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IMMEDIATE SKIN-TO-SKIN CONTACT AFTER A VERY PRETERM BIRTH – SUPPORTING THE PARENT-INFANT RELATIONSHIP

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Stockholm 2024

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2024

ISBN 978-91-8017-328-5
Cover illustration: Ulrika Casselbrant

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Thesis for Doctoral Degree (Ph.D.)

By

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The thesis will be defended in public at Skandiasalen, Karolinska University Hospital, Stockholm, May 17th 2024 at 10.00 am.

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For preterm newborns and their parents, and to my colleagues in neonatal and obstetric care

"You know that the beginning is the most important part of any work, especially in the case of a young and tender thing…"

-Plato, The Republic

Popular science summary of the thesis

Neonatology is the specialty of pediatrics concerned with the care of newborn babies. Some of these babies have been born too soon and need care in a neonatal intensive care unit (NICU) after birth. In this thesis, born too soon refers to babies who were born more than two months early. The quality of life for these babies born early is sometimes poor, with developmental and parent-infant interaction problems/challenges. This has more recently spurred nurses, midwives, and doctors on to try to understand better how these babies better can be cared for in a way that doesn't just save their lives in the hospitals but also supports their early relationship with their parent, and subsequently, their development. Simply put, giving them a start in life that nurtures them, a start that has a positive impact beyond the walls of the NICU.

Vital for any newborn baby and its parent, and for their relationship to be able to develop, is to be able to stay close to each other after birth. Yet, being born too soon often involves separation after birth, followed by many barriers for closeness in the NICU setting. This compromises early opportunity for parents to interact with their newborn babies and care for them in the NICU. This may have a negative impact on both the baby's and the parent's well-being. Therefore, an important area within neonatology is developing caring methods in the NICU that can reduce separation of parents and babies, promote family involvement in care, and that create a supportive environment for the baby and parent together.

One method for keeping baby and parent together is through skin-to-skin contact (SSC) where the baby is placed naked on the parent's chest and covered with warm blankets. This is a caring method for babies born too soon that is practiced in the NICU and proven beneficial for both babies and parents. Directly after birth, SSC is routinely practiced for healthy newborn babies, as it is well known to help the baby adapt to life outside of the womb as well as to support interaction and bonding behaviors between parents and babies. Just recently, SSC started directly after birth has also been shown to be important for babies born too soon, mainly due to improved survival in settings with scarce resources. In a high-resource setting, SSC has also been shown to benefit the baby's stability in heart rate and breathing after being born too soon. Babies also maintain their body temperature better when they are cared for in SSC. However, little is known about the longer-term developmental impact of SSC when started directly after birth for these more vulnerable babies and their parents, and how this might support their relationship early in life. Further, researchers don't know if there is a difference in effects of SSC when started directly after birth for these babies and parents as compared to when practiced later during their NICU stay.

The aim of my thesis was to find out more about whether there are longer-term effects of SSC for babies born too soon and their parents, when started directly after birth and

as compared to later in the neonatal period, and how this might have an impact on the parent-infant relationship within the baby's first year of life. Especially, we wanted to know if the mothers' and fathers' well-being (study II) and the mother-infant interaction quality (study III) were different after care in SSC compared to standard care in incubator or cot after birth. We also wanted to explore how SSC after birth was experienced by the parents (study IV). Further, beyond the immediate period following birth, we wanted to understand better if the duration of parents' physical closeness to their baby in the NICU, including amount of SSC, was associated to parental well-being (study I). Study I was carried out in 23 NICUs in Europe, Canada and Australia, and study II-IV were carried out in three NICUs in Sweden and Norway.

In study I we found that there was a great variation between NICUs in the amount of time parents were present in the NICU, held their babies, and had their baby in SSC. Also, there was a great variation in depression symptoms experienced in mothers and fathers in these NICUs. However, we did not find any association between the amount of physical closeness to the baby in the NICU and later well-being (that is depression symptoms) in parents. We concluded that closeness in the NICU is important, as this is proven beneficial, but that it is probably more about the quality of the closeness to the baby in the NICU, rather than the amount of closeness, that may support parents' well-being.

In study II we found that parents who had their baby born too soon in SSC directly after birth, were feeling better. Mothers had fewer depression symptoms one week after birth and fathers had fewer depression and anxiety symptoms after coming home from the hospital. ***In study III***, we found that babies who had SSC directly after birth were happier and developed better in their social skills as observed when interacting with their mothers at four months. We concluded that SSC started directly after birth may have a protective effect on parents' psychological well-being and enhance mother-baby interaction quality.

In study IV parents described SSC directly after birth as an empowering and valuable experience that gave them a sense of connectedness with their baby and feelings of competence as parents, yet also had challenges at the timepoint surrounding birth. We concluded that SSC directly after birth is a positive experience for parents, but they need to be adequately supported by healthcare staff.

Abstract

Background: Preterm birth poses challenges that may negatively affect parental mental health and infant development. A well-functioning parent-infant relationship can mitigate the risk of preterm birth on infant development, and early interventions that foster close parent-infant contact and support parenthood from birth are therefore warranted. Skin-to-skin contact between parents and infants has been found to decrease distress in parents and improve parent-infant interaction behaviors, yet little is known regarding its benefits when initiated immediately after birth for more vulnerable infants. Further, there is a lack of knowledge regarding the difference in effects of SSC provided during the first postnatal hours and later in the neonatal period. The overall aim of this thesis was to gain knowledge about, and a deeper understanding of, the impact of skin-to-skin contact between parents and very preterm infants when practiced immediately after birth, as compared to later in the neonatal period, on parents' mental health and the parent-infant relationship within the first year of life.

Methods: The four studies in this thesis derive from two multicenter studies: a prospective longitudinal study, "The 2nd International Closeness Survey" (study I) and a randomized clinical trial, "The Immediate Parent-Infant Skin-to-Skin Study" (IPISTOSS) (study II-IV). Study I involved mothers (n=684) and fathers (n=574) to preterm infants born less than 35 gestational weeks of age from 23 neonatal units in 15 countries. In study I, associations between the amount of proximity between parents and infants in the neonatal unit, including time spent in skin-to-skin contact, and parents' symptoms of depression (assessed with Edinburgh Postnatal Depression Scale, EPDS) at discharge and at 4 months were investigated. Study II-IV derived from the randomized controlled trial IPISTOSS that compared care in skin-to-skin contact immediately after birth with standard incubator care for very preterm infants (28–33 gestational weeks of age) in three neonatal units in Sweden and Norway. Study II included 73 parent couples to 91 infants and investigated the effect on parents' symptoms of depression (EPDS) and anxiety (assessed with Spielberger State-Trait Anxiety Inventory, STAI) within the infants' first year of life. Study III included 71 infants and their 56 mothers and investigated the effect on mother-infant interaction quality (measured with the Parent-Child Early Relational Assessment, PCERA) at 4 months. In study IV, 12 parents participated in individual interviews at the time of discharge to home to explore their experiences of immediate skin-to-skin contact and the care and support from healthcare staff.

Results: Study I found no association between the duration of parent-infant proximity in the neonatal unit and symptoms of depression in parents at discharge and at 4 months. Study II found that immediate skin-to-skin contact after a very preterm birth decreased EPDS scores in mothers (mean [SD] 9.8 [6.0] vs 12.3 [5.9] in the control group, p <0.05) at one week after birth and EPDS (mean [SD] 3.0 [2.0] vs 6.4 [4.7] in the control group, p=0.02) and STAI scores (mean [SD] 27.7 [5.7] vs 36.1 [9.5] in the control group, p=0.002) in fathers at term-equivalent age of the infant. In study III, immediate skin-to-skin contact was found to enhance the infants' expressions of positive affect, communication and social skills when interacting with their mothers at 4 months (PCERA subscale 3 score mean [SD] 3.60 [0.47] vs 3.27 [0.50] in the control group, p=0.01). In study IV, immediate skin-to-skin contact was described as an empowering experience that promoted feelings of connectedness with their newborns yet had challenges and required adequate support from healthcare staff.

Conclusion: The main findings in this thesis suggest that the practice of skin-to-skin contact in the immediate postpartum period has an impact on the early parent-infant relationship following a very preterm birth, which is supported by the positive influence of immediate skin-to-skin contact on parents' mental health and mother-infant interaction quality as well as by parents' experiences. Beyond the immediate postpartum period, parent-infant proximity and skin-to-skin contact in the NICU need to be continued to be supported, along with other elements within infant- and family-centered developmental care that may further contribute to parental mental health after a preterm birth

List of scientific papers

I. Lehtonen L, Lilliesköld S, De Coen K, Toome L, Gimeno A, Caballero S, Tameliene R, Laroche S, Retpap J, Grundt H, Van Hoestenberghe MR, Skene C, Pape B, Axelin A; Separation, Closeness Experiences in Neonatal Environment (SCENE) research group. Parent-infant closeness after preterm birth and depressive symptoms: A longitudinal study. *Frontiers in Psychology*. 2022; 22;13:906531. doi: 10.3389/fpsyg.2022.906531.

II. Lilliesköld S, Lode-Kolz K, Rettedal S, Westrup B, Bergman N, Sorjonen K, Ådén U, Mörelius E, Jonas W. Skin-to-skin contact at birth for very preterm infants and symptoms of depression and anxiety in parents during the first year: A secondary outcome of a randomized clinical trial. *Manuscript*.

III. Lilliesköld S, Lode-Kolz K, Rettedal S, Lindstedt J, Linnér A, Markhus Pike H, Ahlqvist-Björkroth S, Ådén U, Jonas W. Skin-to-skin contact at birth for very preterm infants and mother-infant interaction quality at 4 months: A secondary analysis of the IPISTOSS randomized clinical trial. *JAMA Network Open*. 2023; 6(11): e2344469. doi:10.1001/jamanetworkopen.2023.44469.

IV. Lilliesköld S, Zwedberg S, Linnér A, Jonas W. Parents' experiences of immediate skin-to-skin contact after the birth of their very preterm neonates. *Journal of Obstetric, Gynecological & Neonatal Nursing*. 2022; 51(1): 53-64. doi: 10.1016/j.jogn.2021.10.002.

Related papers not included in the thesis

A. Linnér A, Westrup B, Lode-Kolz K, Klemming S, Lilliesköld S, Markhus Pike H, Morgan B, Bergman NJ, Rettedal S, Jonas W. 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 potential physiological, epigenetic, psychological and neurodevelopmental consequences. *BMJ Open*. 2020; 6;10(7): e038938. doi: 10.1136/bmjopen-2020-038938.

B. Linnér 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.

C. Linnér A, Lode-Kolz K, Klemming S, Bergman N, Lilliesköld S, Markhus Pike H, Westrup B, Rettedal S, Jonas W. Immediate skin-to-skin contact may have beneficial effects on the cardiorespiratory stabilisation in very preterm infants. *Acta Paediatrica*. 2022; 111(8): 1507-1514. doi: 10.1111/apa.16371.

D. 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. *Acta Paediatrica*. 2022; 111(9): 1715-1721. doi: 10.1111/apa.16433.

E. Lode-Kolz K, Hermansson C, Linnér A, Klemming S, Hetland H.B., Bergman N, Lilliesköld S, Markhus Pike H, Westrup B, Jonas W, Rettedal S. Immediate skin-to-skin contact after birth ensures stable thermoregulation in very preterm infants in high-resource settings. *Acta Paediatrica*. 2023; 112(5): 934-941. doi: 10.1111/apa.16590.

F. Brimdyr K, Stevens J, Svensson K, Blair A, Turner-Maffei C, Grady J, Bastarache L, Alfy A, Crenshaw JT, Giugliani ERJ, Ewald U, Haider R, Jonas W, Kagawa M, Lilliesköld S, Maastrup R, Sinclair R, Swift E, Takahashi Y, Cadwell K. Skin-to-skin contact after birth: Developing a research and practice guideline. *Acta Paediatrica*. 2023; 112(8): 1633–1643. doi.org/10.1111/apa.16842.

G. Klemming S, Lilliesköld S, Arwehed S, Jonas, W, Lehtonen L, Westrup, B. Mother-newborn couplet care: Nordic country experiences of organization, models and practice. *Journal of Perinatology*. 2023; 43(Suppl 1): 17–25. doi: 10.1038/s41372-023-01812-3.

Contents

List of abbreviations

CA	corrected age of infant
CI	confidence intervals
CONSORT	Consolidated Standards of Reporting Trials
EPDS	Edinburgh Postnatal Depression Scale
GA	gestational age
GCP	Good Clinical Practice
ICS2	the 2nd International Closeness Survey
IFCDC	infant-and family-centered developmental care
IPISTOSS	the Immediate Parent-Infant Skin-to-Skin Study
IQR	inter quartile range
KC	kangaroo care
KMC	kangaroo mother care
NICU	neonatal intensive care unit
PCERA	Parent-Child Early Relational Assessment
RCT	randomized clinical trial
SD	standard deviation
SSC	skin-to-skin contact
STAI	Spielberger State-Trait Anxiety Inventory
WHO	World Health Organization

Concepts and definitions of skin-to-skin contact used in this thesis

Concept	Definition
Skin-to-skin contact (SSC)	Care of newborn infant in SSC with a parent, or by parent chosen other
*Kangaroo mother care (KMC)	Care of the preterm or low-birth-weight infant in continuous or prolonged SSC with mother, almost or exclusive breastfeeding and early discharge from hospital with follow-up at home
Immediate skin-to-skin contact (or Kangaroo mother care)	SSC (or KMC) initiated immediately, or as soon as possible, after birth
Intermittent skin-to-skin contact	Sessions of SSC that are alternated with care in cot or incubator
Continuous skin-to-skin contact	SSC as the primary place of care, continued for up to 8-24 hours/day

*Note: KMC and SSC are often used interchangeably in the literature. In this thesis, when referring to publications, the terminology used in the citations will be used, regardless of the above author's definitions of KMC.

Use of terms

Families come in different constellations and parenting may look different. In this thesis, the terms mother, father, and parent are used throughout, however, with the acknowledgment that not everyone may identify themselves as such.

Prologue

Once when my oldest son was a little boy, we played a game called "what do you see…". When it was my turn, I asked him "what do you see when you think of yourself as a newborn baby"? With closed eyes he sat thinking for a little while, and then he smiled and said "mommy, I see myself in your arms". Many years earlier the famous pediatrician and child psychoanalyst Donald Winnicott had said something similar in his famous statement *"there is no such thing as a baby, there is a baby and someone"* (1). In essence, he implied that the infant cannot exist outside of a relationship, and therefore, neither can the parent.

In my years of clinical work as a pediatric nurse in the neonatal units at Karolinska University Hospital and BB Sophia, I have had reason to revisit these words many times and ponder on their meaning in the clinical context of being born too soon. Somehow, the past decades rapid development within the field of neonatology had brought us to a point where, from the perspective of survival, excellent medical care was being given to the infant, but (most often) this care was being given in another place than close to its parent. At large, the importance of the most basic of human relationships, the one between parents and their newborn, and how this relationship could be supported also after a preterm birth, was being overseen, especially at the time surrounding birth.

From my perspective, the work presented in this thesis has no beginning and no end. It is part of a continuum of shared experiences from parents, collegial discussions, ideas, and hard work put down every day in the neonatal units I have been fortunate to work within, with a focus on addressing this critical shortcoming within the overall advancements of neonatal care, and with an aim at minimizing parent-infant separation and supporting parent-infant closeness after a preterm birth. My hope is that the knowledge generated within this thesis will continue that discussion as well as contribute with new evidence for further change to be made, improving the care for preterm infants and their families from the moment of birth.

1 LITERATURE REVIEW

1.1 Preterm birth and a framework for parent-infant proximity

1.1.1 Preterm birth

Worldwide, approximately 10% newborns, 14 million annually, are born preterm (2). Preterm birth is defined as giving birth at less than 37 weeks of completed pregnancy and is often sub-divided into groups based on gestational age (GA): extremely preterm (<28 weeks), very preterm (<32 weeks) and moderately preterm (<37 weeks). In Sweden, the corresponding number is approximately 5.5%, amounting to around 6,500 newborns born preterm per year (3). Many preterm born infants require hospital care for shorter or longer periods. Preterm birth is one of the largest contributors to mortality up to the age of five, and is related to long-term morbidity in survivors (4). In high-income countries like Sweden, survival rates have continuously improved over recent decades due to medical and technological advancements. Still, these children experience short- and long-term neurodevelopmental impairments and the more preterm the infant is born the more challenges may arise (5). This places a heavy burden on patients, families, and the healthcare system. Therefore, it is of utmost importance to develop effective caring methods that improve not only survival but also the long-term health outcomes in this vulnerable group of newborns and their families. This includes caring methods that reduce parent-infant separation, promote family involvement in care, and focus on creating a neuro-supportive environment for the infant (6).

