm infant for extra-uterine life and should be given as a single course including two doses with a 24-hour interval, the last administered at least 24 hours before birth, prior to birth before 34 gestational weeks (43). Antenatal corticosteroid treatment has improved pulmonary outcomes in EPT and VPT infants (44) and chances for healthy survival are considerably higher if inborn at an appropriate level of care and after antenatal corticosteroids (45). The epidemiological effect of antenatal corticosteroids, however, depends on the setting. A large trial in LMICs found no effect to even increased mortality after unselective administration of antenatal corticosteroids before threatening preterm birth (46, 47). The WHO recommends antenatal corticosteroids with safe dosing at risk of preterm birth within a week, between 24 and 34 weeks, when there is no maternal infection and when the infant can receive adequate postnatal care including thermal care, management of respiratory distress syndrome and treatment for infections (48).

1.3.3 Delayed cord clamping

Standard practice has been to cut the cord immediately after birth, to enable postnatal stabilisation of the preterm or LBW infant and transfer to the NICU. However, in the minutes after birth there is still a large volume of blood in the placenta that continues to flow to the infant through the umbilical cord. Current recommendations are to delay cord clamping, as this is associated with a 27% decrease in mortality before discharge in the preterm population, among other benefits (49). The optimal time for cord clamping remains to be stated, but there is evidence for waiting at least 30 seconds after birth.

1.3.4 Basic resuscitation

Of all newborn infants, 3-6% need assisted ventilation after birth but less than a quarter of infants who need ventilation receive this (50). Of full-term deaths, 30% are due to complications at birth. Training staff in neonatal resuscitation can prevent 5-10% of prematurity related deaths. Helping Babies Breathe is an evidence-based programme to teach neonatal resuscitation in LMICs, initiated by the American Academy of Pediatrics together with a number of global health stakeholders including the WHO and the United Nations International Child Emergency Fund (UNICEF). The key message of the programme is that the newborn infant should be ventilated within the first minute after birth, unless breathing spontaneously (51). Laryngeal mask ventilation has been shown to be safe but not superior to face mask ventilation in terms of death or moderate to severe hypoxic ischemic encephalopathy (52).

1.3.5 Newborn health packages

It has been estimated that 75% of preterm deaths can be prevented without neonatal intensive care (40). A newborn minimal health care package includes thermal control, early breastfeeding support and hand disinfection (53). The Every Newborn Action Plan is a platform for the reduction of preventable intra-uterine and newborn deaths (54), based on the evidence presented in the Lancet Neonatal Survival (55-58) and Every Newborn (10, 39, 59-61) series. The work is steered by a partnership between multiple stakeholders in the field of maternal and newborn health, led by the WHO and the UNICEF. Member states of the 67th

World Health Assembly agreed on the plan in 2014 and that progress would be reported back to the WHO Director General regularly until 2030. The goal is that 75% of newborns be resuscitated if needed and would receive supporting care including antibiotics, if needed. It was also stated that 50% of small newborns should receive Kangaroo mother care (KMC) by 2020 and 75% by 2025.

NEST360 is an international alliance of public health, clinical and technical experts who work with policy making, technology, education and toolkits applicable in neonatal care (62). The goal is set at halving neonatal deaths in African hospitals by 2030. This will be done by increasing the quality of care in areas involving respiratory support, prevention and control of infections, thermal control, management of jaundice, diagnostics, hydration, nutrition and pharmaceuticals.

1.4 PRETERM CARE IN SWEDEN

1.4.1 Epidemiology

The preterm birth rate in Sweden has remained relatively constant at 6% during the past decades (2). In 2020, 0.9% were born VPT, corresponding to almost 1000 VPT infants (2). The mortality in EPT and VPT infants has been decreasing slightly during the past years (63, 64). During 1992-2016, neonatal mortality ranged from 27/1000 at 31 to 61/1000 at 28 gestational weeks in Sweden. This corresponded to risk ratios of death of ten to 24 compared to term infants (21). The decrease in mortality in VPT infants in HICs during the past decades is mainly attributed to an increase in use of antenatal corticosteroids and to improvements in neonatal intensive care such as the introduction of surfactant therapy for respiratory distress syndrome and the use of caffeine for apnoeas of prematurity (65).

In VPT infants, late sepsis, bronchopulmonary dysplasia, necrotising enterocolitis and severe intraventricular haemorrhage (grade 3-4) occur in 3.5%, 9%, 1.3% and 2.5%, respectively (45). Early morbidities in the preterm infant may lead to long-term sequelae due to immature and vulnerable organs. Neurodevelopmental sequelae such as autism spectrum disorders, attention deficit and hyperactivity disorder and cognitive problems are diagnosed later in childhood and contribute to the burden of VPT birth (66). Despite the decrease in mortality, cognitive outcomes after VPT birth have not improved during the past decades (67).

1.4.2 The care

1.4.2.1 Regionalisation

Neonatal care in Sweden is organised in six regions, each with at least one referral level 3 unit (45). Level 1 neonatal units care for term and moderately preterm newborn infants without respiratory support, whereas level 2 units care for VPT and more mature infants in need of non-invasive respiratory support. Level 3 units deliver care of EPT infants and above, including intensive care with invasive ventilation for all GAs. In addition to the care delivered at level 3 units, level 4 units have surgical care including cardiology and/or extracorporeal membrane oxygenation. Antenatal transport to level 2 and level 3 neonatal units should be done, whenever safe for the woman, for women in risk of VPT and EPT birth.

1.4.2.2 Conventional preterm care

Preterm newborn infants need support of vital functions to different degrees, depending on the GA and the conditions preceding birth. For VPT infants, this may include respiratory support, thermal care, enteral and parenteral nutrition, phototherapy and antibiotics. There is an effort to deliver a minimally invasive care, knowing that VPT infants will need support to survive and thrive but that for example invasive ventilation is associated to a higher risk of bronchopulmonary dysplasia (18). The large majority of VPT infants in HICs receive non-invasive ventilation with CPAP, all receive gavage feeds in parallel to breastfeeding support and most get a proportion of their nutritional demands via parenteral nutrition during the first days. Some VPT infants, mainly those born before 30 gestational weeks, are provided with umbilical catheters for parenteral nutrition and blood sampling during the first week.

1.4.2.3 Family-centred care

Infant- and family-centred developmental care (IFCDC) (68) is implemented throughout Scandinavia based on the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (69). It strives to deliver neuroprotective care with the best possible neurodevelopmental and psychosocial outcomes in mind. Parents are supported to gradually take on the role as primary caregivers and are well-informed on their infant's medical and nursing needs (70). In most NICUs, parents stay with their infant throughout the hospital stay, during which time they are supported financially by the national parental insurance system. Intermittent skin-to-skin contact (SSC) is an essential component of the conventional care of VPT infants.

1.4.2.4 The national neonatal follow-up programme

In order to identify children in need of support, there is a national neonatal follow-up programme in Sweden. This consists of clinical assessments of VPT infants by a neonatologist, a neonatal nurse and a physiotherapist at corrected ages full term, three and 12 months. For EPT infants and infants with additional risks such as birth asphyxia treated with therapeutic hypothermia, cerebral insults and severe intra-uterine growth restriction, there are also assessments by a neonatologist, neonatal nurse, physiotherapist and psychologist at 24 months and 5.5 years (71). An additional purpose of the follow-up programme is to keep a register for quality improvement. In-hospital and follow-up data from neonatal care are reported to the Swedish Neonatal Quality Register (SNQ), which has a high coverage and validity (72).

1.5 SKIN-TO-SKIN CONTACT

SSC refers to the infant being provided care in SSC with a parent. KMC, or Kangaroo care when acknowledging the role of the father or a relative (73), and SSC are often erroneously used as synonyms. KMC by definition refers to the care of the LBW infant in continuous SSC with the mother, support for breastfeeding or breast milk feeding and early discharge from hospital to home with follow-up (74). The rationale behind SSC is that it is considered to be the natural, least stressful way of caring for the newborn infant in non-separation from the mother after birth (75). Current WHO recommendations are that all stable infants with a birth weight above 1200 grams should be cared for in KMC (74). There are no uniform

criteria for when an infant is considered stable, hence this varies between settings. In the international literature stable commonly means when an infant no longer needs respiratory support, intravenous fluids or medicines and is able to feed by mouth (76). Consequently, it may take days or weeks before an infant is eligible for KMC. KMC units are generally seen as step-down units for well LBW infants who need to feed and grow, bridging the care in the NICU and discharge to home. The reasons for postponing KMC are both infant concerns and practical aspects, the main practical aspect being space issues in the clinic. In busy units infants frequently share beds and there is no or very limited room for parents. In NICUs in HICs, intermittent SSC has become part of the conventional care (77). The focus of recent studies include early initiation of SSC (78), implementation and scale-up (79) and follow-up (80).

KMC and SSC are used interchangeably in the literature. In this thesis, the term SSC will be used to depict the care of the infant in SSC with a parent. The term KMC will refer to the above-mentioned bundle of interventions including continuous SSC and non-separation from the mother. When referring to publications, the terminology used in the citations will be kept, regardless of the authors' definitions of KMC.

Skin-to-skin contact: concepts	
Concept	**Definition**
Skin-to-skin contact	The care of the newborn infant in SSC with a parent or surrogate caregiver.
Kangaroo mother care	The care of the LBW or preterm infant in continuous SSC with the mother, breastfeeding support and early discharge with follow-up at home
Immediate skin-to-skin contact	SSC initiated immediately after birth
Immediate Kangaroo mother care	KMC initiated immediately after birth
Intermittent skin-to-skin contact	Sessions of SSC alternated with care in incubator or cot
Continuous skin-to-skin contact	SSC as the primary place of care, continued for 8-24 hours per day
Community initiated Kangaroo mother care	KMC initiated at home after early discharge from the hospital

Table 1: Core concepts involving skin-to-skin contact. SSC=skin-to-skin contact, LBW=low birth weight, KMC=Kangaroo mother care

1.5.1 The history of Kangaroo mother care

The Kangaroo method was first officially used in Colombia in the late 1970s as a way of keeping small infants warm in the absence of incubators (81), even if the method had likely been used by parents long before, striving for their LBW infants to survive and thrive. The Kangaroo position is the infant placed in a frog-like position, undressed, sternum to sternum on the parent's bare chest, wearing a diaper and sometimes a hat and socks, in order to gain as much warmth as possible from the parent (74). KMC was first described in a scientific paper in 1985 (82).

KMC and the Kangaroo position were introduced more formally at scientific meetings in the late 1990s along with clinical trials investigating its effects (83). During the period that followed, the benefits of KMC, or SSC, became more known and were summarised in systematic reviews (76). After this, in the 2010s, KMC reached the global agenda because of its potential to save a large number of newborn lives. Today, the main priorities involving KMC are earlier initiation, implementation and scale-up. The above phases of facility-based KMC implementation have been described as the pioneer phase, the newborn care phase and the scale-up phase (84).

1.5.2 Outcomes of skin-to-skin contact

There is evidence for KMC in stable LBW infants in LMICs in terms of increase in survival, thermal control, breastfeeding rates, growth, mother-infant attachment and a reduction in infections (76). Continuous KMC has shown greater benefits than intermittent KMC and early, defined as initiation within 24 hours of birth, seems to be better than late (76). Other studies confirm that KMC in unstable LBW infants is safe, but not superior to conventional places of care (85, 86). Community initiated KMC has been shown to reduce infant mortality at 6 months (87). The definition of KMC varies greatly between publications, frequently refers to the SSC only, and overall the coverage of KMC is low despite its benefits (73, 88).

The outcomes of SSC in LBW as well as in preterm and term infants have been studied to a lesser extent in HICs.

Below is a table with examples of outcomes of the above-mentioned topics. This table should be regarded as a selection of the published research and not as a complete review of the field. The literature on temperature and cardiorespiratory effects of SSC will be described more in detail in the next sections 1.5.3 and 1.5.4.

Examples of outcomes of skin-to-skin contact			
Area	**Setting**	**Population**	**Outcome**
Breastfeeding	LMIC, HIC	Term, PT, LBW	Higher proportion breastfed (76, 89, 90)
	HIC	PT	Earlier full breast milk feeds (91)
	HIC	PT	No difference in long-term breastfeeding outcomes (91)
	LMIC, HIC	PT	Longer breastfeeding duration (89, 92)
Growth	MIC	LBW	Better weekly mean head growth (93)
	MIC	LBW	Higher daily weight gain (94-96)
Bonding	MIC	Term	Better bonding at 1 year (97)
	HIC	PT	More mother-infant interaction at 6 months (98)
Sepsis	LMIC, HIC	PT and LBW	Lower risk of invasive infections (76, 90)
	HIC	Term, PT	No increased risk of sepsis with umbilical catheters (99)
Neuroendocrinology	MIC, HIC	Term	Reduces procedural pain (100)
	HIC	PT	Lower stress reactivity as per salivary cortisol levels at one month (101)
	HIC	Term, PT	Co-regulation of cortisol between the mother and infant (102, 103)
Epigenetics	HIC	PT	Early SSC modulates mRNA of stress related genes (104)
Neurodevelopment	MIC	LBW	Better cognition, persisting to young adulthood (105, 106)
	MIC	LBW	Larger grey matter, basal nuclei and cerebellar volumes in young adulthood (80)
	HIC	PT	Better self-regulation and sleep-cyclicity in childhood (107)
	HIC	PT	Better sleep organisation in childhood (108)
	HIC	PT	Brain connectivity in adolescence (109)
	HIC	PT	Better autonomic and neurobiological maturation (110)
	HIC	PT	Better psychological organisation in childhood (111)
SSC with partners	HIC	Term	Stable infant physiology (112)
	HIC	Term	Good infant behaviour (113)
	HIC	Term	Fathers keep infants warm (114)
Risks	HIC	Term	Sudden unexpected postnatal collapse in unsurveilled SSC (115, 116)
	HIC	PT	Risk of IVH in early SSC not confirmed (117)

Table 2: Examples of studies reporting on SSC and breastfeeding, growth, bonding, infections, neuroendocrinology, epigenetics, neurodevelopment, SSC with partners and the risks associated with SSC. SSC=skin-to-skin contact, LMIC=low- and middle-income country, HIC=high-income country, MIC=middle-income country, PT=preterm, LBW=low birth weight

1.5.3 Thermal control in skin-to-skin contact

In a Cochrane review, SSC was stated as one of the interventions to maintain normothermia in the newborn (32), relying on the finding of one study that infants with birth weights of 1.2 to 2.5 kg maintained normothermia better in SSC immediately after birth compared to in conventional care (118). Other studies have confirmed the superiority of SSC compared to conventional care in terms of thermal control in the LBW or VPT newborn infant (119-122). However, in these studies there has been heterogeneity in modes of providing thermal control in conventional care. A common feature has been that access to well-controlled incubators is rare. While thermal control in SSC is well described, concerns have been raised about fluid loss through evaporation when small newborn infants are cared for outside an incubator. A study on SSC in the birth room showed that the thermo-hygrometric environment is optimal during SSC for term infants (123), whereas this aspect has not been studied in the preterm population. A study investigating SSC for EPT infants during the first postnatal week in the NICU found that SSC helps maintain normothermia (124). To summarise, the literature describes positive effects of SSC on thermal control in LBW infants.