1.1.2 Parent-infant proximity in the NICU

The field of neonatology has been in rapid development over the past decades where the standards of care provided for preterm infants in neonatal intensive care units (NICUs) have significantly improved. Alongside medical advances, there has been an increased awareness of the importance of parents as essentials caregivers in the care provided for the infants in the NICU setting, with a recognition of the critical role parents play in promoting the health outcomes of their infants (7, 8). With this, the nurse's role has also shifted from being the primary caregiver to providing care in partnership with the parents, based on the individual needs of each infant and family (9). A large part of the brain's development after birth takes place in daily interactions with the early environment the infant is exposed to, most importantly being the parents (10, 11). As such, supporting a healthy development of the parent-infant relationship

during the neonatal period is critical, and emphasis is placed on parent-infant proximity at the beginning of life for this relationship to develop (12).

In the historic perspective, parents had to give up the responsibility of their newborn to the healthcare staff when admitted to the NICU. Parents have been excluded from NICUs out of fear of them spreading infections and they have been perceived as visitors, often only permitted to enter the unit when the infant was ready to be discharged (13). Overtime, observations of the effects of mother-infant separation and in contrast, mother-infant proximity, on the mother-child relationship, has inspired groundbreaking work; to give an example to such as what became known as the Attachment Theory (14). According to the attachment theory, *who* takes care of the newborn infant matters. Parents need to develop a strong emotional bond with their infant (bonding), and the infant needs their parent to be available and provide adequate responses to its signals and behaviors (attachment). Importantly, this has provided a theoretical base for the necessity of keeping parents and hospitalized newborn infants together from birth. Further, non-separation of parents and newborn infants has legal and ethical support in the UN Convention on the Rights of the Child from 1989, which also became Swedish law in 2020.

During the past decades, efforts to increase parent-infant proximity in the NICU setting have involved changes in social policies and NICU design (allowing parents to stay 24/7 in the NICU) as well as efforts to influence the caring culture provided by the healthcare staff within the units (supporting parent-infant proximity in daily care practices) (15, 16). Skin-to-skin contact (SSC) between parent and their newborn has been recommended as best practice to promote proximity in the NICU (17). Still, there is a wide variation regarding the amount of parent-infant proximity occurring in NICUs, ranging from parents' sole presence in the unit to being in direct SSC with the infant (16, 18). Thus, although advancements are being made to increase proximity between parents and infants during the NICU stay, the birth of a preterm infant and subsequent admission to a NICU still often involves parent-infant separation, impairing the early processes of becoming a parent (16, 19)

1.1.3 The rationale for parent-infant proximity from birth

The concept of *Infant- and Family-Centered Developmental Care* (IFCDC) is today being recommended in Swedish NICUs (20), and is at large implemented throughout Scandinavia based on the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (21, 22). IFCDC is a descriptive term for a generic framework that describes how to provide appropriate care to support newborn infant neurobiology and development, and at the same time to

recognize the parental role and parent-infant relationship as a vital base for later child development, supporting parenting capacities (23). Within this framework, keeping parent and infant in close physical proximity to each other from birth, is key. IFCDC builds on the fundaments of *Nurturing Care,* promoted by the World Health Organization (24). Nurturing care is defined as a stable environment sensitive to the child's needs and giving opportunities for interactions that are emotionally supportive and developmentally stimulating for the child's brain and body to grow and develop optimally (24, 25). Overall, the concept of nurturing care offers a salutogenic approach to the provision of neonatal care (26), with the vision of each newborn not only to survive, but thrive.

It has been suggested that a stable environment for the newborn is in direct SSC with a parent from birth as a mother (parent) and her newborn infant are inextricably linked (27). As such, SSC offers the expected evolutionary environment for early development, as well as a "buffering protection of adult support", especially needed when born preterm (27, 28). In this context, SSC is seen as a *place* of care rather than the care itself, i.e., providing the newborn with a neuro-supportive environment, and the role of both parents is emphasized. The rationale builds on the paradigm that mother-offspring separation is the potentially harmful intervention (29). Extensive research, in both animals and humans, has documented the universal stress reactions experienced by both mothers and newborns when they are separated (30, 31). The physiological response to stress has critical implications for short- and long-term outcomes for infants in the NICU (32). The opposite effect of mother (parent) infant separation and stress is reached through SSC. To give an example, SSC may operate through sensory experiences such as touch and warmth, activating sensory nerves that in turn stimulate the oxytocinergic system in the brain with release of the hormone and neurotransmitter oxytocin. Oxytocin has been shown to reduce the activity of the stress system, i.e., reduces the activity of the hypothalamic-pituitary-adrenalin (HPA)-axis and sympathetic nervous system and, consequently, stimulates activity of the parasympathetic nervous system which is related to restoration and growth (32, 33). Oxytocin may also reduce activity of the amygdala reducing fear, thus invoking a sense of calm in the infant and parent. Oxytocin has also been shown to stimulate social engagement with the infant to promote bonding, all of which is important to support directly from birth (34). Thus, parent-infant SSC may benefit the preterm infant by providing a buffer from being born too early and from the stressful physical environment of the NICU and may provide regulatory physiological and behavioral support (27).

Further, evidence suggests that there are sensitive periods for the impact of maternal care on offspring development during the early postpartum period and

beyond (35), which has also been described in humans (36). Importantly, early experiences of proximity, including SSC during the early postpartum period, have been shown to affect parent behavior and the parent-infant relationship later (37-39). For example, Bystrova et al. (38) found in their randomized clinical trial (RCT) on full-term infants that mother-infant interaction (maternal sensitivity, infant's self-regulation, dyadic reciprocity) was positively affected still after one year when SSC started immediately after birth as compared to being separated for the first two hours. This indicates that the first postnatal contact between parent and infant is important.

1.2 Preterm birth and parenthood

1.2.1 Becoming a parent in the NICU

Becoming a parent to a preterm infant is in many ways a challenging experience, both in relation to parenthood coming earlier than expected as well as to the specific conditions of becoming a parent in the unfamiliar and intimidating environment of the NICU. In this setting, parenthood is often described as a delayed process with an alteration in the parenting role: separation after birth, often attributed to the newborn's medical condition and need of technological support, can lead parents to feel disconnected from their newborn (40) and incompetent in their parenting role (40, 41). Parental feelings of exclusion, distress and loss of control have previously been reported as predominant related to the care of the newborn in the NICU (42). Further, mothers and fathers might present sets of different needs and coping strategies that require specific nursing support (43). Indeed, separation from the infant has been described as one of the most difficult and stressful aspects for parents when their newborn infant is hospitalized in a NICU (42, 44). Still, separation is accepted by parents as being an unavoidable part of NICU care (45). As most of the factors that cause separation, such as procedures, treatments and care routines are not controlled by the parents, it is important that healthcare staff are reflective of their everyday practices, to develop approaches that further support proximity between the parent and preterm infant starting directly from birth (46).

1.2.2 Parental mental health

Parents with a preterm infant admitted to a NICU are exposed to a range of potentially distressing experiences that may compromise their mental health. As such, preterm birth, and hospitalization in the NICU, has been linked to both acute and sustained mental health impairment in parents (47, 48), which may negatively influence parental functioning and ability to engage in their infant's care. A variety of distressing reactions are common following a preterm birth,

including feelings of sadness, fear, and grief. Prolonged parental distress may also occur and is of greater clinical concern due to its implications on parents' mental health outcomes, the parent-infant relationship, and subsequent child development (49-51). Therefore, early and preventative interventions are warranted to decrease distressing experiences and support parental mental health after a preterm birth, and this is an important component of any approach to improve child health outcomes (52).

There is today a growing body of literature on the mental health of parents of preterm infants admitted to the NICU. Reviews report on a wide range of mental health issues including depression, anxiety, stress, and trauma symptoms, especially in the first year, and these are known to measure higher compared to parents of infants born at term (48, 53). For example, parents of preterm infants are more likely to experience symptoms of depression and anxiety within the first year after birth, as compared to parents of term infants, with rates of clinically significant depression and anxiety as high as 40-50% during the early postpartum period (54, 55). Recent meta-analyses have concluded that preterm birth significantly increases the risk of postpartum depression in mothers, especially within the first 6 months after childbirth (56). Further, anxiety and post-traumatic stress was shown to affect two in five parents to infants admitted to the NICU, which is higher than rates in the general perinatal population (57). Over several years, these measures of mental health decrease significantly (53), although symptoms might remain elevated as compared to parents to infants born at term (51). Risk factors for more sustained mental health symptoms include lower socioeconomic status, lower maternal education, lower gestational age, higher medical acuity in the child and lack of social support (53, 55). Previously, fathers have often been disregarded as essential caregivers in the NICU (43, 58). This is reflected in the published research on parental mental health after a preterm birth, which has focused mainly on the mother, and there has been a call for research to report and follow-up on the mental health needs in both parents (48).

1.2.3 The parent-infant relationship

The psychological bonding of the parents to the infant, the infant's attachment to the parents, and subsequently their capability to adequately interact with each other, are of great importance for the development and well-being of both infants and parents (59). Attachment is the secure base the caregiver provides for its child (e.g., comfort and safety) and is built on the caregiver's responsiveness, continuity in behavior and sensitivity for the child and its key signals (60). These psychological processes start already during pregnancy and may be interrupted by the preterm birth (61). Further, behavioral cues of preterm

infants are weaker and often more difficult to interpret and respond to. This may complicate early bonding and attachment processes between parents and infants, as do crisis reactions of parents and the separation experienced for example when the infant is cared for in an incubator (62). Furthermore, parental mental health issues, such as depressive symptoms may affect not only the parent but also the infant. For example, depressed mothers have been shown to act less sensitive and responsive with their infants, with reduced engagement and playfulness in their interaction with their infant, thus disturbing maternal behaviors important for the infants' socio-emotional development (63).

Good-quality parent-infant interactions have protective effects on infant social-emotional, cognitive, and behavioral development (64). The parent-preterm infant relationship has been studied mostly in mother and preterm infant dyads by describing and assessing the quality in interaction behaviors and attachment patterns. Regarding interaction behaviors, mothers to preterm infants have been found to be less sensitive and emotionally involved and more anxious, controlling, and intrusive than mothers to full-term infants while preterm infants have been shown to be less responsive, and more passive and compliant (65-67). This is especially manifest when the mother has experienced high levels of stress during the perinatal period (65) and is associated to less favourable infant developmental outcomes (66). However, it has been suggested that differences in maternal sensitivity and interaction quality could represent a mother's adaption to their preterm infant's condition and behaviors, rather than ineffective parenting (67). In a systematic review (68), differences in mother-preterm infant dyadic interaction behaviors were found to be most evident during the first 6 months of life compared to mother-full-term infant dyads. However, findings are inconsistent, with five of 18 studies showing an equal or even higher quality of interaction in the mother-preterm infant group. Regarding attachment patterns, Korja et al. (68) conclude in a meta-analysis that preterm infants seem to be as likely to form secure attachments to their mothers as full-term infants at 1 year of age, despite early interactional differences, although high rates of insecure attachment patterns in preterm infants have also been reported up to early school age (69).

To summarize from a clinical perspective, it is important to support a healthy parent-infant relationship already in the NICU by avoiding early separation, decreasing parental distress, and facilitating positive early parent-preterm infant interactions.

1.3 Preterm birth and parent-infant skin-to-skin contact

1.3.1 Skin-to-skin contact: initiation time and duration after birth

Skin-to-skin contact refers to the infant being provided care in SSC with a parent (or by parent designated other) and involves placing the naked infant prone on the parent's bare chest, adequately covered to remain warm, for shorter or longer periods. To receive care in SSC is indisputably the least stressful and most supportive way of caring for the preterm infant (27, 28). It is also a method proven beneficial for parents and families (70). Globally, the wider term of Kangaroo Mother Care (KMC), also known as Kangaroo Care (KC), is often used to refer to a method of care for preterm infants involving continuous or prolonged SSC, almost or exclusive breastfeeding and early discharge from hospital (71). Initiation time of SSC after birth and hours spent in SSC per day often depend on the gestational age and medical condition of the infant. Other factors that may affect how SSC is practiced are staff attitudes, local unit routines and facilities for parents (18). The timing of initiation and duration of SSC between parents and preterm infants after birth has been seen to vary greatly, even between NICUs in the same country (72-74).

In high-income settings, such as Sweden and Norway, immediate SSC starting directly in birth room has been shown feasible and safe, both for moderately (75) and very preterm infants (76, 77). However, although early initiation of SSC has been an area of clinical focus during the past years in our setting, initial stabilization and care in incubator is still the routine care practice in most NICUs when born very preterm. For example, in a Swedish population-based register study with data from 2020-2021, only a minority of infants born before gestational week 32 received SSC within their first day of life, and SSC was initiated at median 14 hours post birth for the very preterm infants (74). Further, SSC is most often practiced intermittently (a few hours per day) as part of the routine care practice in our NICU setting (17). In a comparison between European NICUs for infants born less than 35 weeks (2013-2014), units in Sweden were found to be leading with SSC practiced at an average time of 8 hours per day (18). In contrast, the Swedish register study reported that SSC had been practiced for very preterm infants on average 5 hours per day (74).

1.3.2 Guidelines and clinical recommendations

There has recently been an update in recommendations regarding when SSC should be initiated following a preterm birth. Previously, it has been recommended that SSC (or KMC) should start as soon as the preterm infant is clinically stable (78). Initial stabilization of the infant post birth can mean different things in different contexts, and there have been no uniform criteria

when an infant is considered "stable enough" for SSC. Globally, this has often meant that the infant should be off respiratory support or intravenous fluids (79), thus sometimes taking days to weeks until SSC has been initiated. A recent large RCT studied the effects of immediate KMC, i.e., with SSC initiated before the infant was considered clinically stable. In those infants that had received immediate KMC (SSC initiated at median 1.3 hours post birth), mortality was reduced with 25%. The RCT included low-birth-weight infants (between 1000 – 1799 g) in five low-and middle-income settings in Africa and Asia (80). Following this, new guidelines from the World Health Organization (WHO) were issued in 2022, recommending SSC (or KMC) for preterm or low-birth- weight infants to be started "*as soon as possible after birth, before the infant is clinically stable, unless the infant is unable to breathe spontaneously after resuscitation, is in shock or needs mechanical ventilation"* (81). Furthermore, the WHO recommends as much subsequent SSC as possible, or at least 8 hours a day. Implementation strategies have also been issued for scale-up in different caregiving settings (82). Based on the current evidence on the benefits of early SSC for all gestational ages, a systematic review and practice guideline from 2023 concluded that that "*immediate, continuous, uninterrupted skin-to-skin contact should be standard care for all mothers and all babies (from 1000 g with experienced staff if assistance is needed)"* (83).

1.3.3 Beneficial effects of skin-to-skin contact

1.3.3.1 Benefits in stable preterm infants

There is today a large body of evidence for the benefits of SSC in stable preterm infants. The benefits have both short-and long-term consequences (84). For example, stable preterm infants cared for in SSC, as compared to care in incubator, show better temperature control (85), cardio-respiratory stability (86) and improvement in self-regulation (e.g., sleep-wake cyclicity) (87), with enhanced neurodevelopment later in childhood (88). Further, SSC decreases pain response during painful procedures (89) as well as physiological stress, by reducing cortisol and increasing oxytocin levels in preterm infants (90). The practice of SSC has been associated with increased prevalence of breastfeeding in preterm infants (91) as well as earlier attainment of exclusive breastfeeding (92). In a Cochrane review (79), a 40% mortality reduction was reported among stabilized low-birth weight infants (<2000 g) cared for in KMC as compared to conventional care. Other reported benefits were lower rates of sepsis and improvements in some measures of infant growth, breastfeeding and mother-infant bonding and attachment (79). Further, being cared for in KMC during the neonatal period has been shown to enhance brain development in young adults

born preterm, suggesting neuroprotective effects of KMC that may improve lifetime functionality (93).

1.3.3.2 Benefits immediately following birth

During the first hours after birth, the infant and mother appear to be extra primed towards one and each other if kept in close physical proximity (94-96). For example, it has been shown how SSC triggers several innate biological breastfeeding behaviors in the infant if left undisturbed on mother's chest for the first postnatal hour (97). In healthy term infants, benefits of SSC early in life (first 24 hours) include enhanced breastfeeding behaviors, better glucose homeostasis, better temperature control, and enhanced mother-infant bonding (98). Subsequently, SSC is the recommended place of care when born healthy and at term, promoted by WHO and UNICEF through the Baby Friendly Hospital Initiative, and widely practiced in birth units in Sweden (99). More recently, SSC has also been shown to support the preterm infant's physiological transition to extra-uterine life including adjustments in temperature, heart rate and respiration, as well as early breastfeeding behaviors and parent-infant bonding (100-103). Overall, there is today a growing body of evidence regarding the short-term physiological effects of SSC when initiated directly after birth also for preterm infants. Yet, reports on more long-term developmental effects of immediate SSC for preterm infants are still lacking. Also, little is known on the difference in effects of SSC provided immediately after birth and later in the neonatal period.

1.3.4 Impact on parental mental health

Mechanisms by which SSC might increase well-being and support mental health in parents to preterm infants have been described as both psychological and physiological. For example, SSC facilitates a feeling of connectedness between the parent and preterm infant and helps the parents feel more confident in their parenting role (104, 105). SSC has also been shown to regulate stress in both parents and infants by biological indicators such as release of hormones oxytocin (increase) and cortisol (decrease) (106).

There is evidence suggesting that SSC might reduce the risk for postpartum depression in mothers to preterm infants. However, findings are inconclusive. In a meta-analysis from 2019 (107), including seven SSC intervention studies with 643 mother-infant dyads, the effects of SSC on postpartum depression symptoms among mothers to preterm infants was found to be small, yet significant, suggesting that a possible protective influence might exist. These results correspond with findings from a previous systematic review (108), examining the impact of KMC on maternal mood (e.g., anxiety, depression). In five

out of nine studies, significant findings suggested a protective association between KMC and maternal mood. However, both reviews have also highlighted several methodological limitations to be considered, such as an underreporting of intervention features in the studies. One intervention feature commonly not reported was the latency period in hours or days between birth and SSC initiation (107). Similarly, a meta-analysis from 2021 (109) found SSC as practiced in the NICU to significantly reduce levels of mothers' anxiety and stress, yet the timing of initiation of SSC after birth was not considered. Thus, from the current state of evidence, effects of SSC on maternal depression, anxiety, and stress regarding timing (time from birth and SSC initiation), but also in relation to duration and frequency remain unclear. Further, studies evaluating the effects of SSC on paternal mental health are scarce. A systematic review and meta-analysis from 2023 on effects of KMC on parental health confirmed beneficial effects on maternal mental health but found no clear effect on paternal depression or stress (110). However, from the 30 included trials, only three trials reported on paternal health outcomes.

1.3.5 Impact on the parent-infant relationship

There are several follow-up studies up to a year after birth that show continued positive effects of SSC interventions on the parent-infant relationship after preterm birth, although results remain inconclusive. In a systematic review from 2014 (108), seven out of nine studies found that KMC significantly helped improve parent-infant interaction behaviors, but they also highlighted a large heterogeneity among the studies with several methodological limitations to be considered; for example differences in intervention performance and the use of standardized assessment tools. Longer-term follow-up studies are rare, but positive effects of SSC on mother-infant interaction have been reported up to 10 years of age (88), while other studies have not been able to confirm more long-term effects (111). Further, it is unclear whether there is a dose-response effect of SSC. In one study including 31 mother-preterm infant dyads (112), no differences were found in interaction behaviors at four months after practicing continuous vs intermittent SSC during their NICU stay. This suggests that the interaction quality between preterm infants and mothers does not necessarily improve by spending more time in SSC, although it should be noted that the intermittent study group practiced as much as 6 hours of SSC per day. At the same time, SSC interventions practiced as short as within the first two hours after birth, have been seen to affect mother-infant interaction in a positive way when measured at 6 months (113) and at 1-year of age (38). This raises the question not only of the impact of duration of SSC, but if there are critical timepoints post

birth when the intervention of SSC is especially important for the developing parent-infant relationship.

1.4 Summary, research gap and the contribution of this thesis

The parent-infant relationship is today recognized as a vital base for later child development. Early interventions that support parenthood and foster close parent-infant contact from birth are therefore warranted, especially for smaller and more vulnerable infants. Skin-to-skin contact is a well-studied and evidence-based place of care for the term and stable preterm infant, commonly practiced in the NICU to enhance both infant and parent outcomes. Immediately after birth, SSC is the recommended place of care for healthy term infants when transitioning from intra- to extrauterine life, supporting the infant's physiological adaptation and breastfeeding behavior post birth, as well as the parent-infant relationship. Just recently, the recommendations have changed to also provide immediate SSC after birth for preterm and low-birth-weight newborns, mainly due to the convincing effects on short-term infant outcomes, such as mortality and physiological adaptations following birth. Thus, immediate SSC is considered safe and feasible for preterm infants, and the desirable standard of care. Yet, little is known about parental experiences and the longer-term effects of SSC when practiced directly after birth for very preterm infants and their parents. Further, there is a lack of knowledge regarding the difference in effects of SSC provided during the first postnatal hours of transition and later in the neonatal period. This is focus of the present thesis. This knowledge is needed to advance clinical recommendations regarding timing and duration of SSC in the NICU. It is also needed to learn how to best support the early processes of becoming a parent to a vulnerable infant, and eventually to support early child development.

2 RESEARCH AIMS

In the light of the literature presented above, the overall aim of my thesis was to gain knowledge about, and a deeper understanding of, the impact of SSC between parents and very preterm infants when practiced directly after birth (immediate SSC), as compared to later in the neonatal period, on parents' mental health and the parent-infant relationship within the first year of life.

The specific aims were:

1. To assess the amount of proximity between parents and infants in the neonatal unit after preterm birth and its associations to parents' symptoms of depression at discharge and at 4 months of corrected age (study I)

2. To determine the effect of immediate SSC versus standard incubator care at birth for very preterm infants on parents' symptoms of depression and anxiety within the infants' first year of life (study II)

3. To determine the effect of immediate SSC vs standard incubator care at birth for very preterm infants on mother-infant interaction quality at 4 months of corrected age (study III)

4. To explore how parents to very preterm infants experienced the intervention of immediate SSC at birth and care and support from healthcare staff (study IV)

3 MATERIALS AND METHODS

3.1 Design

The present thesis project is based on two multicenter studies: a prospective longitudinal study (ICS2, study I) and an RCT (IPISTOSS, study II–IV). Table 1 presents an overview of the characteristics of the included studies.

Table 1. Overview of studies and methods included in the thesis.

Study	Study design	Study sample (n) / Setting	Measures	Time of data collection	Analyses
I ICS2	Longitudinal cohort	684 mothers and 574 fathers of infants born <35 wGA 23 NICUs from 15 countries in 2018-2020	*Closeness Diary* (presence/holding/SSC; self-reported) *Edinburgh Postnatal Depression Scale* (EPDS; self-rated questionnaire)	2-week period in NICU Discharge and 4-months CA	Descriptive statistics Linear mixed models for repeated measures
II IPISTOSS	RCT	91 infants born at GA 28+0-32+6 and 73 parent couples 3 NICUs from Sweden and Norway in 2018-2021	*Closeness Diary* (SSC; self-reported) *Edinburgh Postnatal Depression Scale* (EPDS; self-rated questionnaire) *Spielberger State-Trait Anxiety Inventory* (STAI; self-rated questionnaire)	First week post birth At 7 days, term-age, 3-4- and 12-months CA At 7 days, term-age, 3-4- and 12-months CA	Descriptive statistics Non-parametric bootstrapping Linear and logistic regression Full information maximum likelihood estimation
III IPISTOSS	RCT	71 infants born at GA 28+0-32+6 and 56 mothers 3 NICUs from Sweden and Norway in 2018-2021	*Closeness Diary* (SSC; self-reported) *Parent-Child Early Relational Assessment* (PCERA; video recordings of mother-infant interaction)	First week post birth At 4 months CA	Descriptive statistics Multilevel regression analysis
IV IPISTOSS	Qualitative	12 parents (6 mothers and 6 fathers) 2 NICUs from Sweden in 2018-2019	*Semi-structured interviews*	Discharge	Reflexive Thematic Analysis

3.2 The 2nd International Closeness Survey (Study I)

The "2nd International Closeness Survey" (ICS2) is an international multicentre longitudinal cohort study that emanated from the Separation and Closeness Experiences in the Neonatal Environment (SCENE) research collaboration network. SCENE is an international multi-disciplinary group of professionals interested in studying various aspects of separation and closeness experiences in the neonatal environment. I have been an active member of the group since 2016 and represent the neonatal units at Karolinska University Hospital in this study, together with a fellow senior researcher. As a doctoral student, I was involved in all the study preparations, setting up the study at the neonatal units at Danderyd, Solna and Huddinge (all the neonatal units within Karolinska University Hospital), as well as overseeing the data collection of the study, with the help of a research nurse at each unit. The study was coordinated by the principal research team in Turku, Finland. The ICS2 had two main aims; 1) to assess the association between early parent-infant physical proximity in the NICU and later depression symptoms among parents to preterm infants, and 2) to assess the association of family-centered care as perceived by the parents with later depression symptoms. I was involved in reporting on the first study aim of this study (study I).

The study was performed in 23 NICUs from 15 countries: Australia, Belgium, Canada, Croatia, Denmark, England, Estonia, Finland, Iceland, Lithuania, the Netherlands, Norway, Poland, Spain, and Sweden. The aim was to include 30 families from each unit. Parents of preterm infants born below 35 weeks of gestation admitted to a participating NICU were invited to participate in the study within the first week of life. Written informed consent was obtained from either or both parents, depending on if the mother, father, or both, wanted to participate. The exclusion criteria included: estimated hospital stay length less than 3 days, any life-threatening medical condition of the infant, triplets, and parent who were unable to read English or the local language of the study site. The family also needed to have a mobile phone for data collection for the second aim of this study (114).

3.2.1 Settings

The ICS2 study included NICUs from various countries within Europe, Canada and Australia providing diverse caregiving settings regarding parental leave policies, NICU design, local unit routines and care culture. Thus, this diversity in settings could provide the study with a large variety of parent-infant proximity in the NICU, from being able to be present in the NICU to spending time in SSC with

the infant, as previously had been reported from the 1st International Closeness Survey (18).

3.3 The Immediate Parent-Infant Skin-to-Skin Study (Study II-IV)

The "Immediate Parent-Infant Skin-to-Skin Study" (IPISTOSS) is an international multicenter RCT that was conducted in three NICUs in Sweden (Karolinska University Hospital) and Norway (Stavanger University Hospital). The primary aim of IPISTOSS was to evaluate the effect of immediate SSC for very preterm infants on their cardiorespiratory stabilization after birth in a high-income setting. Secondary aims included breastfeeding, psychological, and neurodevelopmental outcomes for infants and parents. Further, biological mechanisms such as epigenetic changes and HPA-axis functioning, that possibly could mediate effects of immediate SSC onto outcomes described above, were included. Data collection was performed during hospital stay and at follow-up visits at term-age and 3-4, 12- and 24-months corrected age (CA) of the infant (Figure 1). As a doctoral student, I was involved in the Swedish arm of the study and participated in all phases of recruitment and data collection of the study from birth up to 12 months CA. The study was registered in Clinical Trials.gov in spring 2018 with trial registration number NCT03521310, and recruitment was conducted between April 2018 and June 2021. A sample size of 100 infants was estimated to attain power for the main outcome of infant cardiorespiratory stabilization. To compensate for attrition, 150 infants were deemed to be an adequate sample. In the end, 91 infants were included as the trial was terminated earlier because of benefit of the intervention on the main outcome (101). The study design, procedures and outcome variables are described in the IPISTOSS protocol paper (115) and reporting has followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines (116). A pilot study had been conducted between 2014-2016 that showed that immediate SSC in this population was feasible, yet highlighted the need for caution to be paid to maintain normothermia (77).

3.3.1 Settings

Two NICUs from Karolinska University Hospital in Stockholm participated; Huddinge and Danderyd. Huddinge is a level 3 NICU (births from GA 26 weeks and intensive care) with 15 beds, serving a birth unit with approximately 4000 births per year. Danderyd is a level 2 NICU (births from GA 32 weeks, but very preterm infants are also born there at times) with 16 beds, serving a birth unit with approximately 11 000 births. The NICU at Stavanger University Hospital is a level 3 unit (births from GA 23 weeks) with 16 beds, serving a birth unit with

approximately 4500 birth per year. When conducting the study, the clinical trend at these units was to support SSC as soon as possible after birth for moderately preterm infants and above (from approximately 32-33 weeks), but for infants born younger, initial stabilization and transport to NICU in an incubator was still the norm, with SSC initiated as soon as it was considered medically acceptable (which could mean anything from hours to days).

All participating units have a similar setting including a long tradition of providing NIDCAP-based infant-and family-centered developmental care (22). This includes early engagement of both parents in the care of their infant, intermittent SSC as routine care and psychosocial support services for parents. Parental leave policies in the two countries and NICU design in the units enable parents to stay with their infant during the entire hospital stay. In all three units, preterm infants are discharged to neonatal home care at approximately 34-35 gestational weeks, when they are cardiorespiratory stable, can maintain normothermia without external heat sources and have started gaining weight.

3.3.2 PICO – Population, Intervention, Comparison, Outcome

3.3.2.1 Population

The study included inborn infants (singleton or twins) with a GA of 28+0 to 32+6 weeks + days, regardless of mode of birth and with a parent or significant other available for SSC within the first postnatal hour. The GA limits were chosen to select the preterm population in our settings where immediate SSC was not part of the conventional care provided at birth yet deemed to be safe. Exclusion criteria included infants with congenital infection, major malformations, or other conditions deemed contraindicating study participation according to the physician in charge. Parents also had to be able to read information about the study in Swedish, Norwegian or English.

Screening was performed daily for women admitted to the obstetric units with threatening preterm labour in gestational weeks 28+0 to 32+6. The parents were informed about the study by a research team member and asked to participate. All parents gave written informed consent. Definite inclusion and randomization of infants took place shortly before birth, for those who still matched the inclusion criteria. The infants were randomized to either the intervention of "immediate SSC" (iSSC) or "conventional care" (CC) through a randomization software. The electronic randomization was performed in uneven block sizes, with a 1:1 ratio, and stratified by site and gestation (28+0 to 30+6 and 31+0 to 32+6 weeks). Twins were allocated to the same study group.

3.3.2.2 Intervention

The intervention lasted throughout the first 6 postnatal hours. All monitoring, nursing and medical care were identical in both groups – it was only *the place of care* that differed. Routine care at birth for all infants included nasal continuous positive airway pressure (CPAP), nasogastric tube feeding and monitoring with electrocardiography electrodes and pulse oximetry.

Immediate SSC: SSC was started as soon as possible at the discretion of the neonatologist in charge and could be provided by either parent. After a vaginal birth, the infant was most often placed directly on the mother's chest, with positioning and monitoring by the neonatal team. The infant was initially cared for in the birth unit and later transferred to the neonatal unit while maintaining SSC with either parent. Following cesarean section, SSC was initiated with the father until the mother could be transferred to the neonatal unit. Midwives from the obstetric department were responsible for the mother's postpartum care. Twins were either placed together with one of the parents or cared for with one parent each. SSC was only interrupted in need of care procedures that must be performed elsewhere (for example insertion of umbilical catheters, x-rays), but infants returned to SSC as soon as their condition allowed.

3.3.2.3 Comparison

Control: Directly after birth, the infants were stabilized on a resuscitative or in an incubator and then transported to the NICU in an incubator for continued care. As per standard care, parents were allowed to stay at their infant's bedside and were able to touch the infant in the incubator. Intermittent SSC was initiated after the first 6 hours if considered medically acceptable as per unit guidelines.

3.3.2.4 Outcome

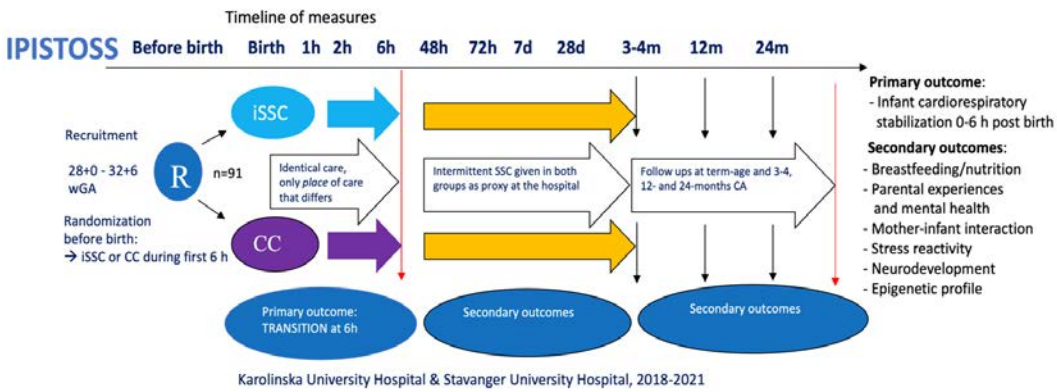
Outcomes in the present thesis are parental mental health, mother-infant interaction, and parental experiences.