1.5.4 Cardiorespiratory stabilisation in skin-to-skin contact

SSC in preterm or LBW infants has traditionally been associated with a more stable heart rate and oxygen saturation (125, 126). Two studies described higher heart rates in VPT infants during SSC (127, 128). Studies investigating bradycardic events have been conflicting in that they have shown both a decrease in bradycardic events during SSC (27) and an increase (129). Heat stress was discussed as one of the explanatory factors behind bradycardias, but this hypothesis was later rejected by the same group (130). SSC is associated with lower respiratory rates (90), and the meta-analysis presented in the table below suggests a magnitude of 3.5 breaths per minute less (131). Searching for the mechanisms behind cardiorespiratory effects of SSC, a study found that the parental heart rate variance affected the infant respiratory inter-breath variance and hence respiratory control but that the mechanisms remain to be explored (132). Better cardiac output has been seen in SSC (126). With regards to the FiO2 in VLBW infants during SSC, reports are similarly conflicting and have described both lower (133) and higher (134) FiO2. Other studies report no differences in heart rate, respiratory rate or oxygen saturation during SSC (128). SSC reduced the work of breathing, decreased mean airway pressure and decreased back-up ventilation in a study involving mechanically ventilated VPT infants (135). It has been hypothesised a dose-response relationship between SSC and physiological outcomes, but a positive effect is indicated on VLBW infant physiology even with hour-long sessions of SSC (136).

Table 3 summarises the GA, birth weight, postnatal age, SSC duration and physiological parameter measured in the studies included in a meta-analysis by Cristóbal Canadas et al. (131).

Studies investigating physiological parameters in skin-to-skin contact								
Year	**Setting**	**Mean GA (weeks)**	**Mean BW (grams)**	**Postnatal age**	**SSC duration (min)**	**Parameter**	**Sample size**	**Reference**
1995	Canada	30	1225		30	HR, RR, sat, temp	61	Legault (137)
2003	Brazil	34	1740	11 days	60	HR, RR, sat, temp	23	Miltersteiner (138)
2004	USA	34	1941	15 days	180	HR, RR, sat, temp	24	Ludington-Hoe (122)
2005	India	34	1464	3 days	588	RR, sat	89	Kadam (139)
2010	Denmark	25	735	8 days	98	HR, RR, sat, temp	22	Maastrup (140)
2014	South Korea	30	1100	>32 corrected GA	30	HR, RR, sat, temp	34	Lee (141)
2014	USA	30	1393	2 weeks	41	HR, RR, sat, temp	11	Bloch-Salisbury (132)
2016	South Korea	29	1551	>33 corrected GA	30	HR, RR, sat, temp	40	Cho (142)
2017	Australia	28	969	8 days	90	HR, sat	40	Lorenz (143)
2018	Australia	31	1370	14 days	90	HR, sat	40	Lorenz (127)
2020	USA	32	1734	3 days	60	Temp	51	Forde (144)
2020	Turkey	31	1455	3 weeks	180	HR, RR, sat, temp	30	Özdel (145)

Table 3: Physiological parameters in skin-to-skin contact, adapted from Cristóbal Canadas 2022. GA=gestational age, BW= birth weight, HR=heart rate, RR=respiratory rate, sat=oxygen saturation, temp=body temperature

1.6 CLINICAL STUDIES

The frame of my thesis has thus far introduced the epidemiology and management of VPT and LBW infants, the physiology during the period of transition from foetal to newborn life and to the impact of SSC. In addition to the above topics investigated in my studies, my doctoral education has largely covered the methodology of planning and conducting randomised clinical trials (RCT).

Clinical studies are observational or interventional and their hierarchy in terms of the level of empirical evidence has traditionally been illustrated by a pyramid with RCTs second to the top, below meta-analyses (146).

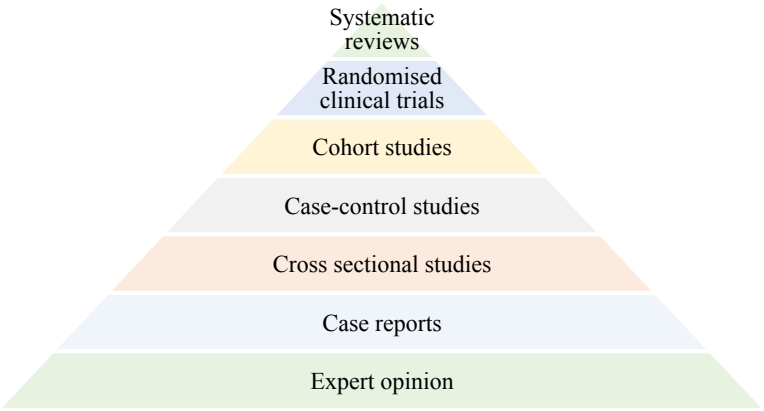


Figure 1: The level of evidence from clinical trials.

1.6.1 Study types

Observational studies are descriptive or analytical. Descriptive studies present the incidence or prevalence of a condition in a time, place or a population without a comparator. They can be hypothesis generating and lay the ground for further research. Register studies are an example where exposure and outcome are measured on a population level. Case reports are another example of descriptive studies. Analytical studies can be both observational and experimental, but in the observational form, examples are cohort and case-control studies. Cohort studies are longitudinal studies where the exposure is known for a population that is at risk of the outcome and followed over time. In case-control studies, the approach is the opposite; the outcome is known, and the cases and controls are assessed for the exposure. Hence, the strength of the cohort study is that it works well for studying rare exposures, whereas the case-control study is preferable when studying rare outcomes.

In experimental studies, subjects are actively exposed to an intervention and assessed for primary and secondary outcomes. They can be exposed to the intervention based on pre-specified indications or at random. Intervention when a certain indication is present may introduce a risk of confounding by indication, meaning that it is the indication and not the exposure that is correlated to the outcome. The RCT is a type of intervention study where individuals who meet inclusion criteria are randomised to the one of several treatment arms.

1.6.2 Randomised clinical trials

The RCT is a study design that has a high potential of providing knowledge on the relation between an intervention, or exposure, and an outcome (147). Given the smaller risk of confounding when covariables are equally distributed between allocations, effects inform on causal inference. RCTs risk being resource demanding due to the time between the exposure and outcome and because of loss to follow-up.

1.6.2.1 Designing a randomised clinical trial

Designing an RCT starts by formulating a hypothesis that the research question should be able to confirm or reject. A study *population* where the study subjects are at risk of the outcome is selected. Randomisation arms, or allocations, can be two or more and are defined as *intervention* and *control* or several different interventions. RCTs can be blinded or non-blinded. Blinding means that the allocation is unknown to one or more groups of people. Blinding in a single-blinded study refers to the study subject, in a double-blinded study to the study subject and the person delivering the intervention and in a triple-blinded study to the study subject, the person delivering the intervention and the person measuring the outcome. Analysis can be done either according to the intention to treat, the per protocol or the as treated principle. The intention to treat principle is considered the gold standard, meaning that study subjects are analysed according to their allocation regardless of if they received the intervention or not. This describes the real-world scenario, where the outcome on a group level is related to different doses of exposure, for example depending on compliance to a treatment. This provides information on the effectiveness of an intervention. Moreover, the intention to treat analysis keeps the advantages of randomisation. Per protocol analysis means analysing only the subjects receiving treatment according to their allocation. This is an alternate approach that describes the actual effect of a treatment and the situation in an ideal world; the efficacy of an intervention. A third approach is the as treated analysis, which means that the study subjects are analysed according to their actual treatment, regardless of allocation. With this approach, crossover between allocations is allowed and the advantages of the randomised design are lost.

Hypothesis testing and sample size calculation

In the hypothesis testing of a clinical trial, a null and an alternative hypothesis are formulated. These hypotheses are exclusive, meaning that one but not both are true. The probability of the null hypothesis to be true is the significance level, the alfa or the p-value of the test. A significance level of 5% means that the null hypothesis is rejected 5% of the times when the null hypothesis is true, corresponding to a Type I error, confirming a false hypothesis or a correlation by chance. The opposite, the probability of rejecting the null hypothesis when the alternative hypothesis is true, is the power or the beta of the test. A Type II error is the complement of the power or failure to confirm a true hypothesis. A power of 80% refers to the probability of confirming a true alternative hypothesis.

To calculate the sample size for a clinical trial, factors that need to be considered are the significance level, the power and the estimated effect size of an intervention or the difference between allocations. The standard deviation or the square root of the variance refers to the distribution of outcomes and has implications for the effect size. The lower the significance

level, the higher the power, the smaller the effect size and the larger the variance; the larger the sample size needs to be to make statistical inference of a correlation.

If multiple comparisons are made, for example when analysing several outcomes or conducting interim analyses, one needs to acknowledge that the false positive rate increases with the number of tests. Consequently, the significance levels of multiple comparisons are frequently set lower than at 5%. The pre-specified significance level for stopping a trial early should consider the number of sequential analyses planned and which order the current analysis is. Stopping rules frequently used are the O'Brien Fleming and the Haybittle-Peto guidelines, that use different statistical approaches to series of analyses (148).

Missing data

Data collected within a trial can be missing to different extents and according to different patterns; completely at random, at random or non-at random. Missing completely at random is rare. Missing at random refers to a randomness between missing non-at random and missing completely at random. Missing data needs to be accounted for, especially if it is non-at random, which means that the missingness may be related to the characteristics of the population. For example, missing data could be more frequent in study subjects with certain baseline characteristics or in one of the allocations. In this example, the results of the study risk being skewed and unrepresentative of the population. Strategies in handling missing data can be complete case analysis, marginal mean imputation, imputation of the most frequent response or the last observation carried forward.

1.6.3 Tools for reporting clinical trials

There are guidelines for reporting study protocols, interventions and clinical trials. The purpose is to increase the quality of the report by standardising the format. *The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)* guidelines is a tool for planning clinical trials and writing study protocols (149). The guideline includes trial registration, versions of protocols, funding, setting, eligibility criteria, consent procedures, exposure and outcome, participant timeline, sample size calculation, randomisation strategy, blinding, data collection and management, statistical analysis plan, monitoring, ethics and dissemination plan. *The Template for Intervention Description and Replication (TIDierR)* guidelines (150) is a specification of the intervention including the rationale, intervention provider, location, delivery, dose, modifications and adherence to an intervention. *The Consolidated Standards of Reporting Trials (CONSORT)* guidelines is a tool for reporting from RCTs (151), including a flow chart presenting the numbers assessed for eligibility, randomised, allocated and analysed with the numbers lost to follow-up at each level.

2 RESEARCH AIMS

The overall aim of my thesis was to fill the knowledge gap concerning the effects of SSC with a parent *immediately after birth* for *unstable* VPT or LBW infants *in need of medical support* compared to care in conventional places such as incubator or cot. The specific aims were to learn if SSC initiated immediately after birth:

- ✓ Is feasible in terms of thermal control
- ✓ Affects the cardiorespiratory stabilisation during the first hours to days of transitioning from foetal to newborn physiology
- ✓ Affects neonatal mortality

To set the above in context, we wanted to know to what extent SSC is practiced in Swedish NICUs.

3 METHODS

3.1 OVERVIEW OF STUDIES

Study (trial registration)	Design	Setting	Population	Primary outcome	Statistical analyses
I IPISTOSS temperature (NA)	RCT	HIC 2014-2016	55 infants born in Sweden at GA 28+0-33+6	Axillary temperature at 1 hour after birth	Descriptive statistics Student's t-test Spearman's correlation
II IPISTOSS SCRIP (ClinicalTrials NCT03521310)	RCT	HIC 2018-2021	91 infants born in Sweden and Norway at GA 28+0-32+6	Cardiorespiratory stabilisation according to SCRIP score during first 6 hours after birth	Descriptive statistics Student's t-test Mixed models multilevel linear regression
III SNQ SSC (NA)	Register study	HIC 2020-2021	1475 infants born in Sweden at GA 22+0-31+6	SSC initiation time SSC daily duration day 0, day 0-2, day 0-6 and during the remainder of hospital stay	Descriptive statistics Logistic regression Quantile regression
IV iKMC mortality (Australian-New Zealand Clinical Trials ACTRN12618001880235, Indian Clinical Trials CTRI/2018/08/015369)	RCT	LMIC 2017-2020	3211 infants born in Ghana, India, Malawi, Nigeria and Tanzania with BW 1.0-1.8 kg	Mortality at 72 hours and 28 days	Descriptive statistics Linear regression Logistic regression Cox regression
V iKMC cardiorespiration (Australian-New Zealand Clinical Trials ACTRN12618001880235, Indian Clinical Trials CTRI/2018/08/015369)	RCT	LMIC 2017-2020	3211 infants born in Ghana, India, Malawi, Nigeria and Tanzania with BW 1.0-1.8 kg	Heart rate, respiratory rate and oxygen saturation during day 0 to 3 Proportion with supplementary oxygen or CPAP Duration of CPAP	Descriptive statistics Student's t-test Mixed models multilevel linear regression Logistic regression Linear regression

Table 4: Overview of studies included in the thesis.

3.2 SETTINGS

3.2.1 High-income countries: Studies I, II and III

Studies I-III were conducted in the HICs Sweden and Norway. The neonatal mortality rate was 1.4/1000 in Sweden and 1.3/1000 in Norway in 2020, and these rates have been largely unchanged during the past ten years (152). The NICUs in Scandinavia are well equipped and nurse to patient ratios are relatively high at 1:2 to 1:5. The neonatal mortality in VPT infants was 37/1000 in 1992-2016 (21) and mortality before discharge in VPT infants was 17/1000 in 2011-19 (153). Intermittent SSC is part of the conventional care even during neonatal intensive care. There are rooms for parents to stay in the NICUs and there is a generous social security system enabling most parents to stay off work during the hospitalisation of their infant (154). The Immediate parent-infant skin-to-skin study (IPISTOSS) was the name of the Scandinavian RCTs: studies I and II.