3.3.3 Challenges

The IPISTOSS RCT presented considerable challenges and was resource demanding at all steps from screening (daily), acquiring informed consent (before birth), enrolment of study participants (at birth) to data collection (research staff present at birth and during the first six hours, followed by data collection during hospital stay and follow-ups). The exact information on eligible families randomized in IPISTOSS is not available due to heterogeneity in screening routines (the number of mothers screened was recorded in Sweden, but not in Norway), but a prior pilot study conducted by our group at the

Danderyd site at Karolinska had showed a rather low proportion of eligible families randomized (77), illustrating these challenges. Further, within the timeframe of the intervention (0-6 hours post birth), the mothers needed care themselves, but postpartum care routines were not part of the study protocol per se, and the mother's postpartum care was thus subjected to the local routines at each study site. Unforeseen, recruitment was also paused during 2020 due to the Covid-19 pandemic, which extended the recruitment process and subsequently, data collection, over a longer time than initially anticipated. The pandemic also affected the planning for the follow-up visits, with research staff conducting home visits instead of having families coming into the clinic during this time.

Figure 1. An overview of the IPISTOSS RCT and study outcomes



3.4 Participants and data collection

3.4.1 Study I

The study participants in study I included 684 mothers and 574 fathers, with a total of 790 infants. Due to dropouts at the various follow-up timepoints, 542 mothers and 351 fathers were included in the analysis at discharge, and 409 mothers and 276 fathers at the analysis at 4 months CA. For those mothers and fathers included in the final analysis, i.e., where we had data of any of the parents from one or both follow-up timepoints, mothers and fathers background characteristics included a median age of 31 and 33 years, the majority had a paid job (84% and 96%, respectively) and were cohabiting (91% and 95%, respectively). Further, 44% of the responding mothers and 39% of the fathers,

reported siblings in the family. There was a total of 660 infants in the final study group of which 29% were twins. They had a median GA of 31 weeks, a mean birthweight of 1602 grams, and more were boys (57%). Further, 57 % of the infants had been delivered with a caesarean section.

Data collection was carried out between March 2018 and February 2020, lasting from two to 12 months in the participating units. Data was collected prospectively and included data on amount of physical proximity between the parent and preterm infant in the NICU (recorded by the parents) up to 14 days, with three separate measures for parents' presence: present in the unit, holding and SSC. Parental depression symptoms were collected at discharge and 4 months CA. Background data was collected with a questionnaire in the beginning of study participation, including sociodemographic characteristics of the parents and their infants. In this questionnaire, parents could also retrospectively indicate the first time they saw, held, and had SSC with their infant post birth.

3.4.2 Study II

The study participants in study II included the entire cohort of IPISTOSS. The study included 91 infants (40% twins) and 73 parent couples (93% cohabitant). Infants had a mean GA of 31 weeks and birthweight of 1534 grams, and there were more boys (56%). A total of 45 infants and 35 parent couples were allocated to conventional care and 46 infants and 38 parent couples to immediate SSC after birth. Baseline characteristics of mothers, fathers and infants were equally distributed between the groups, except there were more boys in the SSC group (p=0.002). There was also a near group imbalance regarding primiparity, with more first-time mothers in the SSC group (p=0.05). Parent and infant characteristics in study II are presented in Table 2. During the first year of follow-ups, 7 parent couples (10%) left the study.

Data collection for study II was ongoing between 2018-2022. Screening for symptoms of depression and anxiety in both mothers and fathers was performed at 7 days post birth, at term equivalent age (GA 40+0) and at 3-4 and 12-months CA. Except for the first measurement timepoint (in hospital), data collection was done in conjunction to the follow-up visits in the study, managed by me and fellow research team members. These corresponded to the Swedish and Norwegian national neonatal follow-up programs' routine visits. Parents' either filled out the questionnaires during these visits, or shortly before.

Table 2. Parent and infant characteristics in IPISTOSS

Parent and infant characteristics in IPISTOSS	**SSC group** (n= 46 infants, 38 mothers and 38 fathers)	**Control group** (n= 45 infants, 35 mothers and 35 fathers)
Gestational age, mean (SD, range), weeks	31+2 (1, 28+6–32+4)	31+0 (1, 28+4–32+6)
Birthweight, mean (SD, range), grams	1571 (395, 702–2352)	1494 (400, 555–2440)
Apgar score 5 min, median (IQR)	9 (7–9)	9 (8–10)
Vaginal birth, n (%)	14 (37)	8 (23)
Twins, n (%)	16 (35)	20 (44)
Child sex, Female, n (%)	13 (28)	27 (60)
Preeclampsia, n (%)	10 (26)	16 (46)
Primiparity, n (%)	26 (68)	16 (46)
Length of hospital stay, days, median (IQR)	31 (16–47)	36 (23–50)
Maternal age, mean (SD, range), years	31 (5, 21–40)	32 (5, 22–45)
Paternal age, mean (SD), years	33 (5)	34 (6)
Cohabitant parents, n (%)	35 (95)	33 (97)
University education mother, n (%)	22 (58)	26 (74)
University education father, n (%)	16 (42)	23 (66)
Prior mental health diagnosis mother, n (%)	5 (14)	4 (11)

3.4.3 Study III

The study participants in study III represent a subsample of the IPISTOSS cohort, i.e., those who completed the 4-month follow-up that included a video recording of mother-infant interaction. The study included 71 infants (44% twins) and 56 mothers. Infants had a mean GA of 31 weeks, mean birthweight of 1535 grams and there were more boys (59%). Mothers had a mean age of 32 years, and the

majority were first-time mothers (57%). A total of 37 infants were allocated to conventional care and 34 to immediate SSC after birth. Baseline characteristics of infants and mothers, including symptoms of depression and anxiety and parenting stress, were distributed equal between the groups, except for more boys and first-time mothers in the SSC group. There was a dropout of 20 infants (22%) at the 4-month follow-up, which was mainly due to challenges in maintaining data collection during the Covid-19 pandemic.

Data collection for this study was ongoing between 2018-2021. I was responsible for all the data collection (video recordings) in Sweden, and a fellow doctoral student in Norway. The follow-up visit at 4-months CA was done in the clinic or at the participants' homes. This was due to hospital restriction policies during the Covid-19 pandemic, where clinical visits were redirected to the homes if possible. The visits were made at a morning time when the infant had slept and was newly fed. Mother-infant interaction was video recorded according to a standard procedure (117).

3.4.4 Study IV

The study participants in study IV represent a subsample of parents in the IPISTOSS cohort in Sweden. The inclusion to this study was based on a purposive sampling in which parents who were randomized to the intervention group of immediate SSC were asked to participate in an interview regarding their experiences. Sampling criteria included variations in mother's and father's experiences, infant GA, and mode of birth. The sample size was based on the concept of information power (118), i.e., ultimately determined within the process of data collection by the adequacy (richness and complexity) of the data for addressing the aim. A total of 12 parents, 6 mothers and 6 fathers were included (6 parent couples). The parents mean age was 33 years, and 67% of the mothers had a cesarean birth. The mean GA of the infants (n=7) was 31 weeks and there was one pair of twins.

I conducted the data collection between 2018-2019. Individual interviews with the parents were held approximately one to two weeks after discharge from the hospital, allowing for some time to have passed for parents to have gained some perspective. All but two interviews were held in the participant's homes. The interviews lasted on average 33 minutes (range 17-51 minutes).

3.5 Measures

3.6 The main outcome measures in studies I-IV

3.6.1 The Parent-Infant Closeness Diary

The Parent-Infant Closeness Diary is a paper diary that has been developed to prospectively measure parent-infant physical proximity in the NICU (119). The original diary measures the daily duration of parental presence, holding, and SSC (one diary page per day). The paper diary can be kept at the infant's bedside and parents can, with 5-minute accuracy, draw separate timelines showing when they are present in the unit, holding the infant (infant held in parents' arms with clothes on) or providing SSC (infant lying on the parent's bare chest, dressed only in a diaper). Duration times of each measure can then be calculated as minutes or hours per day. The diary includes space for parents to explain the reasons for empty or missing diary days. The Parent-Infant Closeness Diary has been shown to be a reliable and feasible tool when collecting data on parent-infant proximity for up to 14 consecutive days in the NICU, and parents provide reliable documentation on SSC (119, 120).

The Parent-Infant Closeness Diary was used in study I-IV to measure duration of parent-infant physical proximity in the NICU as recorded prospectively by the parents. In IPISTOSS (study II-IV), the diary was slightly modified. The measure "holding" was omitted from the diary, focusing solely on SSC (the definition clarified to also include breastfeeding while in SSC), and the timelines were drawn with 15-minute accuracy, which was considered more feasible for the parents. Further, in IPISTOSS, the diary was used during the intervention period of 0-6 hours post birth, measuring both initiation and duration of SSC during this time, and was then recorded by research staff.

3.6.2 Edinburgh Postnatal Depression Scale (EPDS)

In studies I and II, symptoms of depression in mothers and fathers were screened by using the Edinburgh Postnatal Depression Scale (EPDS) (121). The EPDS is a commonly used self-report questionnaire and has been translated and validated in many languages. It is validated to be used during the postnatal period, which differs from other periods in life, assessing the severity of 10 emotional depression symptoms during the past 7 days. The questions concern the absence or presence of symptoms such as mood, insomnia, tearfulness, and thoughts of self-harm. Each item on the questionnaire is scored from 0-3, with a

higher score indicating more symptoms of depression. The total score can vary between 0-30. Studies across different populations and countries have used different cut-off scores for clinical depression (usually ranging from 9 to 14), depending on sensitivity and specificity on detecting a probable clinical depression (56). In study I and II, we used the mean score of EPDS to report on depression symptoms. Additionally, the incidence of probable clinical depression was reported in these studies using a cut-off of 13 or more for mothers and 10 or more for fathers (as fathers usually rate lower than mothers). These are validated cut-off scores recommended to screen for major depression in mothers and fathers during the postnatal period (122, 123). Further, in study I, an additional analysis was run for the mothers by also using a cut-off score of 10, considering the heterogeneity expected for detecting different levels of postnatal depression across different cultural settings (124).

3.6.3 Spielberger State-Trait Anxiety Inventory (STAI)

In study II, symptoms of anxiety in mothers and fathers were screened by using the Spielberger State-Trait Anxiety Inventory (STAI) (125). The STAI is a widely used and validated self-report questionnaire, translated into many languages, and includes separate measures of trait anxiety and state anxiety. The STAI measures feelings such as for example tension, apprehension, nervousness, and worry. For state anxiety (e.g., the temporary condition of anxiety influenced by the current situation), which was the measure used in study II, 20 items are rated from 1-4. A higher score indicates greater anxiety. The total score can be between 20-80. We used the mean score of STAI to report on anxiety symptoms. Additionally, the incidence of probable clinical levels of anxiety was reported by using the cut-off of 41 or more for both mothers and fathers, as commonly used in previous studies (57).

3.6.4 The Parent-Child Early Relational Assessment (PCERA)

In study III, the Parent-Child Early Relational Assessment (PCERA) was used to measure mother-infant interaction quality (117). The PCERA enables an observational assessment of strengths and concerns in dyadic parent-child interaction and is well used in studies worldwide and suitable for the preterm population (126, 127). For study III, the mothers and infants were videorecorded during free play, i.e., mothers were instructed to play with their infant as they usually would with pre-selected, age appropriate, toys available. The free play situation provides an opportunity to assess mother's capacity to be playful and

express enjoyment and to facilitate her child's capacity for exploratory play. In addition, the dyad's capacity for social interaction, mutuality and reciprocity can be observed. The PCERA is composed of 29 parental, 28 child, and 8 dyadic items. Based on a 5-minute interaction (128), each item is rated on a 5-point Likert scale. Higher scores indicate more positive quality in interaction or lack of negative affect or behavior. Scores 1 and 2 describe an area of concern, score 3 an area of some concern and scores 4 and 5 area of strength. Two blinded coders rated the data and 21% of the data was double scored. Interrater reliability between the two blinded coders was high with 82% of the items agreed on a categorical level. The 5-point scale was used in analyses, and the items were combined into subscales following the general guidelines of the PCERA manual at 4-months (117), that includes two parent scales, two infant scales and two dyadic scales. For our study, the two dyadic scales were combined into one global dyadic scale, producing five conclusive subscales. The internal consistency of the subscales was good (Cronbach's alpha ranging between 0.80-0.89). The scale scores represent the means and SDs of the included items. The five PCERA subscales and their included items are presented in Table 3.

Table 3. PCERA subscales and items rated in study III.

PCERA subscales		**Included items assessed**	Cronbach's alpha
I.	Maternal Positive Affect, Sensitivity and Responsiveness (16 items)	Flat, unemotional, constricted voice; warm, kind tone of voice; positive affect; depressed mood; enthusiastic, animated, cheerful, "joie de vivre"; enjoyment, pleasure; quality and amount of positive physical contact; amount and quality of visual contact with child; amount of verbalization; quality of verbalizations; social initiative; contingent responsiveness to child's positive behavior; reads child's cues and responds sensitively and appropriate; connectedness; mirroring; resourcefulness, creativity	0.89
II.	Maternal Negative Affect and Behavior (13 items)	Annoyed, angry, hostile voice; warm, kind tone of voice; expressed negative affect; irritable, frustrated, angry mood; displeasure, disapproval, criticism; quality and amount of negative physical contact; amount of verbalization; contingent responsiveness to child's negative behavior; structures and mediates environment; reads child's cues and responds sensitively and appropriate; flexibility/rigidity; intrusiveness; consistency, predictability	0.86
III.	Infant Positive Affect, Communicative and Social Skills (11 items)	Expressed positive affect; happy, pleasant, content, cheerful mood; apathetic, withdrawn, depressed; alertness, interest; social behavior-initiates; social behavior-responds; quality of exploratory play; robustness; visual contact; communicative competence; readability	0.87
IV.	Infant Dysregulation and Irritability (*8 items)	Expressed negative affect; anxious, tense, fearful; irritable/angry mood; emotional lability; avoiding, averting, resistance; attentional abilities; self-regulation, organizational capacities Note: *one item, "consolability/soothability", was dropped out in analysis due to scoring "non-ratable" in majority of observations (situation not happening)	0.86
V.	Dyadic Emotional Tone, Reciprocity and Regulation (8 items)	Flat, empty, constricted tone of voice/facial expression; mutual enthusiasm, joyfulness, enjoyment, a sense of dyadic joie de vivre; reciprocity; frustrated, angry, hostile affect; tension, anxiety; joint attention, activity; organization, regulation of interactions; goodness of fit	0.80

3.6.5 Interviews

In study IV, qualitative interviews were conducted with parents using a semi-structured interview guide that was developed by the research team. The interview guide explored participants' experiences with the first SSC with their newborns including care and support from healthcare staff. All interviews started with the question, "Can you tell me about when your son/daughter was born and the first hours surrounding the birth?", followed by questions such as "If you focus on the moment when you had SSC with your baby, can you describe how this felt for you?", "How did the staff support you during SSC at this time point?", and "How has SSC within the first hours following birth affected your experience of becoming a parent?". The questions were open-ended, and when necessary, questions were probed, encouraging further reflection, and thought. Interviews were conducted individually, face-to-face, at a place chosen by the participants themselves (most often in the participants' homes). I conducted all the interviews and had met all the parents prior to the interviews, as I was involved in IPISTOSS data collection at birth and during their hospital stay, but I had not been involved in their infants' care in the NICU or been responsible for their care as a nurse.

3.7 Data analyses

3.7.1 Statistical analysis study I-III

The statistical analysis in study I was performed by a statistician in Turku, Finland, designated the ICS2 study, and results were discussed with the author group. The analyses were carried out using SAS for Windows version 9.4 (SAS Institute INC., Cary, NC, United States).

The statistical analyses in study II and III (IPISTOSS) were performed by me and with the help of a statistician and supervisor. All analyses were done according to intention to treat. The secondary outcomes in these studies were predefined (effect of immediate SSC vs control on parental mental health and mother-infant interaction quality), but we also employed explorative analyses in both studies to investigate whether the potential relationship between immediate SSC vs control on these secondary outcomes were mediated through the accumulated SSC in the early postpartum period. The analyses were carried out using IBM

SPSS Statistics, version 28 (IBM Corp), and R statistical software, version 4.1.3 (R Core Team).

Overall, descriptive statistics were done for background variables. For continuous variables, means, ranges and standard deviations (SD) or medians and interquartile ranges (IQR) were calculated, depending on data distribution (normal or skewed). For dichotomous or categorical variables, frequencies (n) and proportions (%) were calculated. In study II and III, differences between group means were compared with independent t-test (parametric) for the continuous variables, after testing for normal distribution with the Shapiro Wilk test. If the data were skewed, the Mann Whitney U-test (non-parametric) was employed. To test differences in proportions for dichotomous or categorical outcomes between independent groups, the non-parametric Chi-Square test or Fisher's exact test (expected counts <5) were used. Cohen's d effect sizes were calculated to quantify the magnitude of group differences and were interpreted as; 0.2=small, 0.5=medium, 0.8=large. In all studies, values of p below 0.05 were considered statistically significant with a 2-sided hypothesis test. All p-values in study II and III were presented together with 95% confidence intervals (95% CI), providing information about the range in which the true value (for example, the difference between two means) lies with a certain degree of probability.

3.7.2 Study I

To assess the association between amount (minutes per day) of parent-infant physical proximity in the NICU (three outcome measures; presence, holding, and SSC) and parents' symptoms of depression (EPDS scores at two timepoints; discharge and 4 months), analyses employing separate linear mixed models for repeated measures were used. This is suitable for longitudinal data, and when the data is clustered in some way (in this study on unit level). The units were employed as random effects, e.g., accounting for the variability and differences between different subjects within a larger group. All analyses were adjusted for the infants' GA, multiple birth, maternal education, relationship status, and sibling status, as these were considered clinically significant. Associations between the parent-infant proximity measures and parental EPDS scores at discharge and 4 months were presented as Pearson correlations coefficients (r).

3.7.3 Study II

Non-parametric bootstrapping was employed to estimate unadjusted and adjusted effects of SSC vs control on the outcome variables (i.e., parents' EPDS

and STAI scores at 7 days, term age, 3-4 and 12-months) as well as for possible mediating effects on these outcomes (i.e., the accumulated time of SSC at 72 hours and 8 days after birth; for mothers, fathers, and infants respectively). To make effects comparable, the outcome variables and possible mediators were standardized prior to analysis. For twins, data were aggregated across children with the same parents (aggregated as the sum for SSC variables and the mean for the rest of the variables). We adjusted for the near group imbalance regarding primiparity (p=0.05) and child sex, with more boys in the SSC group (p=0.002). Additionally, we chose to adjust for multiple birth and GA, as these were considered clinically significant covariables. Linear and logistic regression were used for the continuous and binary outcomes, respectively. Effect sizes were estimated as the mean difference between the groups, which corresponded to Cohen's d. Missing data varied between the different measurement timepoints, with the lowest number of responses collected at the term-age follow-up for mothers (72% response) and fathers (60% response). Therefore, to account for missing values, statistically significant effects found in the primary analysis were validated by analyses employing full information maximum likelihood estimation. This is a method that uses all available data to estimate parameters, instead of replacing or imputing missing values.

3.7.4 Study III

Unadjusted and adjusted effects of SSC vs control on the five PCERA subscales (measuring mother-infant interaction quality at 4 months) and on accumulated time of SSC (at 72 hours and 8 days post birth) were estimated with multilevel regression analyses. This model was applied to control for the dependence of data from twins with the same mother. Adjustments were made for imbalances found between the groups, with more first-time mothers (p=0.03) and boys (p=0.02) in the SSC group. We also adjusted for observation setting (i.e., setting where the video recordings were conducted; home vs clinic), as this could have caused some variability in the PCERA scores. Effect sizes were estimated with Cohen's d. Further, through bootstrapping 1000 subsamples from the study sample, the size and statistical significance of mediated effects of SSC vs controls on the PCERA subscales via accumulated time of SSC within the first week post birth, were estimated. Additionally, a drop-out analysis was carried out, by comparing the background variables from the group included in the PCERA analysis and the drop-out group at 4 months.

3.7.5 Qualitative Analysis study IV

The interviews were transcribed verbatim by me (S.L.) and then analyzed using Reflexive Thematic Analysis (129, 130). S.L. performed the analysis, based on repeated engagement with the data in six phases as outlined by Braun and Clarke (130), and in an ongoing and reflective discourse throughout the process with senior qualitative researcher and co-author S.Z., who helped refine the analysis. A complete coding of the dataset was conducted by S.L. This was done inductively, based on the semantic but also latent meaning of the data, and each code represented a singular idea relevant to the research aim (131). Theme development was then an active process of examining and clustering codes together into bigger or more meaningful patterns identified across the dataset and was visualized through a thematic map that developed during this process. Theme development entailed going back-and forth between themes, sub-themes, codes, and the raw dataset, to ensure their robustness (that they were representative of the data). Ultimately, themes were constructed that aimed at capturing patterns of shared meaning that were united by a central organizing idea (130), and sub-themes represented different aspects of a theme. Finally, a figure was developed that further synthesized the findings to a comprehensive whole.

Reflexive thematic analysis is theoretically flexible, and the need to be explicit about underlying theoretical assumptions informing the analysis is stressed (i.e., to provide the lens through which data are coded and interpreted) (132). In this study, a constructionist framework was applied, in which meaning, and experience were understood as being co-constructed in and between individuals and societies through lived experiences and interactions with others (133). The constructionist perspective offered an interpretative lens throughout the analysis when reflecting on the meaning of the parents' experiences as situated within the social context of childbirth.

3.8 Ethical considerations

All four studies in this thesis had ethical approval (Table 4) and were conducted in line with Good Clinical Practice (GCP) (134) and the Declaration of Helsinki (135), in which four main ethical principles regarding medical research involving human subjects are outlined: respect for autonomy, beneficence, non-maleficence, and justice. GCP offers a quality standard for designing, recording, and reporting on trials that assures that the rights, safety, and well-being of trial subjects are protected. To ensure that this standard was upheld, The Karolinska

Trial Alliance was involved in the planning phase of the RCT IPISTOSS and all research staff had training in GCP. To respect the participants autonomy and right to make informed decisions about participation in the studies, both oral and written information was provided, and written consent was collected from all participants in study I-IV. Information included the voluntary nature of participation, confidentiality, and the right to withdraw study participation without stating any reason for doing so. To ensure study participants confidentiality and security of data, all retrieved information in the ICS2 study and IPISTOSS were pseudonymized and stored in accordance with the General Data Protection Regulation (GDPR) legislation.

Table 4. Ethical approvals for the studies in this thesis

Study	**Ethical Approvals**
Study I ICS2	2013/332 with amendment 2013/332/1.
Study II IPISTOSS Parental mental health	2017/1135-31/1 with amendments 2019-03361 and 2023-00207-02 (Swe). 2015/889 with amendment 27459 (No).
Study III IPISTOSS Mother-infant interaction	2017/1135-31/1 with amendment 2023-00207-02 (Swe) and amendment 27459 (No).
Study IV IPISTOSS Parental experiences	2018/1110-32

The sampling procedures included in study I-IV were all of non-invasive character. In study I and II, the questionnaires on parental mental health (EPDS and STAI) were scored in conjunction to the timepoint for data collection, and parents exceeding the screening threshold for clinical depression or anxiety were followed-up and referred to mental health services if necessary. In study III and IV, one could expect that video recordings of mother-infant interaction and interviews could be exposing for the participants. Thus, measures were taken to provide a safe environment. Video recordings were short (6 minutes), and they were always followed up with a question to the mother "how did this feel for you?". For the interviews, each participant was asked permission to audio record the interview, and the participants could choose where the interviews were held.

Specific ethical challenges relating to the IPISTOSS RCT are discussed below.

3.8.1 IPISTOSS

In IPISTOSS, seeking informed consent was a delicate matter when the parents were approached in a stage during pregnancy when giving birth to a very preterm infant is at risk. These parents were often worried and may have had a hard time taking in information about a study when under great strain. What more, sometimes the situation was of an acute character, making information giving and decision-making problematic. Although challenging, it has been argued that it is not a contradiction to give informed consent under the conditions described above (136). Parents were informed about the study at the earliest stage possible when admitted to the antenatal or birth unit, but first after having met and talked to the obstetrician and neonatologist in charge. Information was given both orally and in writing and always allowing for follow-up when possible. The understanding of information was facilitated through showing the parents pictures depicting the clinical intervention features. Study-personnel informing parents about the study were also knowledgeable about neonatal care and thus sensitive to the clinical situation.

According to the principles of beneficence and non-maleficence, there is a moral obligation in research to try to do good and avoid harm. Since infants in IPISTOSS were at significant risk of mortality and morbidity, clinical care ultimately overrode research considerations. In a pilot study carried out by our research group (77), potential risks of the intervention of immediate SSC were identified, such as the risk of hypothermia, and measures were taken to minimize this risk (e.g., textiles that are pre-heated to cover the infant with, close monitoring of temperature). A risk that was discussed in our clinical setting, was the possibility that during the study period, more infants would be separated from their parents the first six hours after birth (in the control group) than would have been the case in the current clinical practice. Even if the standardized routine was to provide stabilizing care after birth in an incubator for very preterm infants, in practice as the study went on, healthcare professionals had begun to embrace the benefits of SSC, and the medical decisions could therefore vary depending on the pediatrician in charge. However, we reasoned that before new treatment is introduced it is important to know if it is effective and safe. This study could contribute to such knowledge and thus optimize the care of the very preterm infant and its parents, with the benefits considered to exceed the risks. Still, our initial aim of recruiting preterm infants between 28+0–32+6 weeks had to be reconsidered during the study, as SSC initiated immediately or soon after birth for preterm infants from 32+0 successively had become considered standard care in our clinical setting, and the upper GA limit in the study was lowered to 31+6 in November 2020.

According to the principle of justice, we have a moral obligation not to increase inequalities. In this sense, it can be argued that research results should be assumed to benefit even the most disadvantaged. Regarding research on SSC, there is an important solidarity aspect, and that is the responsibility of high-income countries to conduct research, that is the results of which can be useful, from a global perspective. In low-resource settings, there is a limited access to incubators and other advanced medical technology. In countries with resources, such as Sweden and Norway, if we can conduct research on interventions that does not involve expensive technical equipment, it will have great benefits for the very preterm infants on a global scale.

4 RESULTS

4.1 Study I

In study I, the association between parent-preterm infant proximity in the NICU (presence, holding, and SSC) and parents' symptoms of depression (EPDS) at discharge and 4 months CA was assessed. Between the 23 participating units, parent-infant proximity as well as depressive symptoms varied greatly, as presented in Table 5 and 6, respectively. The variation in time from birth to the first parent-infant contact also varied between the units (Table 5). The diary data collection started on average on the fourth day of life and lasted on average for 12 days. The duration of mothers' and fathers' presence, holding, or SSC in the NICU did not associate with either the mean EPDS scores or the proportion of mothers' and fathers' exceeding the screening threshold for clinical depression at either discharge or 4 months.

Table 5. The time from birth to the first parent-infant contact (hours after birth) and the duration of parent-infant proximity (hours per day) during the diary days in the 23 units.

	In all units	**Shortest time per unit**	**Longest time per unit**
First **visual contact,** median (IQR)			
Mothers	1 (0–5)	0 (0–0)	8 (1–22)
Fathers	0 (0–1)	0 (0–0)	2 (1–3)
First **holding,** median (IQR)			
Mothers	24 (3–72)	3 (2–10)	180 (132–360)
Fathers	24 (4–96)	1 (0–7)	240 (144–408)
First **skin-to-skin contact,** median (IQR)			
Mothers	24 (6–72)	3 (2–24)	204 (144–336)
Fathers	48 (15–120)	3 (1–24)	324 (156–924)
	In all units	**Shortest duration per unit**	**Longest duration per unit**
Presence, median (IQR)			
Mothers	8 (4–18)	2 (1–4)	23 (22–24)
Fathers	4 (2–9)	0 (0–1)	19 (12–21)
Holding, median (IQR)			
Mothers	0 (0–1)	0 (0–0)	2 (0–3)
Fathers	0 (0–0)	0 (0–0)	0 (0–1)
Skin-to-skin contact, median (IQR)			
Mothers	1 (0–2)	0 (0–0)	4 (3–6)
Fathers	0 (0–1)	0 (0–0)	3 (2–5)

Tabel 6. The parents' depressive symptoms (EPDS mean scores) and proportion of parents exceeding the screening threshold for clinical depression (mothers; cut-off 13 or more, fathers; cut-off 10 or more) at discharge and 4 months.

Parent	Discharge				4months			
	EPDS mean (SD) score, all units	EPDS mean score, variation between units	Exceeding the EPDS screening threshold (%), all units	Exceeding the EPDS screening threshold (%), variation between units	EPDS mean (SD) score, all units	EPDS mean score, variation between units	Exceeding the EPDS screening threshold (%), all units	Exceeding the EPDS screening threshold (%), variation between units
Mothers	9.2 (5.0)	5.8–12.5	25.3	0–53.3	6.6 (4.7)	4.7–9.6	12.3	0–27.3
Fathers	6.3 (4.4)	3.3–7.9	8.3	0–23.1	4.3 (4.2)	1.6–7.5	5.8	0–20.0

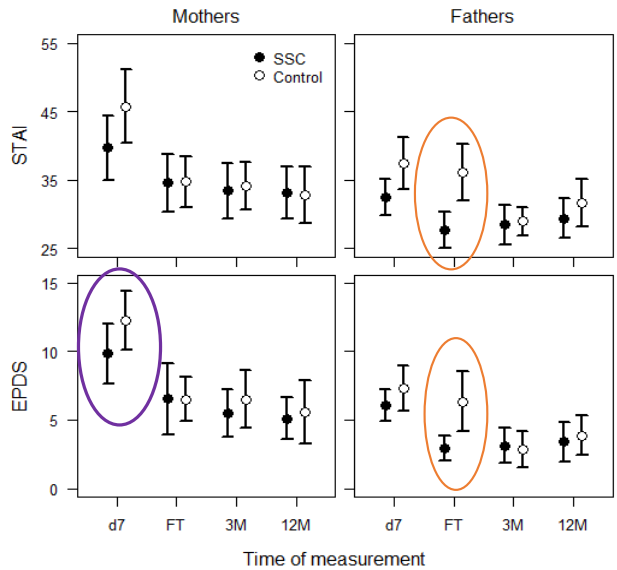
4.2 Study II

In study II, the effect of immediate SSC versus standard incubator care after a very preterm birth on mothers' and fathers' symptoms of depression and anxiety within the infants' first year of life was investigated. In the SSC group, SSC had been initiated at a median (IQR) time of 24 (18-60) minutes after birth with either parent. During the intervention period of 0 to 6 hours, the median SSC duration was 5 hours and fathers provided more SSC than mothers during this period (Table 7).

After adjustments, a significant difference in depression symptoms in mothers was found at one week after birth, with lower EPDS scores in the SSC group; mean (SD) 9.8 (6.0) vs 12.3 (5.9) in the control group, equal to a mean difference of -0.5 SD (95% CI: -1.0, -0.0; p <0.05). Further, a significant difference in depression and anxiety symptoms in fathers was found at term age. At this timepoint, fathers had lower EPDS scores in the SSC group; mean (SD) 3.0 (2.0) vs 6.4 (4.7) in the control group, equal to a mean difference of -0.9 SD (95% CI: -1.7, -0.1; p = 0.02), as well as lower STAI scores; mean (SD) 27.7 (5.7) vs 36.1 (9.5), equal to a mean difference of -0.9 SD (95% CI: -1.4, -0.3; p = 0.002). The effects remained unaffected after accounting for missing values. After term age, the levels of symptoms of depression and anxiety evened out between the groups and no effects on later depression and anxiety symptoms were found (Figure 2).

Further, no significant differences were found between the study groups when it came to exceeding the screening threshold for clinical depression and anxiety within the first year.

Figure 2. Mean depression scores (EPDS) and anxiety scores (STAI) in mothers and fathers in the SSC group and Control group over time since birth; at 7 days (d7), term age (FT), 3-4 months (3M) and 12 months (12M). Error bars represent 95% confidence intervals. Significant differences between the groups are highlighted.



After the intervention period, infants in the SSC group spent more time in SSC with their parents during the first 72 hours and 8 days after birth (Table 7). Mediation analyses were performed to test whether the effect of immediate SSC vs the control on symptoms of depression and anxiety in mothers and fathers were mediated through the accumulated SSC time (for mothers, fathers, and infants respectively) during the first 72 hours and 8 days after birth. No significant mediated effects were found.