3.2.1.1 Sweden

Karolinska University Hospital has three NICUs in Stockholm; in Danderyd, Huddinge and Solna. Danderyd is a level 2 NICU with 16 beds, serving a birth unit with 11000 yearly births. The profile is term and moderately preterm infants but a number of VPT infants are also born there. Huddinge is a level 3 NICU with 15 beds, serving a unit with 5000 births. The NICU in Solna serves about 4500 births per year but mainly admits EPT infants and newborn infants with surgical conditions and was therefore not included as a study site. Postulating that home is best for the family, there is a policy to transfer infants to neonatal homecare as soon as they are cardiorespiratory stable, maintain normothermia without external heat sources, take a proportion of feeds by mouth and have started gaining weight. Thus, as soon after a preterm infant has reached 34 gestational weeks and these criteria are met, breastfeeding support, gavage feeding and growing is continued in the home environment.

The neonatal department at Karolinska University Hospital has a NIDCAP training and research centre and infant- and family-centred developmental care is one of the first priorities. Guidelines state that infants born after 32 gestational weeks should be cared for in SSC as soon as possible after birth and can be transported from the birth room to the NICU in SSC with a parent. Infants born before 32 weeks should be stabilised and transported in an incubator and with SSC initiated as soon as possible when the medical condition allows (155).

3.2.1.2 Norway

The NICU at Stavanger University Hospital is a level 3 unit with 16 beds that serves a birth unit with 4400 births per year. The NICU admits infants born after 23 gestational weeks. The care is based on NIDCAP, SSC is part of the conventional care and parents are allowed in the NICU around the clock. Infants are discharged to home care after 35 gestational weeks if they are cardiorespiratory stable, maintain normothermia without external heat sources, take a

proportion of feeds by mouth and have started gaining weight. In Norway, 0.4% of all infants are born VPT.

3.2.2 Low- and middle-income countries: Studies IV and V

Studies IV-V derive from the Immediate Kangaroo mother care (iKMC) Study that was conducted in Ghana, India, Nigeria, Malawi and Tanzania. Malawi is a low-income country, Tanzania transitioned from a low- to a lower middle-income country in 2020 and Ghana, India and Nigeria are lower middle-income countries, by World Bank definition (156). Hence, the study sites were five heterogeneous NICUs in tertiary hospitals in one low-income and four lower middle-income countries. Acknowledging the differences and similarities, the settings in study IV and V are referred to as LMICs in this thesis.

The neonatal mortality rates are decreasing and in 2020 the rates were 23, 20, 36, 19 and 20 per 1000 live borns in Ghana, India, Malawi, Nigeria and Tanzania, respectively (152). The tertiary hospitals where the study was conducted are referral centres with large uptake areas and teaching hospitals with some experience of and infrastructure for clinical studies. Unit structure, resources, family support and guidelines vary between sites but in general mothers and newborn infants are cared for in different units with mothers being allowed in the NICU for feeds and fathers during visiting hours. All the units have KMC beds for LBW infants to feed and grow before being discharged home. The mortality rates stated for each site below refer to mortality before discharge in the study population as per hospital registers during the planning phase of the study in 2015-17.

3.2.2.1 Ghana

Komfo Anokye Teaching hospital in Kumasi has a decreasing number of births that was about 4000 per year when the study was conducted. The NICU has 130 neonatal beds and in addition, there is a KMC unit with an additional number of beds for stable infants. A space for newborn infants randomised to immediate iKMC with their mothers was created in a hemi sector of the open bay NICU. The study was conducted together with researchers from Kwame Nkruma University of Science and Technology. Intra-hospital mortality in the study population was 21% at the time of study protocol development.

3.2.2.2 India

Safdarjung Hospital in New Delhi is India's largest public hospital with just over 20000 births per year. The NICU has approximately 50 beds but the bed occupancy is sometimes up to 200% as the hospital cannot decline any admissions. A mother-neonatal intensive care unit (M-NICU) was created prior to launch of the study. Newborn infants randomised to iKMC were thus cared for in a different room. The academic institution was Vardhman Mahavir Medical College. In-hospital mortality in the study population prior to launch was 16%.

3.2.2.3 Nigeria

Obafemi Awolowo University in Ile-Ife has close to 3000 births per year. The NICU has 50 beds and there are an additional number of KMC beds. Infants randomised to iKMC, control

and non-enrolled infants were cared for in the same room. In-hospital mortality in the study population was 48% before study launch.

3.2.2.4 Malawi

Queen Elizabeth Central Hospital in Blantyre has 15000 births per year. There are 30 neonatal beds but bed occupancy is usually over 100%. In addition, there are 35 KMC beds. The hospital has many ongoing clinical trials, the academic centre being the Malawi University, later renamed Kamuzu University of Health Sciences. Beds and recliners for mothers and infants randomised to iKMC were placed in the same open bay NICU where infants randomised to control care and non-enrolled infants received their care. Intra-hospital mortality was 23% in the study population prior to study initiation.

3.2.2.5 Tanzania

Muhimbili National Hospital in Dar-es-Salaam is the referral hospital for the whole of Tanzania and the number of births per year is 10000. The NICU has 150 beds but the bed occupancy is usually more than 100%. In addition, there is a KMC unit for stable small infants. The academic centre is Muhimbili University of Health and Allies Services. An iKMC room, or M-NICU, was arranged prior to launch of the study, to care for infants randomised to iKMC together with their mothers. Intra-hospital mortality in the study population was 22% before the study.

3.3 STUDY PARTICIPANTS

3.3.1 Studies I and II: IPISTOSS temperature and SCRIP

Inclusion criteria were based on GA in the Scandinavian studies. In study I, infants born at 28+0 to 33+6 gestational weeks plus days and in study II infants born at 28+0 to 32+6 gestational weeks plus days were recruited. The GA based inclusion criterion was chosen as this is known before birth for almost all newborn infants in the Scandinavian setting. The current GA roughly corresponded to birth weights 1000-2500 grams, with some exceptions of infants small or large for GA. The GA limits were chosen to select the preterm population for which SSC immediately after birth was not part of the conventional care but deemed to be safe. The limit above which immediate SSC is a component of conventional care was lowered between study I and II and is still decreasing in terms of SSC initiation time in clinical practice. Other inclusion criteria beyond GA were inborn and a parent or surrogate caregiver available for SSC within the first postnatal hour. Exclusion criteria were parents unable to read information about the study in Swedish or English, known congenital malformation or condition needing intervention soon after birth, severe congenital infection and any other reason contraindicating study participation according to the physician in charge.

Maternal and infant characteristics in study II						
	Norway n=51		**Sweden n=40**		**All n=91**	
	SSC, n infants=24 mothers=19	Control, n infants=27 mothers=21	SSC, n infants =22 mothers=19	Control, n infants=18 mothers=14	SSC, n infants=46 mothers=38	Control, n infants=45 mothers=35
GA, mean (SD, range), weeks	31+0 (1, 28+6-32+5)	31+0 (1, 28+4-32+6)	31+3 (1, 28+6-32+4)	31+2 (1, 29+1-32+6)	31+2 (1, 28+6-32+4)	31+0 (1, 28+4-32+6)
BW, mean (SD, range), grams	1561 (350, 900-2260)	1468 (390, 555-2440)	1583 (424, 702-2352)	1521 (447, 856-2133)	1571 (395, 702-2352)	1494 (400, 555-2440)
Apgar score 5 min, median (IQR)	9 (8-9)	9 (8-9)	9 (6-10)	9 (9-10)	9 (7-9)	9 (8-10)
Vaginal birth, n (%)	8 (42)	5 (24)	6 (32)	3 (21)	14 (37)	8 (23)
Twins, n (%)	10 (53)	12 (57)	6 (27)	8 (44)	16 (35)	20 (44)
Female, n (%)	6 (25)	16 (59)	7 (32)	11 (61)	13 (28)	27 (60)
PE, n (%)	5 (26)	10 (48)	5 (26)	6 (43)	10 (26)	16 (46)
PPROM, n (%)	2 (25)	2 (17)	6 (32)	5 (36)	10 (26)	7 (20)
ANS, n (%)	24 (100)	26 (96)	22 (100)	17 (94)	46 (100)	43 (96)
Primiparous, n (%)	14 (70)	8 (38)	13 (68)	8 (57)	27 (71)	16 (46)
Maternal age, mean (SD, range)	31 (5, 21-40)	32 (6, 22-45)	32 (5, 22-38)	33 (5, 28-44)	31 (5, 21-40)	32 (5, 22-45)
Smoking mother, n (%)	0 (0)	0 (0)	2 (10)	0	2 (5)	0 (0)
Smoking father, n (%)	1 (5)	0 (0)	1 (5)	2 (14)	2 (5)	2 (6)
University mother, n (%)	11 (58)	15 (71)	11 (58)	11 (79)	22 (58)	26 (74)
University father, n (%)	8 (42)	13 (62)	8 (42)	10 (71)	16 (42)	23 (66)
Elementary school only, mother, n (%)	1 (13)	0 (0)	3 (16)	0 (0)	4 (11)	0 (0)
Elementary school only, father, n (%)	4 (21)	2 (10)	3 (16)	0 (0)	7 (18)	2 (6)

Table 5: Mother and infant characteristics in study II. ANS=antenatal steroids, BW=birth weight, GA=gestational age, IQR=interquartile range, PE=preeclampsia, PPROM=preterm prolonged rupture of membranes, SD=standard deviation, SSC=skin-to-skin contact

3.3.2 Study III: SNQ SSC

Study III was an epidemiological report using data on SSC initiation and duration for EPT and VPT infants registered prospectively in the SNQ in 2020-21. The SNQ is national and population based, has a high validity and completeness (72) and infants with retrospective data registration were not included in the study. The study cohort constituted near 90% of the EPT and VPT population during the above time period.

3.3.3 Studies IV and V: iKMC mortality and cardiorespiration

Inclusion criteria were birth weight 1000 to 1799 grams, birth at study hospital, regardless of singleton or twin status, mode of birth and GA. Exclusion criteria were mother younger than 15 years, mother unable or unwilling to consent to study participation, mother too sick to be likely to provide KMC during the first three postnatal days, mother residing outside the study area, infant not breathing spontaneously after the first postnatal hour, not possible to enrol within the first two postnatal hours or with congenital malformations. Birth weight was chosen as inclusion criterion because prenatal GA assessment was still not always available in the current settings. The lower limit was motivated by the experience that infants with birth weight less than 1000 grams rarely survive provided the care available in the settings. The upper limit was set to include the infants that are admitted to the NICUs but not the well LBW infants who are often assessed and sent home shortly after birth. The birth weight limits were deemed to cover the VPT infants offered active care in the settings and the large number of moderately preterm or term infants small for GA.

3.4 STUDY DESIGNS

Four of the papers in my thesis are based on the results of three RCTs and one is a register study.

3.4.1 Study I: IPISTOSS temperature

Study I was a single-centre RCT conducted at a level 2 NICU in Stockholm in 2014-16, including a convenience sample of 55 preterm newborn infants. The intervention was SSC with a parent immediately after birth, during transport from the birth unit to the NICU and continued throughout the first postnatal hour. The comparator was stabilisation on a resuscitaire or in an incubator. Body temperature at one hour after birth was the primary outcome.

3.4.2 Study II: IPISTOSS SCRIP

Study II was a multi-centre RCT conducted in two HICs, at level 2 and 3 neonatal units in Stockholm, Sweden and Stavanger, Norway in 2018-21. Sample size calculation was not performed, but rather estimated based on a previous publication where 100 LBW infants were needed to show a 10% difference in Stability of the cardiorespiratory system in the preterm (SCRIP) score at six postnatal hours (120). To compensate for an expected smaller effect size in HICs compared to the MIC and for attrition, 150 infants were deemed to be an adequate sample. For reasons described later, only 91 VPT infants were included. The intervention was

immediate SSC with a parent from birth and continued for as much as possible during the first six postnatal hours. The comparator was care in a conventional place such as in an incubator or cot. The primary outcome was cardiorespiratory stabilisation during the first six postnatal hours as per the composite SCRIP score. Secondary outcomes included thermal control, proportion with and length of respiratory support, breastfeeding initiation, proportion and duration, proportion with sepsis, SSC daily duration, length of hospital stay, methylation patterns of genes involved in stress regulation, parental health and well-being, infant stress reactivity as per the Still Face paradigm and salivary cortisol levels, neurodevelopment and psychosocial development.

3.4.3 Study III: SNQ SSC

Study III was a population based register study involving the 1475 EPT and VPT infants that had prospective reports of SSC initiation and daily duration to the SNQ from January 2020 to October 2021.

3.4.4 Studies IV and V: iKMC mortality and cardiorespiration

Study IV and V derived from the same multi-centre RCT in LMICs, conducted at teaching hospitals in Ghana, India, Malawi, Nigeria and Tanzania in 2017-20. Sample size was calculated hypothesising a 20% mortality reduction. The average neonatal mortality in infants with birth weight 1000 to 1799 grams at the sites during the period when the study was planned was 32% and was estimated to decrease to 21% after implementation of a minimal package of newborn care (53) and further to 16.8% in the iKMC group, with a significance level of 5%, a power of 80% and 10% loss to follow-up. A sample size of 4200 was calculated but due to early study closure, 3211 infants were enrolled. The intervention was immediate SSC but, for the purpose of nomenclature in the literature called iKMC, meaning SSC with the mother or a surrogate caregiver from birth and until meeting pre-specified stability criteria. The protocol definition of stability was respiratory rate of 40 to 60 breaths per minute, oxygen saturation of over 90%, no respiratory support including supplementary oxygen, no apnoeas, heart rate of 80 to 179 per minute, axillary temperature of 36.0 to 37.4°C and no need of intravenous fluids for the last 24 hours. The comparator was conventional care, initially separated from the mother in a NICU, intermittent sessions of SSC initiated when the infant was starting to stabilise and transfer for care in a KMC unit when stable. Mortality at 72 hours and 28 days was the primary outcome in study IV, and proportion with hypothermia and time to clinical stabilisation were secondary outcomes. Other secondary outcomes not included in this thesis were proportion breastfeeding at hospital discharge and at a month of age, proportion with sepsis, proportion with hypoglycaemia during the first 36 hours, length of hospital stay, mortality in non-enrolled infants, maternal satisfaction with the care and maternal depression. Cardiorespiratory parameters during the first four days were a post-hoc secondary outcome and the topic of study V.

3.5 DATA COLLECTION

3.5.1 Study I: IPISTOSS temperature

In Study I, axillary temperature was measured at admission to the NICU and at one hour after birth with a thermometer (Terumo ETC205S, Japan). Baseline maternal and infant data and

the outcome data were entered into an electronic data capture platform (OpenClinica LLC, USA).

3.5.2 Study II: IPISTOSS SCRIP

In Study II, cardiorespiratory parameters were collected at 16 time-points during the first six postnatal hours by bedside observations; every 15 minutes during the first and last hour of the six-hour intervention period and every 30 minutes from the second to sixth hour. Heart rate and oxygen saturation were collected by monitoring readings (Intellivue MX800, Koninklijke Philips, N.V. in Sweden and Propaq M, ZOLL, Asahi Kasei in Norway) during four-minute periods. Respiratory support and FiO2 was collected by readings off the device if any, during the same time. Respiratory rate was counted manually during a minute following the above-mentioned four-minute period. The least optimal heart rate, oxygen saturation and FiO2 were translated to a score, similarly to the single value respiratory support and respiratory rate. The purpose of translating the vital parameters to a score was that high and low values would not even out when presenting means, but show as a low SCRIP scores. In addition, the methodology of setting the score based on the least optimal value was deemed to be a sensitive method to register signs of instability. A composite SCRIP score with a range from zero to six was calculated for each observation time-point, six indicating optimal stability.

As infants of this GA in Sweden and Norway were provided CPAP as a prophylactic measure rather than as a consequence of symptomatology, few infants reached a SCRIP score of six. It was hypothesised that the subtraction from the SCRIP score by the use of CPAP would mask any influence of SSC on respiratory rate. Therefore, a modification of the SCRIP score was done, where oxygenation was separated in oxygen saturation and FiO2 and respiration separated in respiratory support and respiratory rate. This resulted in a ten- instead of six-graded scale.

The SCRIP score of study II				
Variable	**Condition**	**Score**		
		2	**1**	**0**
Heart rate		120-160/min	100-119 or 161-180/min	<100 or >180/min
Oxygenation	If on room air	95-100% *and*	90-94% *or*	<90% *or*
	If on oxygen	FiO2 0.21	FiO2 0.22-0.30	FiO2 >0.30
Respiration	If no respiratory support	40-60/min *and*	30-39 or 61-70/min *or*	<30 or >70/min *or*
	If respiratory support	None	CPAP/HFNC	MV

Table 6: The SCRIP score used in study II consists of sub scores 0-2 for heart rate, oxygenation and respiration, amounting to a combined score of 0-6. CPAP=continuous positive airway pressure, FiO2=fraction of inspired oxygen, HFNC=high flow nasal cannula, MV=mechanical ventilation, SCRIP=Stability of the cardiorespiratory system in the preterm

Study data were collected and managed using REDCap electronic data capture tools (Vanderbilt, USA) (157, 158) hosted at Karolinska Institutet.

3.5.3 Study III: SNQ SSC

In Study III, maternal and infant background variables and the SSC initiation time, SSC daily duration and median daily duration of SSC during the NICU stay (these were three separate register variables) were retrieved from the SNQ by export performed by the register keeper from Medscinet (45) to an Excel file.

3.5.4 Studies IV and V: iKMC mortality and cardiorespiration

In Study IV, maternal and infant background variables and infant vital parameters during the NICU stay were collected by interviews, by bedside assessments and from hospital paper files by an outcome assessment team. The same research staff collected information on deaths at 72 hours after birth. A follow-up team collected information on deaths until 28 days after birth at a home visit on day 29. Data collected on paper case report forms were entered into a REDCap electronic data capture tool (Vanderbilt, USA) (157, 158).

In Study V, six-hourly observations of physiology and support parameters were performed by an outcome assessment team. The parameters included were heart rate and oxygen saturation by monitor readings (Masimo Radical, V 5.0; Masimo Corp., Irvine, CA, USA) respiratory rate, CPAP including the positive end-expiratory pressure, supplementary oxygen including the flow, axillary temperature and duration of SSC during the last 12-hour period. Data collected on paper case report forms were entered into a REDCap electronic data capture tool (Vanderbilt, USA) (157, 158).

3.6 STATISTICAL METHODS

The statistical analyses of studies I, II, III and V were performed by myself after having discussed with the rest of the author group, and in consultation with a statistician in studies II and V. Analyses were done using Stata/IC 15.0 (StataCorp LLC). For study IV, statisticians at the WHO performed the analyses and the results were discussed within the iKMC group at workshops. Studies I-II and IV-V were RCTs comparing immediate SSC with conventional care and analyses were done according to the intention to treat. In study I, per protocol analysis was performed in addition. Study III was a register study describing the implementation of SSC in GA strata and regions in Sweden. For all studies, descriptive statistics were done for background variables, using means, ranges and standard deviations or medians and interquartile ranges for continuous variables depending on data distribution. Frequencies and proportions were calculated for dichotomous and categorical variables. Student's t-test was used to test differences in means for continuous variables after testing for normal distribution with the Shapiro Wilk test, and the Chi2 test to test differences in proportions for dichotomous or categorical outcomes. A p-value of <0.05 was used as the cut-off for statistical significance in all studies. Missing data was deemed at random and different strategies to handle this were employed in each study.

3.6.1 Study I: IPISTOSS temperature

The primary outcome in study I was body temperature at one postnatal hour. Temperature is a continuous outcome and the distribution was tested for normality with the Shapiro Wilk test. Differences in mean temperatures were calculated with Student's t-test, as was the same for

other continuous secondary outcomes. The Chi 2 test was used for categorical secondary outcomes and the Spearman's correlation coefficient was calculated for correlations between covariates. Missing data was negligible and complete case analysis was done.

3.6.2 Study II: IPISTOSS SCRIP

In study II, a composite score taking into account heart and respiratory rate, oxygen saturation, FiO2 and respiratory support was used to describe the infant's combined cardiorespiratory state. The distribution of scores was tested for normality using the Shapiro Wilk test. We analysed the score as a continuous outcome, while being aware that scores are scale points and should be regarded as ordinal. This decision was made in order to enable comparisons with previous publications that had analysed the SCRIP score as a continuous outcome. Repeated measures were tested in a multilevel mixed-effects linear regression model with an independent structure taking into account the time-series repeated measures. Acknowledging the SCRIP score to be a scale with ordinal data, in addition to the time series linear regression, ordinal regression was performed. The effect of covariables was first tested one by one in univariable regression models and in a final multivariable regression model. Adjustments were performed for country, GA strata, preterm prolonged rupture of membranes, sex and Apgar score at five minutes. In addition, analyses were performed in strata for GA and country. Missing data was little and missing SCRIP scores handled with imputation of most frequent answer.

3.6.3 Study III: SNQ SSC

In study III, register data were presented with descriptive statistics. Proportions exposed to SSC and median time to SSC initiation and daily SSC duration were compared between regions with quantile regression. Odds ratios of exposure to SSC compared to the largest region were calculated with logistic regression.

3.6.4 Study IV: iKMC mortality

In study IV, mortality at 72 hours and 28 days, dichotomous data, was the primary outcome and risk ratios were calculated using logistic regression with log link models. Survival analysis using multivariable Cox regression was performed for the variable time to stable, which was one of the secondary outcomes. For continuous variables, linear regression was performed to compare groups. Covariables with the potential to be confounders were adjusted for in log-binomial regression modelling and analyses were also done in strata for birth weight, GA, size for GA, mode of birth, multipara and site. Additionally, an analysis was done to look at the efficacy of the intervention on the outcome based on the dose of the intervention, stratifying for daily duration of KMC. Marginal mean imputation was performed for continuous variables and most frequent response for categorical variables. The study was stopped early as pre-specified according to the Haybittle-Peto guideline, for benefit of the intervention with a significance level of <0.001 at the second interim analysis after 75% of the intended sample size.

3.6.5 Study V: iKMC cardiorespiration

In Study V, descriptive data was used to present proportions of infants with supplementary oxygen and CPAP. The continuous outcomes heart and respiratory rate and oxygen saturation were assessed for normality and analysed with a multilevel mixed-effects linear regression model with an independent structure taking into account the time-series repeated measures with adjustments for family income, mother's age, mother's years of schooling, mode of birth, multiple births, birth weight, sex, Apgar score at five minutes and for the clustering of sites. Differences in proportions with respiratory support was analysed with logistic regression and the duration of CPAP was analysed with linear regression. Missing data were handled with marginal mean imputation for heart rate, respiratory rate and oxygen saturation and most frequent answer for respiratory support.

4 RESULTS AND DISCUSSION

4.1 THERMAL CONTROL

In study I, 55 newborn infants with a mean gestational age of 32 weeks and a mean birth weight of 1.8 kg were randomised to SSC or control care during the first postnatal hour. The primary outcome was infant axillary temperature at one postnatal hour. We found that VPT infants cared for in immediate SSC had 0.3°C (95% CI 0.02-0.6), p=0.03, lower mean axillary temperature: 36.3°C (SD 0.5, range 34.4-37.2) versus 36.6°C (SD 0.4, range 36-37.4). Four of the 26 infants allocated to SSC had a temperature below 36.0°C at one hour, compared to no infants in the control group. There was a correlation between birth weight and temperature at one hour (r_s=0.42, p=0.002). The finding of lower temperatures in infants in SSC compared to control was in conflict with the previous literature that had shown SSC to be associated to better thermal control than conventional care (76, 90).

Hypothermia is a challenge in VPT infants and half of VPT infants admitted to European NICUs have body temperatures below 36.5°C. Admission temperature below 35.5°C is associated with a doubled neonatal mortality in this setting and age group (159). The WHO recommends a temperature of 25°C in birth rooms and NICUs, as newborn infants are in need of a thermoneutral environment. Operating room temperatures are often lower because of hygiene guidelines and ventilation. The mean birth room temperature in study I was 23°C which was not significantly correlated to infant temperature. This can be compared with another study that showed a halved incidence of infant temperature below 36.0°C if the birth room temperature was kept at 25°C as per WHO recommendations, compared to a room temperature of 22.5°C (160).

The majority of infants allocated to SSC in study I were cared for in SSC with their father; mean paternal SSC duration was 41/60 minutes compared to 7/60 minutes of maternal SSC duration during the first hour after birth. The birthing mother has a high chest temperature, especially if she has had epidural analgesia (161). Interestingly, infants of women who had epidural analgesia had a smaller increase in chest temperature than those who did not, when in SSC (162). It has been hypothesised, supported by earlier reports, that fathers have lower chest temperatures than mothers and consequently provide their preterm newborn infant with a lower ambient temperature (140). A study on term infants in SSC with their father after Caesarean section showed no significant difference in infant temperature compared to care in a cot (114). It was a limitation of the studies I and II that room and parental temperatures were not measured, nor was information on maternal analgesia collected.

Preliminary temperature data from study II are in line with the findings of study I in terms of the magnitude of difference between allocations. However, in study II, mean axillary temperatures of infants in both allocations were within the normothermic range.

Temperature was a secondary outcome in study IV, where hypothermia was defined as a temperature below 36.0°C after the first two postnatal hours. The rationale for this lower cut-off was the clinical significance in terms of adverse effects of hypothermia. Mean GA in this study was 32+4 gestational weeks and mean birth weight was 1.5 kg, hence somewhat more mature but with lower birth weights than the infants in study I. Of all temperature

measurements in the iKMC and control groups, 5.6% and 8.3% were under 36.0°C, respectively. This corresponded to a risk ratio of 0.65 (95% CI 0.51-0.83) in the iKMC group. Hence, in contrast to the results of studies I and II, infants in SSC in study IV had a decreased risk of hypothermia.

The main interpretation of the conflicting findings of study I and IV was that in study I, temperatures were measured at one postnatal hour whereas only temperatures measured after two postnatal hours were analysed in study IV. Ensuring a thermoneutral environment was a challenge in the first postnatal hour during which the preterm infant was exposed to a series of medical interventions and consequently exposed to cold room air. Moreover, the effect of SSC compared to conventional care in terms of body temperature may depend on the contents of the conventional care. The body heat of a parent can serve as the external heat source that the newborn infant needs. SSC in hospital care of LBW infants was originally seen as an alternative in settings where incubators were lacking (81). Hence the incubator has been regarded the default place of care in NICUs in HICs. The WHO has recommended KMC as the primary intervention for thermal control in stable LBW infants in LMICs since the early 2000s (29). The purpose of incubators is to provide warmth and humidity, but incubators were variably available and used but for some infants in conventional care in study IV. In addition to the incubators, the level of medical and nursing conventional care in study IV was lower than that in study II. This may have resulted in SSC being superior to conventional care in terms of infant temperature, during the NICU stay. The lower temperatures in infants allocated to control care may also be related to a larger number of interventions, causing exposure of the infant to room air. However, this is speculative as the number of manipulations of the infant was not measured within the scope of the study.

In clinical trials, statistical significance of findings does not necessarily mean that the results are clinically significant. The difference in mean temperature in study I was 0.3°C in favour of the control group, which was a statistically significant difference according to the hypothesis testing. The mean temperature of the SSC group was 36.3°C, hence below 36.5°C which is the cut-off for hypothermia, and the mean temperature just above, at 36.6°C for controls. By definition, the infants in one group had hypothermia and in the other group normothermia. For the clinician, both 36.3°C and 36.6°C border the suboptimal and require an increase in the ambient temperature and a re-evaluation, but they are probably not differently associated to other morbidities. A statistically significant difference in temperature of 0.3°C found in the Cochrane review by Moore et al. was not high-lighted as it was not interpreted clinically significant (89).