Table 7. SSC duration times in IPISTOSS; during the first 6 hours and within the first week thereafter

SSC duration, hours	**Control group,** n= 45 infants and 35 parent couples			**SSC group,** n= 46 infants and 38 parent couples		
	Mother	Father	Infant	Mother	Father	Infant
Intervention, 0-6 h after birth, median (IQR)	0	0	0	0.6 (0-2.8)	3.4 (2.3-4.8)	5.0 (4.5-5.5)
Accumulated, 7-72 h after birth, median (IQR) Missing data	5.8 (3.6-9.8)	3.0 (0-4.9)	10.5 (5.8-13.8)	9.0 (6.3-14.6) 2	8.6 (2.8-12.0) 2	17.1 (10.6-25.4) 2
Accumulated, 7 h to 8 d after birth, median (IQR) Missing data	19.6 (16.0-28.4)	12.3 (6.0-18.1)	36.5 (26.0-43.2)	28.5 (20.8-41.3) 6	23.9 (11.6-31.5) 6	53.1 (37.8-70.3) 6

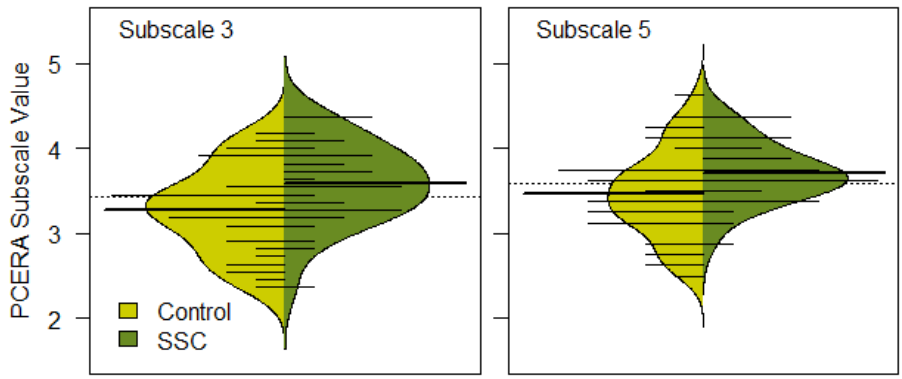
4.3 Study III

In study III, the effect of immediate SSC versus standard incubator care after a very preterm birth on mother-infant interaction quality at 4 months CA was investigated. For infants in the SSC group, SSC was initiated at a median (IQR) time of 15 (0-62) minutes after birth, and during the first 6 hours the median (IQR) SSC duration was 5.3 (4.5-5.5) hours. Fathers provided more SSC than mothers during this time, with a median (IQR) time of 3.3 (2.3-4.5) and 0.8 (0-2.5) hours, respectively.

The mother-infant interaction quality was analyzed through 5 PCERA subscales that related to either maternal (subscale 1-2), infant (subscale 3-4) or dyadic (subscale 5) affect and behavior. A statistically significant difference was found in PCERA subscale 3 (infant positive affect, communicative and social skills), with higher-quality interaction in the SSC group at 4 months; Cohen d = 0.67 (95% CI, 0.17, 1.17; p = 0.01). This effect remained significant after adjustments. Further, for PCERA subscale 5 (dyadic emotional tone, reciprocity and regulation), there was a significant difference found after adjustment for observation setting in favor for the SSC group; Cohen d = 0.56 (95% CI, 0.05, 1.07; p = 0.04). The differences seen between the SSC group and control group on PCERA subscale 3 and 5 are visually displayed in Figure 3. No significant differences between the study

groups were found in the PCERA subscales that related to maternal contributions to interaction quality.

Figure 3. Differences between the SSC group and Control group on PCERA subscale 3 (infant positive affect, communicative and social skills) and subscale 5 (dyadic emotional tone, reciprocity and regulation), presented as beanplots; for each group the mean (bold horizontal lines), the spread of individual observations (small horizontal lines), and the shape of the distributions can be observed.



After the intervention period, infants in the SSC group spent more time in SSC with their parents during the first 72 hours and 8 days after birth than infants in the control group (median [IQR] 17 [10.5-25] vs 10 [5.3-13.5] hours and 51.8 [36.5-70] vs 36.5 [24.8-44] hours, respectively). Mediation analyses were performed to test whether the effect of immediate SSC vs the control on PCERA subscale 3 was mediated through the accumulated SSC time for the infant during the first 72 hours and 8 days after birth. No significant mediated effects were found.

4.4 Study IV

In study IV, parents' experiences of immediate SSC with their very preterm infant and care and support from healthcare staff was explored. The results were described by three themes and eight sub-themes. The themes were further synthesized to a comprehensive whole, understood as the purpose (why), conditions (what), and means (how) for understanding and supporting SSC between parents and their very preterm infants at birth (Figure 4).

The first theme, **"A Pathway to Connectedness**", described how SSC enabled participants to actively participate and feel significant during the care of their newborns during the first hours following birth. Parenthood and early interactions were strengthened by the physical sensations of feeling and seeing their

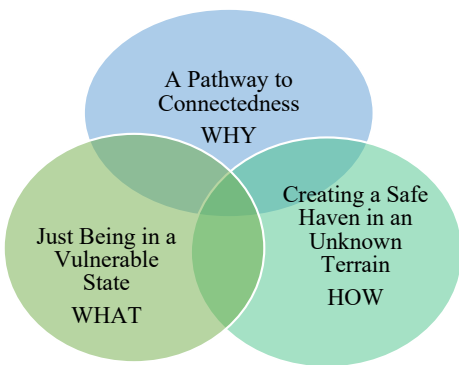
newborn and experiencing a need to be close. In the sub-theme "**Skin-to-Skin Contact as a Positive Sign"**, participants elaborated on what meaning they ascribed to the experience of SSC. For example, SSC was given the meaning that their infant was doing well and helped them uphold a sense of normality within the context of a very preterm birth. Further, participants described how SSC was meaningful in terms of giving them their parenting role, and feelings of helplessness were replaced with feelings of inclusiveness. In the sub-theme **"A Calming Physical Sensation",** participants described how the physical sensations of feeling and seeing their newborn during SSC provided them with an embodied knowledge that helped them regain a sense of control. This was also a starting point for realizing that they had become parents. Participants could feel their newborns responding by becoming calm and relaxed, which strengthened their sense of making a difference. Also, participants perceived that SSC was beneficial for them as well. The knowledge that came from physical sensations when in SSC created reciprocity and connectedness. In the sub-theme **"Building Confidence Over Time",** participants described how their experiences of SSC at birth had provided them with an early seed of connectedness with their newborns. The fruit of this seed was described as a sense of confidence in themselves as parents that evolved over time.

The second theme, "Just Being in a Vulnerable State", related to the act of being present when in SSC, as juxtaposed to the task of being present in SSC, and how the experience of that presence was impaired by various challenges at the time surrounding birth and how the healthcare staff met those challenges. In the sub-theme **"Physical and Mental Readiness"**, participants described various aspects of giving birth to a very preterm infant that impaired their readiness for SSC. Such aspects included seeing their newborn for the first time, so small and fragile, and feeling frightened to do something wrong. They described how staff became an important catalyst for SSC, before they felt more secure. Readiness for SSC could also be impaired by the physical condition of the mother at the time of birth. At such times, seeing the infant together with the father in SSC, gave the mother a sense of relief. In the sub-theme **"Presence: Easy and Hard"**, the task of having their newborns in SSC was perceived as rather effortless, albeit an important one. On the contrary, the act of being present when in SSC, i.e., being "here and now", was more challenging and the time surrounding birth was often experienced as being in a haze, trying to adapt to the physical environment in the NICU and often with thoughts and worries

about the future. In the sub-theme **"A Person With Own Needs"**, the participants described how they put their own needs aside in relation to their newborns. Although the focus of both the staff and parents was naturally on the newborn's needs after birth, there was a risk that participants became tools for giving SSC rather than people with their own feelings and needs. Participants needed help with upholding even basic needs such as sitting comfortably or having opportunity to eat and drink when in SSC with their newborn. Also, when coordination between the maternity unit and the NICU was perceived as lacking, the mothers described their early postpartum care as suboptimal.

The third theme, "Creating a Safe Haven in an Unknown Terrain", described the relationship that was formed between the staff and the participants and how it could provide a safe base for participants to be together with their newborns in SSC. In the sub-theme **"Staff Behaviour Is Key",** participants described the new and unfamiliar reality that followed a very preterm birth, including a different start to parenthood, in which staff were the experts. To adapt to this new reality, participants navigated towards forming relationships with the staff based on trust. Within this relationship, participants constantly interpreted good and bad signs based on staff behavior. The staff's ability to be calm and confident in what they were doing made the participants feel secure. Staff were described as supportive when preparing participants for SSC and providing affirmation when in SSC. In the sub-theme **"Providing a Sense of Availability"**, participants described the need for a restorative space to be together with their newborn in a meaningful way. At the same time, they were dependent on staff to provide them with a sense of availability, so they could feel secure within that given space. This included easy access to staff and communication when in SSC.

Figure 4. Synthesis of the themes to a comprehensive whole; the why, what, and how of immediate SSC after a very preterm birth.



5 DISCUSSION

5.1 Main findings in this thesis

The overall aim of this doctoral thesis was to gain knowledge about, and a deeper understanding of, the impact of SSC between parents and very preterm infants when practiced directly after birth (immediate SSC), as compared to later in the neonatal period, on parents' mental health and the parent-infant relationship within the first year of life.

The main findings were that immediate SSC (as compared to standard incubator care), initiated as soon as possible and provided as much as possible within the first six hours, decreased symptoms of depression in mothers at one week after birth and symptoms of depression and anxiety in fathers at term-equivalent age of the infant (study II) as well as enhanced the infants' expressions of positive affect, communication, and social skills when interacting with their mothers at 4 months (study III). Further, immediate SSC was described as an empowering experience by parents that helped them to attain their roles as essential caregivers and provided a calming physical sensation that promoted feelings of connectedness with their newborn infant, thus enhancing early bonding (study IV). Immediate parent-infant SSC was understood as an interactive process that has challenges and requires adequate support, and a good relationship with healthcare staff facilitated for parents to provide SSC in the immediate postpartum period (study IV).

Beyond the first six hours, no dose-response effects of accumulated SSC on outcomes were found. The duration of parent-infant SSC within the first week of life did not have a mediating effect on symptoms of depression and anxiety in parents within the first year (study II) nor on mother-infant interaction quality at 4 months (study III). Similarly, the duration of parent-preterm infant SSC during NICU stay was not found to be associated with symptoms of depression in parents at discharge and at 4 months (study I). Neither was the duration of other measures of parent-infant proximity in the NICU, such as parents' presence in the unit and holding the infant, found to be associated with symptoms of depression in parents (study I).

In summary, the main findings in this thesis suggest that the practice of SSC in the immediate postpartum period has an impact on the early parent-infant relationship following a very preterm birth. Immediate SSC may be seen as an

avenue in which both the infant, the parent, and the infant and parent together benefit in ways that enhance their relationship. As such, the findings in this thesis may be understood as contributing pathways that individually, and together, support the parent-infant relationship from birth, and will further be discussed below.

5.2 Immediate SSC as an avenue to support the parent-infant relationship

5.2.1 Decreased symptoms of depression and anxiety in parents

Our findings support the practice of SSC in the immediate postpartum period as an intervention that influences parents' mental health. Although there is a growing body of literature on parental mental health after a preterm birth, the effect of immediate initiation of SSC after a very preterm birth on parents' mental health has previously, at large, been unknown. Our findings in study II suggest that immediate SSC, practiced with either mother or father, may decrease symptoms of depression in mothers at one week after birth and symptoms of depression and anxiety in fathers at term-equivalent age of the infant. This is within a timeframe when parents have been reported to experience high levels of distress related to preterm birth and hospitalization (54, 137). In clinical practice, these findings are significant, as the early postpartum-period is an important time for parent-infant bonding and attachment (12, 138), and parents may withdraw, physically or emotionally, their presence or engagement in their infant's care when they are feeling depressed or anxious (19), leading to less interaction with their infant (139). Thus, immediate SSC may mitigate early distress in parents following a very preterm birth, and subsequently support early parenthood and the parent-infant relationship.

Of the few studies that exist on immediate SSC after preterm birth and parental mental health outcomes, an RCT by Mehler et al. (113) showed that 60 minutes of mother-preterm infant (GA 25-32) SSC versus 5 minute visual contact at birth reduced the risk of early postpartum depression in mothers on the third day of life but not at discharge and 6 months, in line with the findings in our study. In an RCT by Mörelius et al. (140), comparing parent-preterm infant (GA 32-35) continuous SSC from birth versus intermittent SSC, no differences were found in depression symptoms in either mothers or fathers at 4 months. Similarly, we did not find any differences on later depression and anxiety symptoms (at 3-4 and 12 months) in parents exposed or not exposed to SSC at birth. Nor did we find

any differences between the groups when it came to exceeding the screening threshold for clinical depression and anxiety. Both Mörelius study and our study were conducted in similar settings that included NICUs with a long tradition of providing infant-and family centered developmental care (22). It is plausible that the general high standard of care provided in these NICUs partially explain why more sustained effects are not observed, as well as differences in more severe symptoms. Research investigating the effects of immediate SSC on parents' mental health in more diverse caregiving settings is warranted.

Overall, parental presence and SSC are important components within an infant- and family-centered care approach. Our findings in study I could not support a dose-response relationship between parent-infant proximity in the NICU, including time spent in SSC, and later depression symptoms in mothers and fathers. However, from the same study cohort as in study I, the provision of other infant- and family-centered care practices such as parental involvement in care, care-related decisions, and emotional support provided to parents by staff were found to be associated to parents' depression symptoms (114). Previously, systematic reviews and a meta-analysis have demonstrated that SSC interventions in the NICU are associated with a reduction in maternal depression symptoms (107, 108). Further, a meta-analysis by Mendelson et al. (141) concluded that NICU-based parenting interventions, with features such as educational and psychological support, decreased maternal depression symptoms. Overall, these findings highlight the complexity when it comes to supporting parental mental health in the NICU and beyond, and which elements of parenting interventions that are effective. The findings from study I suggests that focusing only on parent-infant proximity in the NICU, including SSC, is not sufficient. For the parent, what matters might be more related to the quality of their presence with their infant in the NICU, rather than the amount. Thus, immediate SSC might be seen as a more optimal starting point for parents that may exert a protective effect on their mental health (study II). However, supporting parents' mental health after a preterm birth needs to be further met with a multilayered approach involving different elements of infant-and family-centered care, that together provide a caring culture in the NICU that may contribute to parents' well-being (142).

5.2.2 Enhanced development of the infant's social skills

We found a more long-term effect of immediate SSC on mother-infant interaction quality, in line with two previous RCTs in term (38) and preterm

infants (113). Our findings suggested an enhanced quality in interaction that was mainly driven by the infant. In our study, very preterm infants exposed to immediate SSC displayed a more optimal expression of positive affect, communication and social skills when interacting with their mothers during a free play situation at 4 months, as compared to infants who had received care in an incubator at birth and SSC initiated later. These findings are in line with the more general benefit of SSC as an intervention that supports the preterm infant's brain maturation after birth, with impact on infant developmental outcomes (6, 143). For example, in a meta-analysis (144), SSC was shown to have a positive impact on preterm infants' self-regulation skills, such as regulation of emotions, which is important for social interaction. Overall, studies that have looked at preterm infant behavior have found preterm infants to be less responsive, less interactive and display less positive affect than term infants (50). Due to their immaturity and diffuse behavioral cues, the preterm infant may be perceived as a difficult social partner to interact with. A positive development in the preterm infants' interactive behaviors is important and may support the parent-infant relationship further, as these infants may appear more engaging to parents and easier to respond to.

To the best of our knowledge, we are one of the first to report on effects of immediate SSC after a very preterm birth on mother-infant interaction quality. Previous to IPISTOSS, we are only aware of the RCT by Mehler et al. (113) comparing birth-room SSC between very preterm infants and mothers versus only visual contact at birth. Like our findings, the SSC group demonstrated better responses during interaction at six months. This included improved motor and vocal development of the infants, as well a higher rate of motoric responsive behavior of the mothers, that brought their interaction close to normal when compared to healthy term infant-mother pairs who had been cared for together from birth (145). Although the mothers' contributions to the quality of interaction did not differ between the groups in our study, we did find a benefit on the dyadic aspects of interaction, after adjusting for setting of observation. An interpretation is that the infants exposed to SSC at birth became more mature social partners, easier for the mother to respond and interact with. An important difference in our study, as compared to the RCT by Mehler et al. (113), is that SSC could be provided by either parent at birth. Indeed, fathers spent more time in SSC with their infants than mothers during the intervention period, for reasons explained below. Overall, during the first six hours, mothers spent on average less

than an hour in SSC with their infant. The limited exposure of SSC for mothers in our study might partially explain why we mainly saw a difference in the infants' interactive behaviors at 4 months, but not in the mothers.

5.2.3 The experience of early connectedness

The experience of SSC directly after a very preterm birth was described as valuable and empowering by parents. Our study is, to our knowledge, the first to describe this experience in both mothers and fathers. In line with previous studies on SSC practiced at birth in term (146), moderately preterm (147), and very preterm infants (148) and mothers, SSC was described as supportive in the early processes of becoming a parent, and even for realizing that they had become a parent. This was described both as feelings of meaningfulness when being able to actively engage in the care of their infant from birth, as well as feelings of connectedness with their newborn that came from physical sensations when being in SSC. Importantly, this provided parents with an embodied knowledge of their newborns from birth, which previously has been described as a pathway to parent-infant emotional closeness (149); here described in terms of parent-infant connectedness. Interestingly, these early experiences of connectedness were also described as having an impact over time since birth, providing them with a sense of competence as parents, previously also referred to as the "bonding effect" (150). These findings are in line with the more general findings of SSC as an intervention that supports early bonding and parenthood (151), but now also recognized as a valuable intervention for parents alongside other necessary nursing and medical treatment happening at the time surrounding a very preterm birth.