4.2 CARDIORESPIRATORY STABILISATION

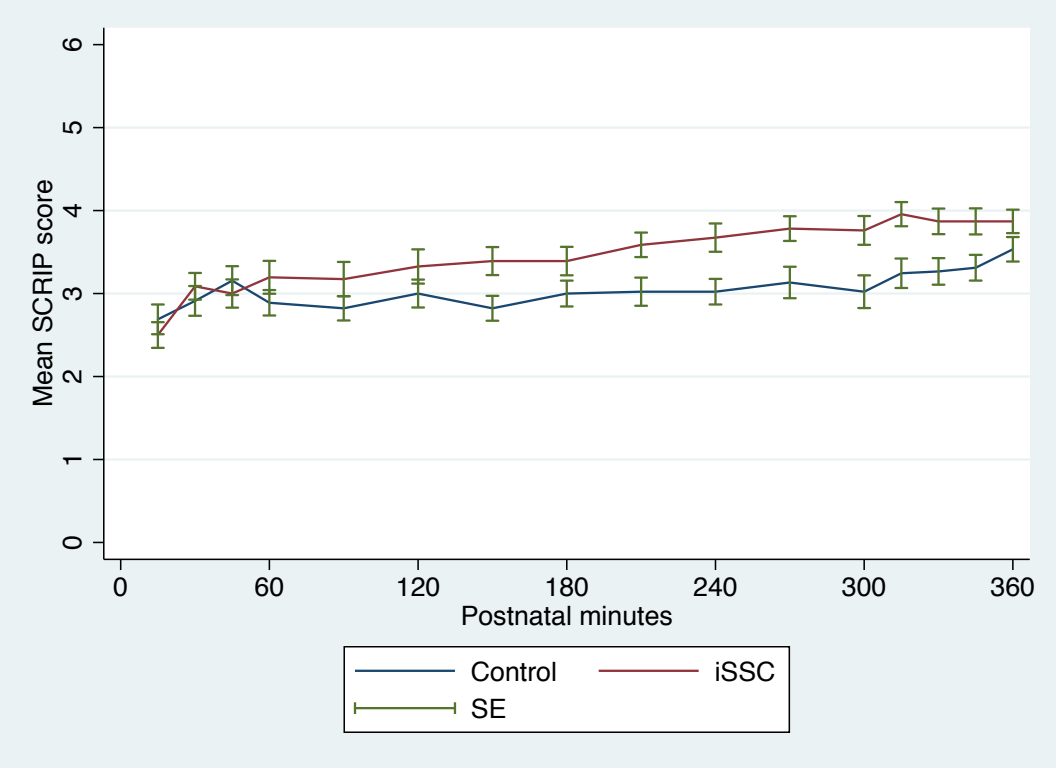
Study II involved the primary outcome of the IPISTOSS: cardiorespiratory stabilisation as per the SCRIP score (section 3.5.2) during the first six postnatal hours. Ninety-one newborn infants with a mean GA of 31+1 weeks and a mean birth weight of 1.5 kg were randomised to immediate SSC or conventional care in an incubator or cot during the first six postnatal hours. Over the six-hour period, there was an adjusted difference in mean SCRIP score of 0.52 on a six-graded scale (95% CI 0.38-0.67), $p<0.001$ in favour of infants allocated to SSC. The interaction effect of SSC and time was 0.003 (95% CI 0.003-0.004), $p<0.001$. The interaction effect refers to the change over time by allocation, or the slope of a curve. The

adjusted odds ratio for a higher SCRIP score was 3.3 (95% CI 1.5-7.1), p=0.002 and the interaction effect of allocation and time was 1.0 (95% CI 1.0-1.0), p<0.001 in favour of the SSC group. The results were in line with previous research from MICs (118, 120) where SSC was associated with an improved cardiorespiratory stabilisation during the first six postnatal hours. The difference in mean SCRIP scores, the change in SCRIP scores over time and the odds ratio of higher SCRIP scores in the immediate SSC group is interpreted as clinically significant. The level of conventional medical and nursing neonatal care in Scandinavia is high and additional benefits of SSC had been expected to be smaller.

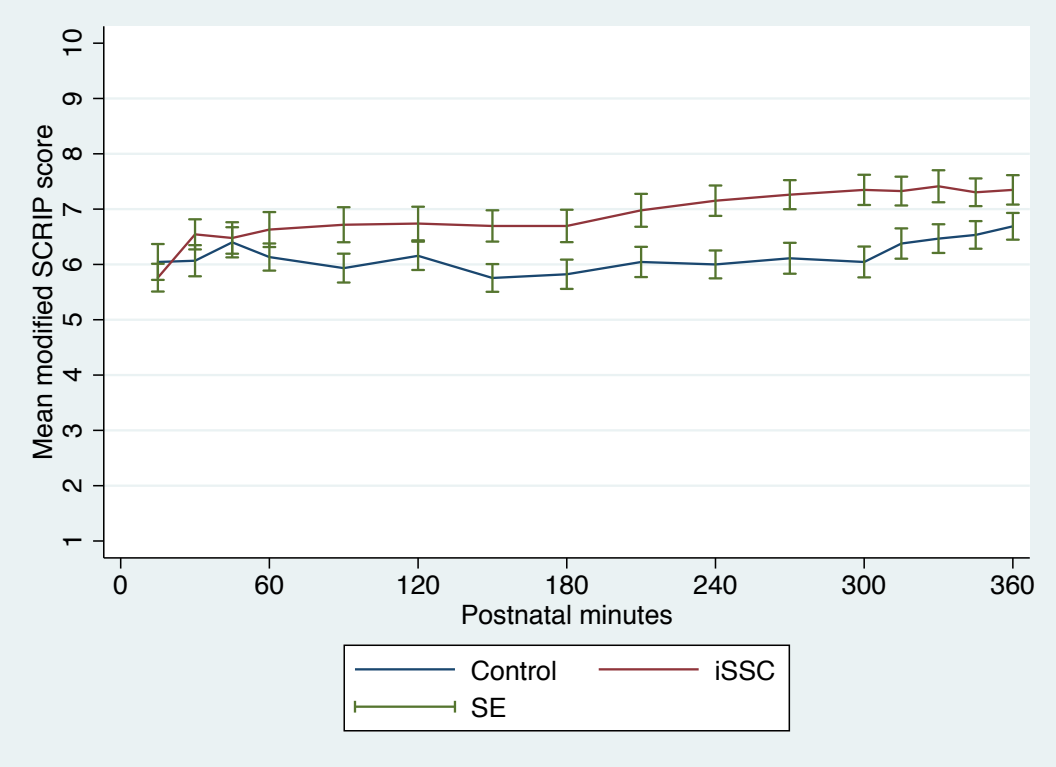
There was a large proportion of twins, 40%, but no adjustment for twins was done. This is a limitation to the study as covariables and outcome within twin pairs may have been more similar than between one twin and other study subjects, which could have been accounted for by clustering.

The effect size of SSC on the SCRIP score did not change significantly with the ten-graded modified SCRIP score, sea Figure 2b. The hypothesised reduction of respiratory rate in SSC was however confirmed in an exploratory analysis of study II, see Figure 2 d. This was interpreted as contributory to the difference in SCRIP score. Infants in SSC had a respiratory rate 2.7 breaths per minute lower (95% CI 0.7-4.8), p=0.009 which is of the same magnitude as suggested in a recent meta-analysis (131). Interestingly, the pattern of respiratory rates in study II was different from that of Chi Luong et al. (120). In study II, respiratory rates first increased, then later decreased and stabilised, which was more pronounced in infants allocated to control. In the study by Chi Luong et al., respiratory rates in infants allocated to immediate SSC decreased from start and respiratory rate in control infants remained on the same level throughout. Moreover, mean respiratory rates in study II were some 10-15 breaths per minute higher than those that of Chi Luong et al.

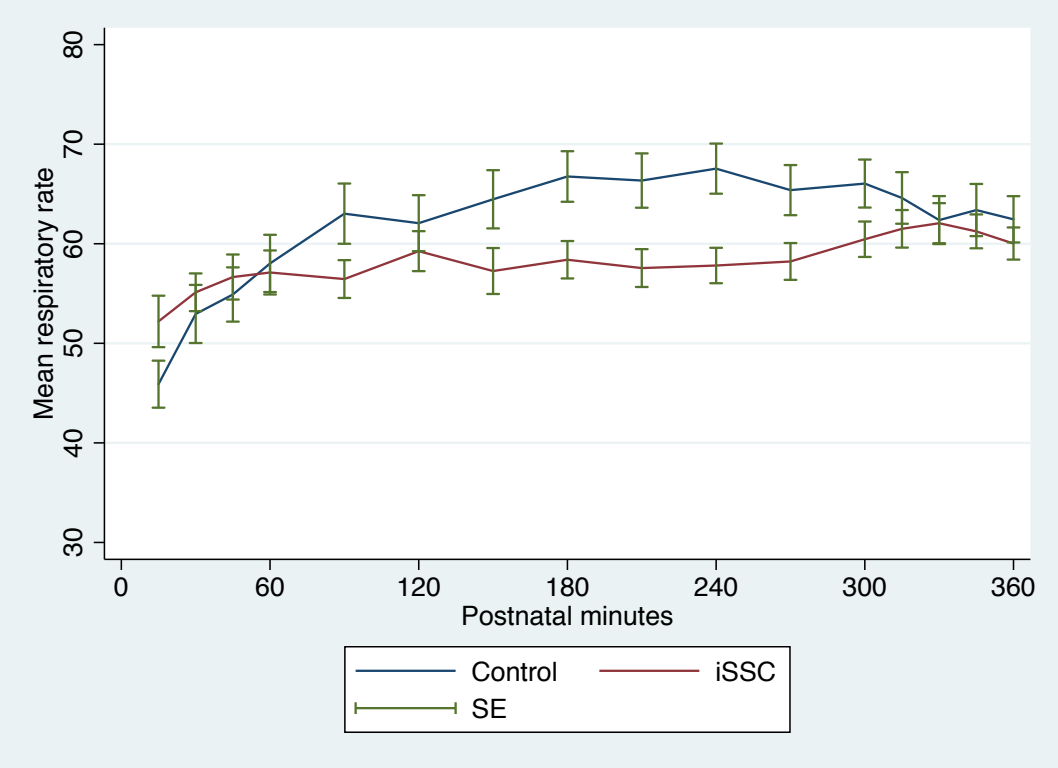
a)


Mean SCRIP score
0
1
2
3
4
5
6
0
60
120
180
240
300
360
Postnatal minutes
Control
iSSC
SE

b)


Mean modified SCRIP score
1
2
3
4
5
6
7
8
9
10
0
60
120
180
240
300
360
Postnatal minutes
Control
iSSC
SE

c)



d)

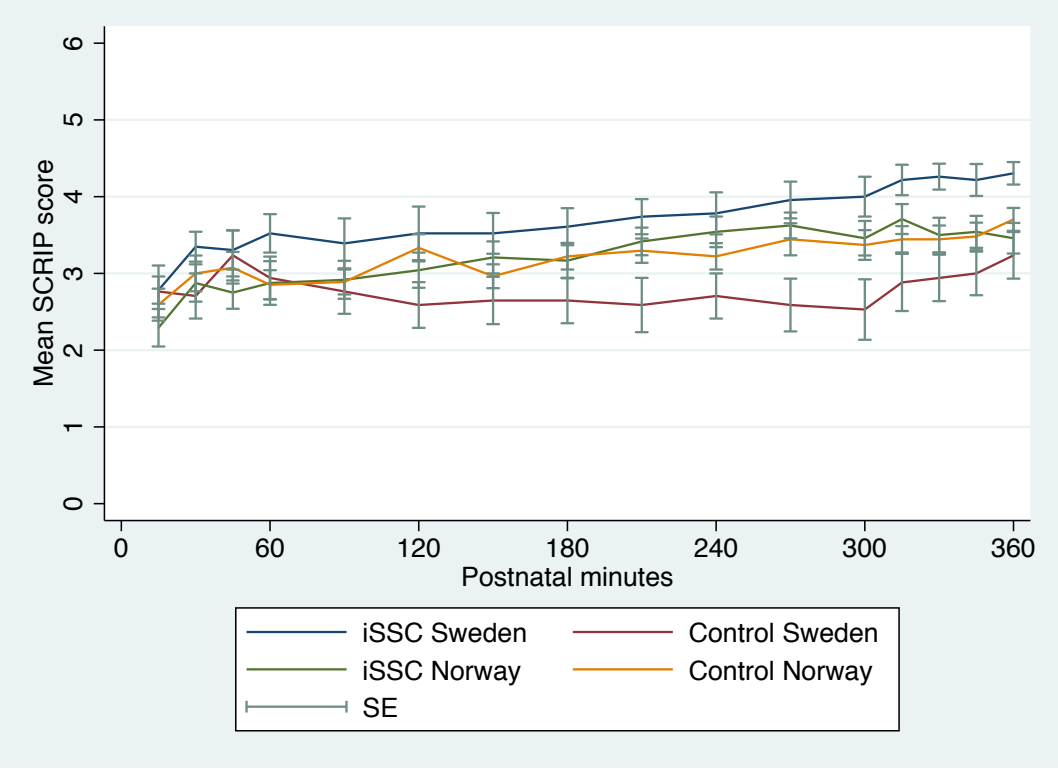


Figure 2: Mean SCRIP scores and mean respiratory rates during the first six postnatal hours, with standard errors (SE) during the first six postnatal hours, n=91. a) mean SCRIP scores (0-6) by allocation, b) mean modified SCRIP scores (0-10) by allocation, c) mean respiratory rates by allocation and d) mean SCRIP scores (0-6) by allocation and site. SCRIP=Stability of the cardiorespiratory system in the preterm, iSSC=immediate skin-to-skin contact, SE=standard error

There was heterogeneity in results between Sweden and Norway. In Sweden, the difference in mean SCRIP score during the intervention period was 0.94 (95% CI 0.71-1.16), p<0.001 whereas in Norway, the difference did not reach clinical or statistical significance, at 0.14 (95% CI -0.04-0.34), p=0.15. The scores of SSC and control infants in Norway were similar but there was a large difference between SSC and control infants in Sweden. The reasons for these differences may include different data collection methods, which will be discussed more in detail in the section on methodological considerations, section 4.5.2.

Study V involved post-hoc analyses of the cardiorespiratory parameters of the 3211 infants recruited to study IV. Their mean GA was 32+4 weeks plus days and the mean birth weight was 1.5 kg. Compared to infants of the control group, infants of the iKMC group had a lower heart rate of 1.4 beats per minute (95% CI -3.1-0.3), p=0.097 and an interaction effect of allocation and time on heart rate of 0.03 (95% CI 0.009-0.05), p=0.004, a lower respiratory rate of 0.4 breaths per minute (-1.5-0.7), p=0.48 and an interaction effect on respiratory rate of allocation and time of 0.01 (95% CI 0.003-0.03), p=0.01 and a lower oxygen saturation of 0.3% (95% CI -0.7-0.09), p=0.14 with an interaction effect on oxygen saturation of allocation and time of 0.0 (95% CI 0.0- 0.0), p=0.93, after adjustments. To conclude, there were no clinically significant differences between allocations in terms of heart rate, respiratory rate and oxygen saturation during the first four postnatal days.

Studies on cardiorespiratory parameters such as heart rate, respiratory rate and oxygen saturation in preterm infants during SSC are few in numbers, have small sample sizes, involve relatively stable infants days after birth, with short sessions of SSC and display a heterogeneity in results, as summarised in the review by Cristóbal Canadas (131), see section 1.5.4. The results of study V contribute to the heterogeneity in results among studies investigating cardiorespiratory effects of SSC.

The relation of SSC during the first hours to days in life and cardiorespiratory parameters during the transition from foetal to extra-uterine life has been less studied. Preceding study II, two studies had described better cardiorespiratory parameters in SSC for unstable LBW infants immediately after birth (118, 120). In these studies, in addition to the study of vital parameters per se, the overall cardiorespiratory state of the preterm infant during the first postnatal hours was assessed with the help of a SCRIP score, similarly to in study II.

Fischer et al. first published a SCRIP score, which took into account bradycardias, apnoeas and desaturations (163). Bergman et al. modified the SCRIP score and applied it for studies on immediate SSC in LMICs (118, 120). There are to date a number of versions of the SCRIP score. The studies that have published SCRIP score data are limited and the SCRIP score has not been validated. Since the publications with SCRIP scores use different versions, comparisons are challenging and the clinical significance of differences remain at the judgement of the individual research group.

The Fischer SCRIP score			
Variable	**Score**		
	2	**1**	**0**
(A) Heart rate	Regular	Deceleration of heart rate >80 bpm <100 bpm	Bradycardia <80 bpm and/or tachycardia >220 bpm = 1 min in quiet sleep
(B) Respiration	Regular	Apnoea <10 s and/or periodic breathing (=apnoea >3 s, regular respiration <20 s at least 3 times)	Apnoea > 10 s and/or tachyponea >80 bpm = 1 min in quiet sleep
(C) Oxygen saturation (pulse oximetry)	Regular >90%	Falls <90% >80%	Falls <80%

Table 7: The Fischer SCRIP score. bpm=breaths or beats per minute

The proportions of infants with any CPAP in the iKMC and control groups of study V were 62% and 60%, respectively. In those infants who did have CPAP, median time with CPAP was 32 hours (IQR 12-66) in the iKMC group and 28 hours (IQR 11-59) in the control group. The difference in duration was 6.6 hours after adjustments, (95% CI 1.64-11.6), p= 0.009, in favour of the control group. To our knowledge, there are no previous studies reporting on the duration of respiratory support in SSC. CPAP machines were variably available at the sites before but were introduced prior to study launch on the initiative of the WHO as part of the introduction of a minimal package of newborn care and to standardise the care between sites. Interestingly, there were site differences in terms of use of CPAP. The sites in Malawi and Tanzania had lower proportions of infants with CPAP, at 55% and 48%, respectively. In Ghana the proportion of infants with CPAP was higher, at 71%. The differences in CPAP duration between allocations may be explained by actual different needs of the infants or by confounding by indication.

Median times to clinical stabilisation, i.e. times to meeting the pre-specified stabilisation criteria listed in section 3.4.4, were similar between allocations at 73.8 hours (IQR 26.8-138.5) in the intervention group and 74.8 hours (IQR 25.3-140.6) in the control group. To our knowledge, there are no previous studies describing the time until stabilisation in immediate SSC.

4.3 SKIN-TO-SKIN CONTACT INITIATION AND DURATION

Study III was a register study. The implementation of SSC in the care of EPT and VPT infants in Swedish NICUs was investigated by analysing prospective recordings of 1475 infants, of the daily duration of SSC during the first postnatal week in the SNQ. Of this cohort, 782 also had recordings of their SSC initiation time. The mean GA was 28 weeks and the mean birth weight was 1.2 kg. The median SSC initiation time was at 88 postnatal hours (IQR 48-156) for EPT infants and 14 hours (IQR 4-36 hours) for VPT infants. The proportion of infants receiving SSC on the first postnatal day was 14% at 28 gestational weeks and 43% at 31 gestational weeks. Median daily SSC durations for VPT infants on the first day, first

three days and first seven days were 0 (IQR 0-2), 1.7 (IQR 0-3.7), 2.4 (IQR 0.9-4.4) and 4.9 (IQR 3.3-6.7) hours, respectively.

Skin-to-skin contact on the first postnatal day by gestational week in study III		
Gestational week	**Any SSC on the first day, n (%)**	**SSC duration first day in infants who received SSC, median (IQR)**
22	1/39 (2.6)	1.5
23	3/65 (4.6)	1 (1-3)
24	2/78 (2.6)	1 (1-1)
25	4/101 (4.0)	1.9 (1.6-2)
26	5/112 (4.5)	2.3 (2-3)
27	12/144 (8.3)	2.8 (1.8-8.5)
28	21/155 (14)	2.6 (1.8-8.5)
29	55/209 (26)	2.5 (1.5-5)
30	105/255 (41)	3 (2-5)
31	135/317 (43)	3 (1.5-5.5)

Table 8: Proportion of infants with any SSC and median SSC duration during the first postnatal day by gestational week. SSC=skin-to-skin contact, IQR=interquartile range.

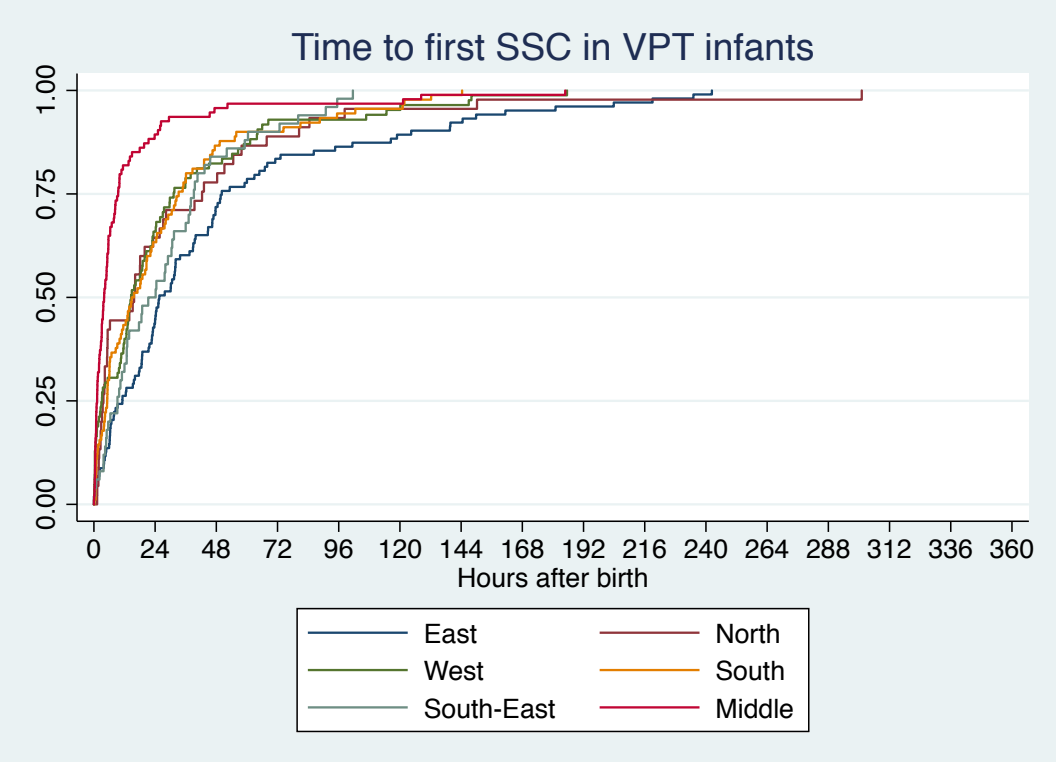


Figure 3: Time to first SSC in VPT infants by region in study III. East (Stockholm); n=103, West (Gothenburg); n=86, South-East (Linköping); n=49. North (Umeå); n=45, South (Lund); n=90, Middle (Uppsala); n=94

In the light of challenges to randomise away from SSC in study II, motivated by immediate SSC being a part of the conventional care, the results from the register study indicated the opposite; that SSC initiated immediately after birth was not part of the conventional care of

VPT infants in Sweden. The SSC initiation time and daily durations of SSC for VPT infants seemed to be much lower than what would have been feasible knowing the background that parents stay in the NICU with their infant around the clock. Moreover, the care claimed to be based on the IFCDC principles (68) and a large proportion of infants were cared for in units either affiliated to a NIDCAP centre or to a unit with a SSC profile where professionals teach about the benefits of SSC.

Since all EPT and VPT infants were provided care in NICUs and all NICUs report to the SNQ, the register data was population based. However, register data relied on that NICU staff documented the SSC in the patient file. Since the absence of SSC is not documented, only the duration of any SSC, it was impossible to discriminate between no SSC provided and missing data. Validation of the data was discussed, but unfortunately this was not possible. During the same time period, SSC durations had not been collected on a large scale for any other purpose but for the SNQ. According to the preliminary results of study II (n=91), the median daily SSC duration during NICU stay was 6.7 hours. This cohort from Stockholm was constituted of infants with parents who had consented to participation in a trial investigating the effects of immediate SSC, probably making them more motivated for long durations of SSC. Hence, a median daily duration of SSC of 4.9 hours may be representative for VPT infants in a Swedish NICU.

KMC involves early and continuous SSC, but most studies referred to in the introduction either do not report on duration or report effects of a couple of hours of SSC daily only. Studies reporting on dose-response effects of SSC are scarce. In HICs, SSC is usually delivered intermittently and total time per day varies between settings, families and also between units (164). In Europe, polices for parents in the NICU have changed over the past two decades and parental presence has increased (165). In addition to parental policies, benefit systems (154) also have an impact on parents' opportunities to participate in the care of their preterm infant and for SSC.

A Swedish population-based study from 2012 involving EPT infants, reported a median SSC initiation time at six days after birth (166). In study III, the median SSC initiation time for EPT infants was shorter, at 3.5 postnatal days. Concerns of early SSC involve a potentially stressful transfer of the infant from the incubator to the parent and fear of heat and fluid loss. These factors may delay the SSC initiation time. However, one study has described that SSC during the first postnatal week is feasible for EPT infants (140). In VPT infants, SSC was started earlier, at six hours, concluding from a report from two Swedish NICUS during the same time period (167). This was an earlier initiation time than our finding in study III. Parents' continuous presence in the NICU was variably encouraged across settings and depended on parental leave systems and ward structures and routines, according to another report (168). NICUs may also have different criteria for when SSC is considered safe. A European study showed that the daily dose of SSC varied between countries, and a NICU in Sweden was in the lead with a mean SSC duration of eight hours per day (169), for moderately preterm infants. Policies regarding family presence in the NICU also varied greatly in Europe (165). The regional differences in SSC initiation time and daily duration in study III confirm that regional guidelines and traditions have a large impact on what opportunity preterm infants have to SSC with their parents.

In study IV, SSC initiation time in the iKMC group was 1.3 hours. The median daily duration of SSC during the first three postnatal days was very high at 17 hours in the iKMC group, compared to 1.5 hours in the control group. This is a very long median SSC duration compared to the studies mentioned above. Dose-response analyses were not possible in this study, because of reversed causality where well infants had the opportunity of long SSC durations and sicker infants less so due to their need of medical interventions.

4.4 MORTALITY REDUCTION

Study IV was a multi-centre RCT led by the WHO, investigating the effect of SSC initiated immediately after birth on neonatal mortality. A total of 3211 infants with a mean GA of 32+4 gestational weeks plus days and a mean birth weight of 1.5 kg were randomised to SSC immediately after birth and continued until meeting pre-specified stability criteria, referred to as iKMC in the study, or to conventional care. Conventional care involved SSC being introduced after an infant had become stable. Hence the intervention period referred to the time in the NICU before a LBW infant in these settings was eligible for SSC. The primary outcome was mortality, presented both as mortality in the first 72 hours of life; 74/1606 (4.6%) infants in the iKMC group and 92/1599 (5.8%) in the control group; relative risk of death, 0.77 (95% CI 0.58-1.04), p=0.09 and mortality in the first 28 days of life, neonatal mortality; 191/1596 (12.0%) infants the iKMC group and 249/1587 (15.7%) infants in the control group; relative risk of death, 0.75 (95% CI 0.64-0.89), p=0.001. The trial was closed early, at two thirds of planned sample size, for benefit in the intervention group. A concurrent single-centre RCT by Brotherton at al. on KMC and mortality did not find any benefit in terms of mortality reduction (86). The authors concluded that their trial might have been underpowered. Similarly to study IV, neonatal mortality decreased significantly during the course of the study, independent of the intervention but speculatively as a consequence of conventional care being improved with basic inventions as a trial sheds light on a study population. Differently to the long median daily durations of KMC in study IV, 17 hours per day, the infants in the study by Brotherton et al. were cared for in KMC for approximately seven hours per day. The Cochrane review by Conde Agudelo indicates that there is a better effect of continuous than intermittent KMC (76).

Study IV was unique in the sense that KMC was initiated immediately after birth, whereas the majority of studies included in the meta-analyses on KMC and mortality investigated KMC as we knew it; initiated after the initial days of medical treatment in a NICU (76, 90). However, the 25% mortality reduction can be compared with 40% and 36% in the meta-analyses by Conde Agudelo et al. (76) and Boundy et al. (90), respectively. These numbers are clinically significant because of the high mortality in LMICs and consequently the large numbers of lives potentially saved by KMC yearly (170).

There were site differences in terms of the magnitude of the mortality reduction and at one site there was even a trend towards an increased risk of death in the iKMC group. The factors underlying the mortality reduction are currently being investigated, but one especially protective factor may be the M-NICU environment. In India and Tanzania, infants allocated to iKMC were provided their initial care with their mothers in a separate room from the infants allocated to control. The medical and nursing care was the same, but the effect of being cared for in a separate M-NICU was probably beneficial for the LBW infant, with or

without SSC. This will be discussed more in the section 4.5.2.

4.5 GENERAL METHODOLOGICAL CONSIDERATIONS

This thesis adds knowledge of SSC initiated immediately after birth on the cardiorespiratory and thermal effects on VPT infants in HICs and suggests a gap between theory and practice in terms of implementation of SSC in Swedish NICUs. Moreover, the thesis confirms the mortality reduction in LBW infants in LMIC with an additional benefit when initiating SSC, or KMC, immediately after birth. However, there are some methodological considerations that should be discussed for a deeper understanding of the implications of this thesis.

4.5.1 Strengths and limitations

The importance of this thesis is underscored by the request of a Cochrane review for future reaearch to specifically address the knowledge-gap concerning the effect of SSC immediately after birth in the unstable preterm or LBW infant in LMICs as well as HICs (76). The results from four of the five studies derive from RCTs, which by design should deliver high quality evidence. A strength of study III, in terms of generalisability, is that the register used is population-based and thus, our results should be representative for Swedish NICUs.