Importantly, being in SSC may be perceived as simple and an easy task (by both parents and staff) but was also described as a challenging act by parents, when being in a position of vulnerability after a very preterm birth. Parents needed healthcare staff to support them in this vulnerability; provide them with affirmation and to be sensitive to their individual need. Ultimately, we found that if these needs are not met, parents can disengage and perceive themselves as tools for SSC, rather than being involved in a meaningful act. A supportive environment has previously been identified as important for the parent's willingness and ability to practice SSC, including an encouraging attitude from staff as well as staff accessibility and practical assistance when in SSC (151). Overall, this highlights the need for building positive ongoing relationships with parents to preterm infants (152) and to understand this also as the fundament

when providing parents with emotional and practical support when practicing SSC at birth.

5.2.4 The important role of both parents from birth

In general, SSC interventions at the timepoint surrounding birth have focused on SSC between the mother and newborn infant, given mutual mother-infant physiological and psychological adaptations after birth including the establishment of breastfeeding (99). Also, in IPISTOSS, to initiate SSC with the mother was the priority. However, to be able to evaluate the very preterm infants' physiological transition after birth (primary outcome of IPISTOSS), the intervention extended over the first six hours after birth and could be provided by *both* mothers and fathers, i.e., if the mother was not available then the father provided SSC. This resulted in fathers spending more time in SSC than mothers during these first six hours. At large, this reflected the clinical situation with the mother often unavailable for SSC during the first hours after for example a cesarean section. Also, during the period that IPISTOSS was conducted, there were limitations for providing mothers' postpartum care in the NICU, i.e., mother-newborn couplet care (153). This is reflecting clinical practice in most maternity and neonatal units after a preterm birth, with early mother-infant separation being the norm (16). Indeed, 15 (39%) of the mothers in the SSC group in our study did not have any SSC during the first six hours, and of those mothers, 12 (80%) had given birth with cesarean section. Still, positive effects were found on mental health outcomes in both mothers and fathers (study II) and in mother-infant interaction quality (study III). Thus, it is likely that other mechanisms beyond SSC were involved during these first hours of parent-infant SSC, for example on a more family-systems level (154), which is also supported in the qualitative findings in study IV. For example, when experiencing medical difficulties at birth, a mother could express her relief when seeing her partner in immediate SSC with their newborn, which allowed her to momentarily "let go" and focus on her own well-being. Also, these findings point to the triadic nature of family relationships (155). In one study by Feldman et al. (156), where SSC between mothers and preterm infants in the NICU was compared to a matched group with no SSC, a positive impact of SSC on both mother- and father-infant interactions were demonstrated. In the group where SSC was provided, both mother-infant and father-infant interactions showed higher sensitivity and lower intrusiveness and with respect to family relations, a more cohesive family style and more frequent affectionate touch of infant and spouse at 3 months were

found. Future research should continue to explore SSC after a preterm birth not just as a dyadic, but also triadic experience. Importantly, the findings in study II-IV highlight the relevance of also involving fathers in the immediate care of their infant after a very preterm birth, as well as the important role fathers have in supporting the development of their very preterm infant, when the mother is not available (58, 157).

5.2.5 The existence of a sensitive period?

The findings in this thesis support the existence of an early sensitive period (36, 95), also after a very preterm birth. We found effects of SSC practiced within the first six hours on parents' mental health (study II) and infants' social development (study III), yet we could not find that these effects were further mediated by the time spent in SSC after these first hours. Similarly, no association was found between duration of SSC per se in the NICU and parents' depression symptoms (study I). Thus together, these findings suggest that the effect of SSC may be heightened during certain time windows, such as the immediate postpartum period. Indeed, already during the 1970s, Klaus and his research colleagues argued that events occurring in the immediate postpartum period substantially influence parental behavior and subsequent child development (70). This early sensitive period has been characterized by neuroendocrine changes that provide a biological and behavioral basis for social interaction, bonding, and attachment (12, 33). The hormone and neurotransmitter oxytocin, released during sensory stimulation of SSC, is suggested to play an important role, known to enhance the sensitivity of the parent and the newborn to each other (158) as well as to cross-talk with important regulatory systems, such as the stress system (33), representing decreased levels of cortisol (159). On a descriptive level, this is also reflected in our findings on parents' experiences of early connectedness with their newborns, which seemed to be mediated by the calming physical sensations that they experienced during SSC (study IV). Maternal and paternal oxytocin levels have been found to significantly increase during SSC with a preterm infant (160), and associate to parent engagement with their infant in the NICU (161). Importantly, the effects of interventions involving parent-infant proximity during this period may be particularly strong on infant brain function (27), which our finding on the enhanced development in the infants' social skills at 4 months also support. Future work on our IPISTOSS cohort will aim to study possible biological pathways mediating the effects of SSC on developmental outcomes. For

example, we will explore epigenetic pathways with a focus on glucocorticoid and oxytocin receptor genes. Overall, our findings point to implications for clinical practice to provide models of care where close parent-infant contact can be maintained also after a preterm birth and during the time when the mother is receiving postpartum care herself (162, 163).

5.3 Methodological considerations

The use of both quantitative (study I-III) and qualitative (study IV) research methods in this thesis is a strength that provided findings that were both broad and deep. The quantitative methodology enabled us to test relationships between physical closeness/SSC and the outcomes in focus, while the qualitative methodology could further provide richness and detail to the parents' experiences of SSC. Although the quantitative and qualitative results from IPISTOSS (study II-IV) are not combined, this may still enhance the understanding of the findings overall, and thus the validity. Some of the main methodological considerations in this thesis will be further discussed below.

5.3.1 Study design

This thesis included both nonexperimental and experimental study designs. Typically, studies are observational or interventional and their hierarchy in terms of level of empirical evidence (primarily concerning association between bias and study design characteristics) are illustrated as a pyramid with RCTs on the top (164). However, the choice of study design is closely linked to the study question as well as to ethical considerations, and therefore the highest level of evidence for a specific research question may be observational and not experimental (165). The ICS2 study (study I) was an observational cohort study. This study design allowed us to follow a selected population over time that were at risk of the study outcome (depression), based on the exposure of the individual (physical closeness to their infant in the NICU), and speculate on possible associations. A strength with this study design is that data is collected prospectively, minimizing recall bias, and thus overall strengthening its internal validity. A limitation is the risk for selection bias. If anything, there was a selection bias in the ICS2 study towards more parent-infant proximity, since the participating units were all part of the SCENE research network group, supportive of infant- and family-centered care practices. Thus, the reality might be more negative from a family perspective. Another limitation is the potential

confounding factors that may affect the true exposure-outcome association, which was reasoned about and considered in the statistical analysis.

IPISTOSS had an RCT design and thus a high potential of providing knowledge on the causal relationship between the intervention (immediate SSC) and pre-defined outcomes in study II and III. Randomization, that is the process of assigning participants to intervention or control group with an equal chance of being assigned to either group, minimizes the risk for confounding when participant characteristics are equally distributed between the groups. This ensures a substantially decreased selection bias and provides an overall strong external validity based on the potential to report on a casual effect (166). Even though groups were randomized, there was a significant difference between the groups with respect to sex of infant and parity, with more boys and first-time mothers in the intervention group. These differences between the groups were considered clinically significant. Preterm boys are generally regarded as being the more vulnerable population than girls (167) and first-time mothers are unexperienced in terms of physiological and psychological aspects of giving birth and parenthood. SSC interventions have previously been reported to have a greater impact on the mothering of first-time mothers as compared to mothers who have given birth before (156). In our statistical analyzes, this was thus considered. There are further methodological issues in study II and III that should be taken into consideration and that are discussed below. Ideally, to minimize bias and maximize the validity of the results, participants and/or providers are blinded to allocation group. For obvious reasons, this was not possible in IPISTOSS. Thus, any preconceived assumptions or attitudes on favorable effects of SSC might have induced a treatment bias in both the parents and the healthcare staff that conducted the intervention in the clinical setting. Yet, this would have been difficult to control for and the overall low drop-out rate from the study during the first year (7 parent couples, 10%) indicates that parents from both groups were motivated to stay in the study.

5.3.2 Sample size

A limitation in IPISTOSS is the small sample size, with early study termination due to benefit of the intervention on the main outcome. Although justifiable, the early termination may have implications for the power of secondary outcomes. For secondary outcomes, such as presented in this thesis (study II and III), subsamples of 50 or more were expected, but no sample sizes were calculated for these outcomes specifically (115). Also, in study III, it would have been difficult

to estimate what a clinical meaningful difference between the groups would have been since the normal distribution in the society is not known. Although it is common in RCTs to not report on power estimations on non-primary outcomes, it poses a limitation when interpreting the results from these outcomes (168). For example, a negative result may be reported due to low power when in fact a real difference exists between the groups (type 2 error). Still, sample sizes in IPISTOSS were comparable to previous studies on immediate SSC in a preterm population (113) and statistically significant results were found in both study II and III, with medium to large size effects, indicating clinical relevance. There is a possibility though that the negative results from the exploratory analyses on accumulated SSC in study II and III were due to a type 2 error given the small sample sizes, and that a mediating effect of accumulated SSC on the described outcomes actually exists.

5.3.3 Exposure and outcome

In IPISTOSS, the intervention of immediate SSC involved both infants and parents, yet the intervention per se was designed based on the infant and the primary outcome of the infants' physiological stabilization during the first 6 hours after birth. The protocol assumed that both parents were required to provide the intervention, and the outcome shows this to be true. As previously discussed, fathers spent more time in SSC during the first 6 hours than mothers, and the difference was not one that we had anticipated to be so large (3.4 vs 0.6 hours, respectively). Of the 38 mothers in the SSC group, 15 (39%) mothers had no SSC within the first 6 hours. The corresponding number for fathers was 3 (8%). A methodological concern is thus how to best analyze an intervention designed for the infant on later outcomes on parents? In study II and III we analyzed the data according to intention to treat, i.e., included all parents that were randomized regardless of exposure to SSC and did not consider with whom the SSC was (mother or father) nor the initiation time or duration within these first 6 hours. Findings are also discussed accordingly, and with an understanding that inferences about immediate SSC on parent outcomes in study II and III cannot be interpreted as just a direct effect from individual exposure of SSC on outcome, and that other possible mechanisms leading to these results must also be considered. Per-protocol analysis, i.e., only including the mothers and fathers exposed to SSC during these first 6 hours, was not applied in study II and III. But this approach could and will be applied in future sub-studies, for example on breastfeeding.

5.3.4 Generalizability

The ICS2 study included NICUs from 15 different countries spread over three continents, strengthening its external validity regarding different contexts. Although a majority of eligible families participated in the study, it is likely that those with little presence at the hospital were not approached and those with more depressive symptoms declined participation. Mothers participated to a higher degree than fathers, which might reflect the fact that mothers also spent more time in the NICU. Still, the study included a large variation of parental closeness (presence, holding, SSC) and depression symptoms in both mothers and fathers, which indicated that this had provided us with a representative group of families in the NICU setting. However, the response rate varied between the two follow-up timepoints and attrition bias was thus considered. Importantly, no differences were found between the responders at both follow ups and responders at only one follow up in terms of depression symptoms.

In IPISTOSS, the study population was from a high-income setting offering high-quality neonatal care, including decades long experience, training, and implementation of IFCDC, and the results should be interpreted within this context. This limits the generalizability of the findings to other more diverse caregiving settings and situations. It can only be speculated on that benefits of SSC in lower-and middle-income settings would be more pronounced, as previously has been reported regarding outcomes on maternal mental health (110). Also, the participants had to be able to speak Swedish, Norwegian or English, which excluded participants with more diverse cultural backgrounds. Because of the antenatal consent procedure, it can be assumed that there was a selection of more prepared, well infants and parents, which may also limit the generalizability. Overall, the drop-out of parents from IPISTOSS within the first year was low (7 parent couples, 10%), minimizing attrition bias in study II. Still, number of responders varied at the various follow-up timepoints in the study, and missing data was thus accounted for in the statistical analysis, with findings remaining unaffected. At the 4 month follow up in study III, 22% of the originally randomized infants were lost to the PCERA analysis. However, no significant differences were found when comparing the group included in this study and the dropout group at 4 months, minimizing the risk for attrition bias also in this study.

5.3.5 Trustworthiness

The choice of qualitative method depends at large on the research question. Reflexive thematic analysis was chosen in study IV as it is well suited to seek in-depth description of experiences previously unexplored (129). There are some methodological considerations when employing and evaluating reflexive thematic analysis that distinguishes this approach from other qualitative analytic methods, for example qualitative content analysis or other types of thematic analysis, and that informed the analyses process in study IV: 1) the analysis clearly being positioned within a qualitative paradigm where subjectivity is valued as an intrinsic part of meaning making and interpretation, 2) the theoretical approach being made explicit for the reader (as it does not come "inbuilt"), 3) the final analysis being a product of prolonged data immersion, involving thoughtfulness and reflection and described as an active process where themes are constructed rather than "emerging" from the data, and 4) themes that are conceptualized as patterns of shared meaning across the dataset rather than "domain summaries" (132, 169). By applying a constructionist framework, the data were thought of as reflecting ways the individuals made meaning of their experience but also, in turn, the ways the social context influenced those meanings. For example, the sub-theme *SSC as a positive sign* can be understood within the broader social context of childbirth and the understanding of what constitutes "normality" within that context. Thus, the meaning of SSC as a positive sign is not just a reality per se, but the meaning is shaped by the social context in which it is experienced.

Trustworthiness has to do with the rigor of the study and is built into the whole study design and research process as well as how the study is presented to the reader. Arguably, concepts used to determine rigor in quantitative studies, i.e., validity and reliability, are not fruitful when determining rigor in qualitative studies. How can a subjective experience be validated when there is no objective measurement or "truth" to validate it against? Concepts more relevant for discerning rigor in qualitative studies have been described as credibility, dependability, confirmability and transferability (170). These were addressed in study IV, together with a check-list of quality criteria for reflexive thematic analysis (132). Considering credibility, this was addressed through the recursive engagement with the data that included a reflexive audit trail documenting the various steps in the analysis process including the researcher's reflective notes, as well as peer debriefing sessions with the co-author group. To increase

dependability, the same researcher conducted, transcribed, and coded all the interviews whereas nuances in coding and interpretations were discussed with a second researcher that was familiar with the raw data set. To enhance confirmability, illustrative data extracts were used together with the findings. Finally, transferability was addressed by using purposive sampling and providing contextual information of the participants and study setting.

5.3.6 Reflexivity

In their qualitative method, Braun and Clarke stress the importance of reflexivity, i.e., the examination of one's own beliefs, assumptions, and practices during the research process and how these may have influenced the research (130). I believe reflexivity is important, not only in qualitative research but in all the research we conduct, with an overall acceptance that the researcher is part of the research (although we with a more positivistic approach try to contain it). Overall, my over 20 years of experience of working as a neonatal nurse in the NICU has given me a preunderstanding of the context that has been a resource during this thesis project. My understanding of neonatal care was helpful during the recruitment process in IPISTOSS and when meeting families at the follow-up visits. This gave me a sensitivity to what they might be going through and how to convey information in a way that could be understood. Importantly though, in being able to maintain an overall objective approach to the research being conducted, I only met the families in my role as researcher and not as a nurse responsible for their care. When analyzing the qualitative data, I was aware of my preunderstanding of SSC as something I believed to be good for parents and preterm infants (based on prior theory/literature/clinical experience). However, I believe the themes that were constructed from the data on parents' experience of immediate SSC, show a more nuanced experience that go beyond my own preunderstanding. For example, the notion of SSC as both an *easy task* but also a more *challenging act* in terms of being in *presence* with their newborn was an interesting aspect that should remind us of the need to be mindful when implementing SSC at the timepoint surrounding a very preterm birth.

6 CONCLUSIONS

Based on the findings in this thesis immediate parent-infant SSC after a very preterm birth

- may have a protective effect on parents' mental health,
- enhances mother-infant interaction quality,
- generates effects that seem specific to SSC practiced in the immediate postpartum period versus later in the neonatal period and
- provides a valuable and empowering experience for parents, that support feelings of connectedness with their newborns and a sense of competence as parents that is sustained beyond their NICU stay.

Thus, from the above, immediate SSC may have an impact on longer-term developmental outcomes after a very preterm birth, such as the quality of the parent-infant relationship.

For clinical practice

- the timing of initiation of SSC may be an important factor to consider for optimal support of the parent, the infant, and the parent-infant relationship after a very preterm birth,
- the place of care for the infant should be in direct SSC with a parent after a very preterm birth, alongside other necessary nursing and medical care, but requires that parents are adequately supported by healthcare staff and the health care system,
- fathers have an important role in supporting the development of their very preterm infant immediately from birth on when the mother is not available, and immediate SSC should be considered not only as a dyadic, but also triadic experience and
- beyond the immediate postpartum period, parent-preterm infant proximity and SSC in the NICU needs to be continued to be supported by the health care system, as this is proven beneficial, along with other elements within infant- and family-centered developmental care that may further contribute to parental mental health.

7 POINTS OF PERSPECTIVE

7.1 Clinical implications

7.1.1 Incorporate parent-infant SSC in "Golden hour" bundles

The "Golden Hour" is a term that refers to the time immediately after birth when the NICU team is focused on stabilization of the preterm newborn. Commonly, care practice bundles focused on optimizing care during this timeframe often include interventions targeted at team communication, maintaining normothermia, establishing effective ventilation, and timely initiation of parenteral nutrition (171). An important goal is to provide the least invasive support needed to help the newborn through the transition to extra-uterine life. Still, the promotion of a positive environment for the infant, being a cornerstone in neonatal neuroprotective care, is often overseen or neglected during this timeframe and the *place of care* is seldom defined within golden hour bundles, with parent-infant separation still being the standard practice (172). Previous findings from our research group on improved infant cardiorespiratory stabilization (101) and thermoregulation (102), as well as more long-term effects presented in this thesis on infant development (study III) supports SSC, when integrated with other nursing and medical care provided in a high-resource intensive care setting, as being a more optimal place of care than incubators for the very preterm infant directly after birth. Incorporating SSC as the primary place of care in golden hour bundles would thus offer a non-invasive method to further optimize infant stabilization and support neurodevelopment from birth. However, for this to be safe, healthcare staff need to be comfortable in providing care on the parents' chest instead of in an incubator or open bed (173). This may be demanding to implement, and implementation strategies need to consider both staff attitudes and motivation, systematic training and monitoring as well as the provision of adequate equipment and guidelines to support immediate SSC also in smaller and more vulnerable infants (174). Importantly, and a clinical implication as described in study IV, parents need to receive adequate support and guidance, which is also an aspect for safe SSC when practiced from the moment of birth (83).

7.1.2 Strive for systems change to provide maternal-neonatal care together

This thesis adds to the ample evidence for keeping parents and newborn infants together from birth, also when the infant is born preterm. Still, parent-infant

separation during infant and/or maternity care continues to be very common in NICUs in Europe, despite the implementation of infant-and family care practices (16). This was also observed in the IPISTOSS RCT, with maternal postpartum care routines identified as a barrier for mother-infant SSC during the first six hours post birth. The recommendations issued by WHO in 2022 (81), proposing immediate and continuous KMC to be the new standard of care along with other life-saving interventions for mothers and small and/or sick newborns across all settings, requires a system change for mothers and infants to be able to receive their care together from birth. This systems change has been described as *"a service delivery model where mothers, newborns, parents and families form an inseparable center around which the entire maternal-newborn service delivery is organized, with close collaboration between health-care providers"* (175). Mother-newborn couplet care is an innovative concept that incorporates the systems changes needed towards keeping mothers, infants and families together from birth (153). This concept of care describes a service delivery model where the care for a preterm or sick newborn and care for the mother is provided together from the infant's birth through the length of time that the mother needs hospital care, and is currently being implemented throughout NICUs in the Nordic countries (163). The scale-up of service delivery models such as mother-newborn couplet care will go hand in hand with successful implementation of immediate SSC for all newborns (176) and should be fully endorsed and supported by healthcare providers.

7.2 Future directions

My thesis has covered the first reports from the IPISTOSS cohort on more long-term outcomes of immediate SSC after a very preterm birth, in addition to the previously reported short-term outcomes on infant physiological stabilization (177). Previous research on longer-term outcomes after immediate SSC is scarce, and it will be important to continue to evaluate how the early environment has impact on health and development during infancy and later in life in this vulnerable group of infants and their parents. From the IPISTOSS cohort, there are additional secondary outcomes that will be analyzed and disseminated over the coming years. This includes collected data on breastfeeding, neurodevelopment, stress-reactivity, epigenetics, mother-infant physiological attunement as well as follow-up on mother-infant interaction quality at 12 and 24 months. Also, longer-term effects of immediate SSC need to be investigated in other caregiving settings than the high-income setting. In low- and middle-

income countries, immediate SSC has been proven to reduce mortality rates in preterm and low-birth-weight infants (80), and more follow-up studies are now needed to evaluate the impact this has on infants and parents when growing up.

I believe this thesis also has shown that we need to think of immediate SSC as not just a dyadic act between a parent and infant, but also as an intervention that involves both the parents and infant at the time surrounding birth (even if only one of the parents is involved in SSC). In the future, it would be interesting with studies that explored SSC in the immediate postpartum period on a more family-systems level (e.g. exploring how this affects the relationship between the parents and the developing infant) and with a focus on the triad (not only the dyad).

When it comes to supporting the parent-infant relationship after a preterm birth, parental mental health plays an important role. Our findings in the ICS2 study did not confirm our hypothesis that the duration of parents' presence in the NICU, including time spent in SSC, has a major role in the prevention of parental depression symptoms. Future research needs to continue to study the different elements within infant-and family-centered developmental care and how they interplay and possibly enhance each other in supporting parental mental health. For example, being present with their infant in the NICU is a necessary starting point, and vital for the infant, but to ensure the quality of that presence and support in interpretating and responding to the immature behavior of the preterm infant might be what is important for the parents' overall well-being (e.g., feeling that they have a meaningful and normal co-regulating role with their infant when present). How we create a supporting caring culture in the NICU is an important area for nursing and health research and with advantage in collaboration with parents and parent representatives (178, 179). Further, the findings from the ICS2 study highlight a great inequality in care provision for families across different units and countries when it comes to opportunities for parent-infant proximity in the NICU. Collaborations such as The European Standards of Care for Newborn Health project (180) presents solutions that address disparities in the care of preterm infants by identifying current best practice together with parents, and is one avenue to advocate for change in countries in Europe and worldwide.

Finally, the research questions that this thesis are based on have primarily emanated from clinical practice and run parallel to the development we have

seen during the past decades in addressing the question of parent-infant proximity in the NICU setting. However, a strive towards what often is labelled as "zero-separation" in clinical practice could also be perceived as burdensome for parents when this is not achieved. This research should not be interpreted in a way that adds to any parent's burden of being separated from their infant, but rather to inform healthcare staff and administrators on ways to improve the care for preterm infants and parents from birth, and if any burden, it should be laid on us, the health care providers and hospital systems. Based on the current evidence, a relevant question that should be raised is if it is ethically justifiable to continue to conduct RCTs on SSC after a preterm birth (81). For infants born from 28 gestational weeks and above, probably not. We might be at a tipping point, and the question to ask the Ethics Committee may soon no longer be for permission to keep parents and preterm newborns together after birth (i.e., our current intervention group), but rather the opposite. Thus, moving forward, and continuing to evaluate important outcomes from practices such as immediate SSC for preterm newborns, will probably entail other study designs beyond RCTs, such as well conducted longitudinal, prospective observational studies. Further, implementation studies are needed to support the dissemination of evidence into clinical practice and should include the experiences of those who provide the initial care in the postpartum period - nurses, midwives, neonatologists, and obstetricians.

8 ACKNOWLEDGMENTS

It takes a village to raise a child, and this is certainly true for a doctoral student as well! There are so many people; supervisors, colleagues, friends, and family, that in different but equally important ways have contributed to making this thesis possible. For that I am deeply grateful.

A warm and special thank you to

All infants and parents participating in the studies, you are the reason for this work!

Wibke Jonas – my main supervisor. Thank you for believing in me and providing me with the support I have needed consistently throughout these past six years. You are a brilliant researcher, but sometimes even more importantly, a kind human being, and I very much admire your unique combination of mind, courage, and heart in research as well as in life. Above all, and especially through the more challenging times in this project, we have always found ways to have fun when conducting research together. I could not have wished for more!

Ulrika Ådén – my co-supervisor. I think of you as a lighthouse, paving the way for others to reach the shore and standing strong in a storm. So full of knowledge and with an impressive engagement in the quest for improving care for preterm infants and their parents. Your support has meant a lot to me during this journey!

Sofia Zwedberg – my co-supervisor. Your mindful supervision within the "qualitative paradigm" was just what I needed, and our collaboration was both enriching, fruitful, and fun. I very much enjoyed the qualitative research process together with you!

Evalotte Mörelius – my co-supervisor. Long-distance zoom meetings from Australia and shorter-distance real life meetings in Linköping. Whenever I talk to you, I always become a little bit wiser, and I have appreciated both your well-grounded advice as well as curious questions that have pushed me forward in just the way I have needed!

Anna Axelin – my mentor. You are a role model for me when it comes to combining neonatal nursing with high quality research done in a collaborative and inclusive manner. Your contributions to improving the care for infants and parents in the NICU are impressive and ongoing! Thank you for collegial

friendship and support throughout the years and I look forward to future collaborations.

Hugo Lagercrantz – Professor emeritus and former Head of Department of Neonatology at Karolinska – for supporting NIDCAP at Karolinska and creating a sensitive environment for preterm infants and their families.

Björn Westrup – from the formative "early" days at Karolinska Danderyd under your leadership, and throughout continuous collaborations and travels to conferences and experiencing fun things together (your energy outlasts me any day ☺)…thank you for seeing my qualities, believing in my abilities, and giving me opportunities from the very start! I cannot drink an "Appletini" without thinking of you.

Agnes Linnér – it seems we have been through it all and I can't thank you enough! Data sampling bedside during the night (why do babies decide to be born at 1 am?), endless follow-up visits in the clinic and in the homes (Stockholm tour 2.0) and almost everything in between. You know exactly how to counter my "vemod" and bring humor back into any situation. Even in the absolute low points throughout this thesis project, you have made things doable and bearable! Come next Friday, you'll have your "fredagsdrink" tips again, promise.

Kerstin Andersson – conducting an RCT is challenging to say the least, but with research nurse sisu and a never-ending good spirit you have worked together with me and navigated me through every detail. Thank you for everything! Without you, I would still be wondering if I was using the right version CRF, reported an SAE correctly, stored the blood samples per SOP etc etc…

Stina Klemming – With an eye for the detail in combination with a vision for the whole, thank you for all hard work together be it late night SCRIP-scoring in IPISTOSS to collaborations in papers and networks! While some of us need to take a nap at times, you seem to tirelessly be able to go on.

Nils Bergman – you are simply one of a kind and always miles ahead, thank you for laying the ground for IPISTOSS and for being a catalyst for change!

Thomas Brune – for years of working together in the NICU and sharing ideas and reflecting on care – your "mindful" approach to neonatology has had a great influence on me.

Björn Salomonsson – I very much appreciate your curious mind, deep knowledge, and valuable input on our work. To discuss things with you always leads me on a new path of discovery and I hope we will continue discussing in the years to come!

Sari Ahlqvist-Björkroth and Johanna Lindstedt – for so patiently introducing me to the PCERA method and for a fun and enriching collaboration on the paper, thank you! I thoroughly enjoyed my visit to you at Turku University. Looking forward to more to come, you are the best!

The IPISTOSS research team – to the extended research team in Stockholm and Stavanger, including **Siren Rettedal, Karoline Lode-Kolz, Hanne Markhus Pike, Kirsten Engevik, Gordana Printz and Camilla Halzius**, thank you for making it all possible! And always with gratitude to the dedicated **staff at the IPISTOSS study sites at Danderyd, Huddinge and Stavanger** for all your help!

The SCENE research network – and especially, **Liisa Lehtonen**. I have learnt so much from you and very much enjoyed our dialogue and collaboration on the ICS2 paper (from kindly giving me praise that my texts read like poems, to showing me how academic writing really is done☺). You are a true force and inspiration and I deeply respect your hard work!

Kajsa Bohlin-Blennow – for a nice collaboration when conducting the ICS2 study at Karolinska and for all the encouraging words whenever we meet, your positive energy is contagious! And to the research nurses that helped in the ICS2 study at Karolinska – **Michaela Melakari, Bernadette Wenngren, Ami Lee Martinez** – thank you!

The Department of Women's and Children's Health (KBH) and Doctoral School in Health Care Science (FiV) at KI – I am so grateful for the academic learning environment you have provided me with and all the learning activities along the way! Thank you, **Kristina Gemzell Danielsson** (Head of Department KBH), **Kay Sundberg** (Director FiV) and **Sofia Alsing** (Head of Division of Reproductive Health), as well as **Anna Gustafsson**, **Emilija Wilson, Ewa Andersson, Michael Wells, Kristin Svensson, Eva Nissen** and so many others at the department for all your feedback and support along the way! Also, a special thank you to **Caroline Rådestad** for all your administrative support.

Kimmo Sorjonen – thank you for bringing statistics "alive" and dealing with all my questions like a true zen master! I have very much enjoyed working with you.

Andreas Widström – my "desk partner" at KBH - we came to share the doctoral journey, but also helped each other remember the more important issues in life over coffee and lunch breaks. I am so happy for our friendship and always look forward to talking and sharing experiences and ideas with you!

Martin Färdig, Charlotta Bergström, Kristina Fagerqvist, Pernilla Dillner, Caroline-Aleksi Olsson Mägi, Karl Hybinette, Henrik Hjelmgren – fellow doctoral colleagues and friends along the way, it wouldn´t have been the same without you!

Jessica Schiött - Head of Department of Neonatology/Nursing at Karolinska - for your dedicated leadership, unwavering support and for creating possibilities for nurses in your department to combine clinical work with academic studies and research! It has meant a lot to me.

Lars Navér - Head of Department of Neonatology at Karolinska – for your calm presence as a leader in combination with a great sense of humor that has been much appreciated. Thank you for support along the way!

Kristina Jonsson – we always have something we need to discuss, preferably over a glass of wine! Thank you for all the good times and for cheering me on when needed during this doctoral journey.

Ann-Sofi Ingman – no one "sees" the infant like you. Thank you for your guidance and support during the past years!

Ylva Thernström Blomqvist – for being such a great inspiration for other nurses, including myself, thank you for fun collaboration throughout the years!

Kajsa Brimdyr and The Healthy Children Project – for inviting me into such a great international research collaboration, the work trip to Island was a true joy and learning experience! Looking forward to more adventures together with you.

Ulrika Casselbrant – for the best thesis cover illustration, you beautifully captured what I wanted to convey!

To my former colleagues at the neonatal unit at Karolinska Danderyd "Samvårdsavdelning 21" and BB Sophia – I will always be proud of our vision for a better care for infants and families in the NICU and our hard work to provide it. What I have learnt about infant-and family centered developmental care and

couplet care in practice – I have learnt together with you! No names mentioned, none forgotten!

To my present colleagues at "Neonatal Mottagningen och Hemsjukvården" Karolinska Danderyd – Sofie, Helena, Madde, Sanna, Veronica, Rebecka, Annika, Ellen, Eva, Noni - I simply love working together with each one of you! Throughout my doctoral studies, my clinical weeks during the summers with you have been so important. Thank you for your committed work and all the laughs together!

Maria Midstam – my dear friend and amazing midwife colleague. You have saved me more than once. I am so grateful for having you in my life. "Tillförsikt" is the word.

Karin and Stina Berggren – from our "Husarö" days and still now, thank you for your genuine friendship!

Jonas Hedegard – we met at a Dee Dee Bridgewater concert in San Francisco 30 years ago and have been going to jazz concerts together ever since…thank you for sharing such great moments with me! And together with **Josua & Anna, Martin and all our families** – always looking forward to good times with you!

Clara Svärd, Emilie Nyman and Emma Vetter – my oldest friends, thank you for not giving up on me yet. Being together with you is always like coming home, no matter how long time has passed since we last saw each other. Thank you for being you and for friendship throughout so many years!

My dear parents, Christine and Anders – you are my beginning! Thank you for holding me close, letting me fly free and providing me with unconditional love and support.

My siblings Edward, Katja and Elise with families – so close to my heart and always an important part of me!

My extended Swedish family Jan and Therese – you are both so dear to me, as is **Yvonne** although not with us anymore in this life. Thank you for your support!

My relatives in the US – you are many☺ and each one of you are special to me. I listen to "Moonlight in Vermont" and dream of days together. Let's make it happen soon!

My husband and best friend, Jesper – 26 years and still going, nothing would have been possible without your endless support. I love you very much! Come summer, and we will be walking the fields in Grevlunda together again. No better place to be, than together with you. **And above all, to our children, Theo, Viktor, and Elvira –** being your mother is the greatest gift. Nothing compares to you! I am so very proud of you, every day. Thank you for keeping me grounded and reminding me of what is important in this life.

9 FINANCIAL SUPPORT

The studies in this thesis were financed by Swedish Research Council (VR, 2017-01497; 2021-03169), Region Stockholm (ALF, 2019-0374), Strategic Research Area Health Care Science (SFO-V) at Karolinska Institutet, Doctoral School in Health Care Science (FiV) at Karolinska Institutet, Little Child's Foundation, Kempe Carlgrenska Fonden and Swedish Order of Freemaisons Foundation to W. Jonas, BabyBjörn AB to B. Westrup, and Laerdal Foundation to B. Westrup and S. Rettedal. These are greatly acknowledged.

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