The major limitation of the thesis is the small sample sizes in studies I and II. The reason for the small sample size in study II was partly the limited resources in terms of research staff, imposed pauses of the recruitment due to the COVID-19 pandemic and, consequently, slow recruitment rates, but also questions about equipoise between allocations. All this contributed to early study termination. There was still a statistically significant result, but the early termination may have implications for the power of secondary outcomes. Another limitation is differences in data collections methods, which will be more discussed in section 4.5.2. The lack of validation of the register data is a third limitation of this thesis.

4.5.2 Definition of exposure and outcome

The collection of outcomes and covariables need to be thoroughly defined, standardised and validated in a clinical trial, to be able to conclude on correlations between exposure and outcome and make comparisons between groups.

4.5.2.1 Exposure

In the clinical trials, studies I-II and IV-V, the exposure was SSC between the newborn infant and a parent or surrogate caregiver initiated as soon as possible after birth and continued for as long as possible during a defined period, compared to conventional care. The mean SSC duration in study I was 49 minutes (SD 19) of the intended 60 minutes. In study II, the median SSC initiation time was 0.4 hours (IQR 0.3-1), immediate initiation intended, and the median SSC duration during the intervention was 5.0 hours (IQR 4.5-5.5), of the intended six hours. There was a trade-off between immediate initiation and continuous delivery of SSC in study II, because some procedures such as weighing, placement of umbilical catheters and radiology could not be done in SSC. These procedures were variably done prior to SSC initiation to enable as undisturbed as possible SSC thereafter, or the SSC was initiated directly after birth and interrupted for procedures later on if needed. The SSC durations in

study IV were presented in section 4.3. There was a difference in non-mother SSC providers between studies I-II and IV. The dominating SSC durations with fathers in studies I-II are representative for the Scandinavian settings where fathers to a high extent are involved in the care of children whereas fathers were not involved in SSC in study IV. In the settings of study IV, female relatives were surrogate SSC providers who alternated with the mother. Paternal involvement was suggested during the study planning phase, but was regarded controversial for cultural and privacy reasons in these settings. In all studies, maternal SSC was considered the priority, motivated by that the mother had carried the infant throughout pregnancy and for breastfeeding. Earlier research has focused on maternal-infant SSC, but to our knowledge, in most settings SSC with any caregiver is considered valuable. Analyses were done according to intention to the treat in studies I-II and IV-V and did not consider with whom the SSC was nor the SSC initiation time or duration.

4.5.2.2 Outcome

In the period during which study I was conducted, the temperature was initially assessed either rectally or axillary but in the study, measurement was standardised to axillary measurements with the same type of thermometer. Axillary temperatures have been deemed sensitive in terms of finding central hypothermia, but are less sensitive in measuring hyperthermia (171). Different modes of measurement would have biased data collection.

In study II, the SCRIP data collection was complex and involved bedside observations, including the judgement of the observer whether the value on the monitor was true or an artefact. The hypothesis and the rationale for the protocol (172) were that this would be a more fine-tuned method for collecting subtle signs of instability in the VPT infant. However, as research resources were limited, bedside observations were in some cases replaced by retrospective monitor readings at one of the sites. In the analysis phase, it was a challenge to estimate the impact of the different data collection methods on the results. This was an important aspect of study II and will be discussed further in section 4.5.3. Further, it was a limitation that the SCRIP score exists in different versions and that the score has not been validated. The present version of the SCRIP score was adapted for HICs, published with the study protocol (172) but not used in previous studies. The consequence is that comparisons between studies using versions of the SCRIP score need to be done with caution.

Study III relied on the SSC data entered into a register, with a standardised, nation-wide instruction but a probable actual heterogeneity in terms of data collection. Exposure to SSC was registered, but discrimination between missing data and no exposure to SSC was not possible. In addition, in the busy clinical environment it cannot be excluded that the durations of SSC sessions were approximated, especially if registered retrospectively at the end of a shift.

In studies IV and V, considerable investments in terms of staff, training and monitoring visits were done to ensure the quality of conventional care and of the intervention and to optimise data quality. Still, in study V there seemed to have been a misunderstanding in the collection of FiO2 data. This was suspected as for some infants, a FiO2 above 0.21 was registered concurrently to the negation of supplementary oxygen or CPAP. An inadvertent mix-up with

of FiO2 and oxygen saturation in a number of observations could not be ruled out and analyses involving FiO2 therefore had to be omitted from the manuscript.

4.5.3 Random and systematic errors

A study finding can be a true correlation between an exposure and an outcome or be affected by systematic or random errors. The proportion of systematic errors remains constant with increasing sample size but the proportion of random errors decreases. Systematic errors include selection bias or information bias such as observer bias, and confounding bias. Confounding refers to the outcome being related to another variable rather than the exposure and is generally managed with adjustments for these covariables.

In study II there was heterogeneity in results with a large difference in SCRIP score between allocations at the Swedish sites and no difference at the Norwegian site. In Sweden, three researchers and one research nurse collected data at bedside observations. In Norway, researchers and designated NICU nurses shared this task and in addition, a proportion of bedside observations were replaced by retrospective monitor readings. The following two types of information bias may have contributed to the difference in effect between sites: 1) Since the study was not blinded, any expectations from the researchers may have introduced information bias affecting data collection and an overestimation of the effect size. 2) A more heterogeneous group of data collectors and methods may have led to a lower fidelity and an underestimation of the effect size; effect towards the null.

Clinical trials often strive to find causal relationships between an exposure and an outcome, but correlations rarely infer causal relationships. The Bradford Hill criteria aim to investigate a causal relationship where a correlation is found (146). The criteria are strength, consistency, specificity, temporality, dose-response relationship, plausibility, coherence, results of experimental data and analogy. The effect of SSC may be difficult to separate from underlying protective or harmful genetic and environmental factors. Observational studies on SSC risk confounding the effect of these factors with the effect of SSC per se. For example, a well preterm infant is more likely to be exposed to SSC than an infant in need of medical support and interventions. Similarly, well-informed and high-resource parents may be more motivated to provide SSC, but the contribution of genetics and other unknown factors in the environment may also correlate with the outcome.

Direct acyclic graphs (DAGs) illustrate the relation between exposure and outcome, the role of covariables, highlight potential confounding and may be helpful both in the planning of data collection and in the analysis phase (173). For small sample sizes, the number of covariables to adjust for must also be small, for the model to be robust. If randomisation has been successful in an RCT, variables will already be equally distributed between allocations. Adjustments may still be indicated where distributions are skewed or for stratification variables. If there is collinearity, such as between GA and birth weight, only one of the covariables should be included in the model.

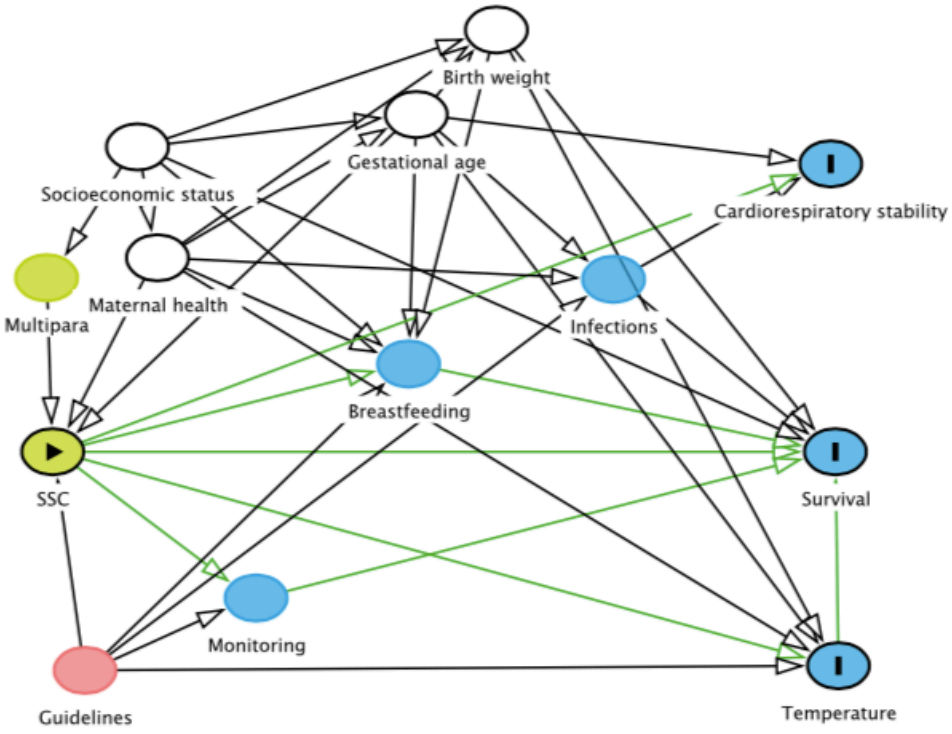


Figure 4: A direct acyclic graph (DAG) that illustrates the complexity of finding causal inference between an exposure and an outcome. The relation between the exposure (SSC) and the outcomes (temperature, cardiorespiratory stability and survival) are investigated in three clinical trials included in this thesis. Some covariables are adjusted for, some are or will be presented as secondary outcomes. Green dot=exposure or ancestor of exposure, red dot=ancestor of exposure and outcome, blue dot=outcome or ancestor of outcome, white dot=variables adjusted for in the models, green line=causal path, black line=other path. SSC=skin-to-skin contact. See www.dagitty.net

4.5.4 Generalisability

In study I, 21% of eligible families and 48% of consenting families were randomised. This illustrates that clinical trials are resource demanding at all steps from screening, acquiring informed consent, enrolment of study subjects to data collection. A similarly low proportion of eligible families was randomised in study II, but the exact information was not available due to heterogeneity in screening routines at the two sites; the number of mothers screened was recorded in Sweden but not in Norway. Because of the antenatal consent procedure, there was a selection of more prepared, well infants and parents to the studies. This may have decreased the generalisability of the results. However, the randomised design distributed participant characteristics over allocations and the internal validity is therefore high.

A frequent limitation when referencing to the benefits of SSC between parents and infants is that the setting, timing and GA are not taken into account. Evidence from one setting, from later in life versus immediately after birth, from stable versus unstable infants and for term versus preterm or LBW infants are erroneously interpreted as a general benefit of SSC in all infants everywhere. This may pose infants in circumstances less studied at risk.

In this thesis, two clinical trials were performed in HICs and one in LMICs. The result of study I may seem in conflict with other publications mainly deriving from LMICs. However, it illustrates that the effect of SSC on infant temperature may be dependent on the setting, referring to the contents of conventional care or the timing. In analogy, the results of study II

and V are not conflicting but describe cardiorespiratory parameters during different postnatal ages and with different granularity. Study II was done with a relatively high-frequency sampling during the dynamic period in the VPT infant's transition from foetal to extra-uterine life following birth whereas in study V, data collection was performed as snap shots four times daily during the first four days of life.

4.5.5 Ethical considerations

All studies had ethical approval and these are summarised in the table below.

Ethical approvals	
Study	**Ethical Approvals**
I IPISTOSS temperature	2010/52-31/4
II IPISTOSS SCRIP	2017/1135-31/3 with amendments 2018/213-32/1, 2019-03361 (Swe). 2015/889 (No).
III SNQ SSC	2021-04065 with amendment 2021-04186
IV iKMC mortality	ERC.0002910 (WHO), CHRPE/AP/372/17 (Ghana), NIMR/HQ/R.8a/Vol. IX/2621 (Tanzania), P.08/17/2235 (Malawi), IRB/IEC/ 0004553 NHREC/27/02/2009a (Nigeria), IEC/ SJH/VMMC/Project/August-2017 (India)
V iKMC cardiorespiration	

Table 9: Ethical approvals of the trials involved in the thesis

4.5.5.1 Good Clinical Practice

The studies were conducted according to Good Clinical Practice (GCP) and the Declaration of Helsinki. The GCP principles involve that trials should be conducted in accordance with ethical principles, the risks should be weighed against the benefits for the individual and the society before initiation, the safety for the study subjects should be prioritised and prevail over the possible benefits of others, the trial should be scientifically sound, be described in a protocol and approved by an ethical review board, the medical care of the study subjects should be the responsibility of a physician, all research staff should have training in their specific tasks, consent should be obtained from study subjects prior to trial participation, all trial information should be stored so that it can be reported on and verified, ensuring that the confidentiality of the study subjects is protected and there should be a system to assure the quality of every aspect of the trial (174). The Declaration of Helsinki is a guideline that emphasises the rights and integrity of the individual, pronounced by the World Medical

Association (175). The Karolinska Trial Alliance was involved in the planning phase of study II including the development of consent procedures and case report forms and all research staff had training in GCP.

The recruitment process for clinical trials involving interventions around birth is delicate. Parents to be, especially when expecting a VPT infant, when the mother has health issues of her own or if the labour has started, may be in a vulnerable state which needs to be acknowledged in the consent process. In the studies involved in this thesis, parents were provided oral and written information about the study, needed time to discuss and after discussing they had questions about study participation. Consequently, the recruitment process often took several days. Still, research on immediate interventions around birth, similarly to other medical emergencies, is needed in order to improve the care (176). It would not be ethical to refrain from conducting such research. In future studies by our group, deferred consent may be an option for two purposes; to recruit a less selected population of infants and to dedicate research staff resources to other areas.

There was a large contrast in terms of the proportion of women consenting to study participation in the iKMC and IPISTOSS studies. Consent rates were higher in study IV (95%) than study I (66%), and by experience also in study II where the number of women asked was unfortunately not documented, as described in section 4.5.4. This may reflect the differences in relations between patients and medical staff in the different settings. However, in all studies research staff were instructed and had training to give neutral information about the study allocations, to explain the difference between medical care and research, that study participation was voluntary and that the parents could withdraw their consent at any time.

Mothers committed to long hours of SSC within study IV and V. Study IV reported no differences between allocations in terms of maternal satisfaction with the care. The primary outcome was the survival of her LBW infant, but the obstetric outcomes remain to be analysed.

As mentioned in earlier sections, there were questions concerning equipoise between allocations in the trials in the HICs. During the study period we observed a gradual change in conventional care with a shift towards earlier SSC, where routines changed mainly based on the experience of the nursing staff, rather than on evidence from research. We concluded that the change did not reflect in clinical practice on a large scale, that SSC immediately after birth was still not part of the conventional care and that it was ethical, and needed, to conduct the studies and disseminate the results.

4.5.5.2 Early study termination

Studies II and IV-V were closed early. For study IV-V, stopping rules had been pre-specified in the study protocol, were based on interim results, and study closure was done according to this. Stopping rules were not included in the protocol for study II, but upon consultation study recruitment was stopped on the recommendation of an external data safety monitoring board. There are many ethical considerations in regard to early stopping of a clinical trial. First, it is emphasised in GCP that trials be conducted according to their registered protocol and that analyses are performed as planned to avoid bias. Second, it is in the interest of funding organisations that the trials are conducted as described. Trials are demanding with

investments in funding and human resources and thus effort should be made to use these investments wisely. Finally, parents have consented and committed to study participation to contribute to increased knowledge. Having discussed these ethical considerations, specifically in study II, we closed the study early to prioritise dedication of available resources to extracting, analysing and disseminating the data.

4.5.5.3 Publishing negative or null-results

Publishing negative results or null-results is less common than publishing positive results. This is attributed to a selection by the scientific journals. However, negative results are important and contribute to increased knowledge. This was the case for the results of study I that found lower temperatures in VPT infants in immediate SSC. The null-results in study V were interpreted as non-inferiority, even if the hypothesis was formulated as a superiority trial. The body of literature describing many benefits and very few risks or side effects of SSC are probably to some extent attributed to the selection of positive results in publications. In the current phase of implementation and scale-up, the risks of SSC also need to be addressed.

4.6 CLINICAL IMPLICATIONS

To date, less than 20% of studies on KMC have involved VPT infants and even with the existing evidence, coverage of KMC is estimated to be around 10% globally (73, 88). The mortality reduction seen in study IV and consequently the estimated 150000 LBW infants potentially saved globally per year is of a magnitude that has initiated an update of WHO guidelines to recommend KMC immediately after birth (170). This will only be possible with a systems' change; the understanding that mothers and newborn infants must be provided their care together, in mother-newborn couplet care (MNCC). In order for this to be safe, evaluations will need to be done alongside the gradual scale-up with attention to the safety of the infant and the mother and potential heterogeneity between settings. To budget for KMC and to find indicators for quality improvement is required in the implementation and follow-up process. A combination of champion led, project initiated and health systems based pathways has been described successful in the implementation (88). The WHO will publish a global position paper on KMC shortly, in which the evidence for KMC is summarised followed by strategies in implementation at different levels.

The clinical implication in HICs, as described in study II, is that improved cardiorespiratory stabilisation indicates that SSC is a non-invasive method of helping the VPT infant through the transition from foetal to extra-uterine life. With improved stability, some interventions may become redundant which consequently may protect the infant from invasive or painful procedures that could potentially be stressful or have side effects. The mechanisms that orchester the cardiorespiratory effects may involve the nurturing deep touch systems that have earlier been described to contribute to a decrease in heart rate and an increase in oxygen saturation (177). Moreover, this deep touch including the release of oxytocin contributes to social bonding between the parent and the infant (178). Seen from another angle, the results can be interpreted that VPT infants separated from their infant for incubator care display signs of stress. A stressful environment early in life and particularly in the NICU has been shown to have epigenetic effects on genes involved in stress regulation and bonding (179).

4.7 IMPLEMENTATION

Alongside the benefits of SSC, there are also publications describing the barriers for implementation. These barriers are mainly related to staff and facility resources; support of staff, staff and management priorities and attitudes, staff awareness of benefits and space (180, 181). One study showed that nurses believed they would lose control of the situation because of limited access to the infant and also that mothers would feel trapped (182). Hence, barriers may involve parents too. Studies describe that the support from the NICU staff is very important for parents when in SSC with their VPT infant immediately after birth (183, 184). Most parents have not experienced preterm birth or care in a NICU before, and they rely on the judgement, advice and attitudes of the NICU staff (183).

In LMICs, pain and fatigue in the mother has been stated as barriers to practice SSC (180). These are important factors to acknowledge. The mother is often a patient too, as preterm birth is strongly linked to poor obstetric health. Practicing SSC for long hours is an opportunity but it is also a challenge for the mother that needs to be recognised. Limited knowledge of the benefits of SSC, the perception that the umbilicus needs to be handled carefully and that the newborn infant covered with amniotic fluid, blood and vermix caseosa is dirty have also been described as barriers for SSC (185). In addition, there may be an effect on families of infants cared for in SSC. If the mother stays with her newborn infant around the NICU, family members will need to take care of the household and older children. Further, a component of KMC is early discharge with follow-up at home. This has been identified as a key challenge when investigating the obstacles for KMC implementation globally (186), as follow-up necessitates additional structures.

The discrepancy between evidence and implementation is sometimes referred to as the "Know-Do gap". This illustrates the need for an understanding of the context when an intervention is implemented into clinical practice (187). The Indian site of study IV have published their experience of providing MNCC in M-NICUs (188); in their view a successful paradigm shift in terms of obstetric and newborn care. General challenges in implementing evidence based treatments include that existing guidelines are very many and complex, resources are scarce both on national and facility levels. Moreover, there are limitations in engagement and communication with and within the community (189). A strategic and technical advisory group of experts at WHO have recommended focus on coordination, monitoring gaps in knowledge translation and strategies to improve uptake of guidelines (189). Hence, in addition to finding new therapies, another focus is to make the existing evidence available for every patient.

The results of study III, the description of SSC initiation and daily duration in a HIC, are interesting in terms of implementing SSC as part of the conventional care of LBW infants also in NICUs in LMICs. In Swedish NICUs, SSC is considered beneficial for preterm infants, there is experience of intermittent SSC integrated into neonatal intensive care, parents are present, there is space and nurse to infant ratios are relatively high. The late SSC initiation times and low daily SSC durations imply either that SSC is not considered important enough in this setting to be a priority, or that NICU staff experience risks and obstacles that are not described in publications.

The COVID-19 pandemic was a global example of how the fear of potentially harming newborn infants and staff by infected mothers resulted in separation of infants from their parents in the NICUs (190). The situation was complex with the safety of NICU staff righteously prioritised but consequently led to deprivation of many infants of KMC. A publication has described the theoretical harm to LBW infants by the lost opportunity of KMC due to restrictions during the pandemic, suggesting a 65 to 630-fold risk of mortality (191). A deeper understanding of the benefits of KMC might have led to other strategies in newborn care during the pandemic. It remains to be seen how KMC routines will be revisited or updated after the COVID-19 pandemic (88).

5 CONCLUSIONS

- SSC initiated immediately after birth for VPT and LBW infants, i.e. not waiting for the infant to become “stable enough”, is beneficial.
- KMC initiated immediately after birth for LBW infants in LMICs reduces neonatal mortality compared to when initiated after becoming stable.
- Immediate SSC may help VPT infants in making the cardiorespiratory transition from fetal to extra-uterine life, which increases their chances of spending this time undisturbed with their parents.
- Immediate SSC is a feasible alternative to care in an incubator for VPT and LBW infants, but attention needs to be paid to maintain a thermoneutral environment.
- VPT infants in Sweden are rarely cared for in SSC immediately after birth, nor continuously during their NICU stay.
- Infants should be provided their care together with a parent and SSC should be integrated in the medical and nursing care.

6 FUTURE DIRECTIONS

My thesis has covered the initial work and the primary outcomes of the IPISTOSS and iKMC trials. The report on SSC initiation times and duration from SNQ was done when prospective registration had just been implemented in a larger scale and should be followed up with validation of the data when improved routines for registration are established.

Within the scopes of the RCTs, there are many secondary outcomes; already collected data and follow-up data that will be analysed and disseminated. The long-term effects of SSC and especially of the increase in survival in LMICs are important to investigate. Have we gained healthy survival or a population with poor neurodevelopment? This is currently investigated in a follow-up study of the iKMC cohort and the results will be published within the next couple of years.

The IPISTOSS cohort is also currently followed-up with regards to neurodevelopment, psychosocial development, stress-reactivity, parent-infant interaction and parental wellbeing. We hypothesise that the early environment has impacts on health and disease later in life and that early parent-infant interaction may initiate a positive cascade of continued protective exposures for the infant. It is well-established that epigenetic programming governs the relation between early environment and later health and disease (192) and that preterm birth involves exposure to a stressful environment (179). Hence we have collected series of samples from the IPISTOSS cohort to study DNA methylation patterns in stress-related genes. Analysis of these samples will start shortly.

There was a reduction of clinical sepsis in the infants randomised to iKMC in study IV. We speculate that these infants are shielded from the NICU environment; from the equipment, from the staff and from other infants. A reduction in the sepsis rate is not expected in Scandinavia, with other types of NICUs; less crowding, higher nurse to patient ratios and better opportunities to maintain good hygiene. Nevertheless, we will report on the relation between immediate SSC and late sepsis in the IPISTOSS cohort. In future studies, it would be interesting to collect samples from the mother and infant to study the microbiome of the infant with the hypothesis that infants in immediate SSC are colonised with parental bacteria instead of hospital bacteria, which may have implications for long-term outcomes involving the immune system and the gastrointestinal systems.

The large reduction in neonatal mortality described in study V is an imperative for a systems' change; mothers and infants need to be provided their care together. However, implementation should not be done without close monitoring on what the effects are in other settings and in a larger scale. These effects may involve infants, mothers and health systems. Implementation studies are underway.

7 ACKNOWLEDGEMENTS

I would like to thank the following people without whom this thesis would not have been possible:

All the infants born too soon or too small recruited to the studies, and their parents.

Nils Bergman for the idea laying the ground for it all.

Björn Westrup for not hesitating at anything and for always suggesting a beer and a strategic meeting after 12-hour flights, when older people like myself want to nap. I am so thankful that I happened to be in the neonatal unit at Danderyd in 2010-11 before and after my rotation in Tanzania and that we started talking about EPISTOS/IPISTOSS.

Béatrice Skiöld for stepping up as the supervisor I needed and for carrying me through.

Wibke Jonas for carrying the IPISTOSS luggage and herding the IPISTOSS cats.

Siri Lilliesköld for sharing nightly data collections, for 5 x 52 Friday drink ideas and for a large number of WhatsApp big sister pieces of advice. Upcoming papers (no data should be wasted): "Correlation between IPISTOSS consent and birth between 1 and 6 a.m.", "Skin-to-skin contact and paternal weight gain", "Skin-to-skin contact and the transition from meconium to baby poop"

Stina Klemming for her stamina stretching from study recruitment to manuscript perfection and beyond.

Thomas Brune for an important contribution to the (unexpected) decision to become a neonatologist, for early study planning and for nice travel company.

The Research School for Clinicians Generation 16 and especially **Matteo Bottai** for opening the door to the wonderfulness of statistics (and for being one of few people I would like to have as a poster on my wall after the age of 25) and to fellow students **Elena Palleri** and **Essi Whaites Heinonen**.

Malin Almgren for the introduction to epigenetics that unfortunately could not be part of the thesis (but hopefully waiting first in line after dissertation) and for lovely travel company.

Anna-Karin Edstedt Bonamy for well needed senior co-supervisor pieces of advice.

Rajiv Bahl for listening when we presented the IPISTOSS protocol and for taking the lead of the iKMC Study when it outgrew us. Your philanthropy has been an inspiration to me.

Asante sana to each and everyone of the **iKMC Study Group** for teaching me more about clinical trials than he rest of the doctoral studies altogether. You have truly compensated for the years of writing applications and protocols and struggling and grinding and being constantly available and ready to recruit study subjects "at home".

To the research nurses for keeping an eye on the logistics, missing nothing; **Camilla Halzius**, **Gordana Printz** and especially **Kerstin Andersson**, also for the mutual love of schlager.

Jan Kowalski for consultations at the dangerous point when I thought I knew what I was doing in Stata.

Stavanger IPISTOSS colleagues **Siren Rettedal, Karoline Lode Kolz, Hanne Markhus Pike** and **Kirsten Engevik.**

Lars Navér for prioritising clinical research in his department and for always finding a reply to any silly meme or quotation I would send.

Alexander Rakow for supporting clinical progress when I needed that and for letting me off the hook when I needed this. (Sorry for being high maintenance and violating conference budget rules just a tiny ten-fold bit in 2018.)

Kajsa Bohlin-Blennow for a positive and encouraging attitude towards everything.

Viveka Nordberg for your can-do persona, your commitment to what really matters and for letting me copy applications for doctoral education etc. Just changed ESBL for KMC and everything went smoothly ever after as always when following your advice. (P.S. I'll come out of my thesis cave and recommit to the task of texting you when your dog's been walked and if your kids remembered violin class, when årshjulet lets me bike via your street, that is.)

Dirk Wackernagel, my go-to person at work and the president of Neonatal Climbing Club. I only recently, after climbing with other partners, understood that you were actually dragging me up when climbing – shocked and thankful at the insight. I really appreciate your way of making other people feel confident about themselves.

The clinical colleagues at the neonatal department; **Anne, Anna C, Anna G, Elisabeth, Emma, Emmanuelle, Emöke, Ewa, Evi, Feven, Giulia, Helena, Ingrid, Isabella, Jakob, Jenny A, Jenny S, Jessica S, Jessica W, Josef, Kajsa K, Katarina, Kolbrun, Leif, Louise, Malin, Marco, Martino, Mats, Mikael, Nika, Noni, Peter, Snorri, Sofia L, Sofia P, Sonja, Utku, Ulrika, Vala, and Veronica.** What a rich work environment. Thanks for the perfect balance of tailwind and friction.

Rebecka Lagercrantz for the best cover art work. You perfectly captured what I wanted to convey.

Constanze & the Associates, Dårfinkar & Dönickar and other dear friends; let's meet more!

My parents **Stig** and **Barbro** for decades of support.

My sister **Elsa**, brother-in-law **Michalis** and nephews **Alexander** and **Aris** for cousin hangout from Sjöstan to Brussels.

In-laws and an explosive number of cousins; **Roffe, Åsa, Tina, Örjan, Arvid, Hanna, Olle, Hannes, Hanna-Klara, Måns, Viktoria, Mattias, Maria, Knut, Mejt, Ture, Kai, Maj, Elling, Ilse, Sindra, Walton, Linnie, Gabbe, Ebbe**…and counting?

My husband **Love** for hanging around since being picked up by farmakologenssingelklubb@hotmail.com in 2001; for distance studies in Paris and parental leave in Dar-es-Salaam, for data management and for the annoying "people may see it the other way around, darling" responses to the last year's accelerating complaints. Our kids, my "sjalbarn", **Ivar**, **Vera** and **Saga**; you have quadrupled (or more) your mass during the course of my doctoral studies and you outsmarted me long ago. Thanks for keeping it real.

Thanks to the morning jog, the afternoon "fika" and the Friday drink. Couldn't and wouldn't have done it without you.

The studies in this thesis were financed by Bill and Melinda Gates Foundation, Region Stockholm, Barnforskningen, Kronprinsessan Lovisas Fond, Lilla Barnets Fond, Stiftelsen Samariten, Acta Paediatrica, Laerdal Foundation and BabyBjörn AB.

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