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Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life

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Breastfeeding Behavior in the First 24 Hours of Life

Cynthia Ann French, PhD

University of Connecticut, 2015

Abstract

Epidural opioids and local anesthetics may depress the neonatal reflexes necessary for breastfeeding success. Literature review yielded no data for hydromorphone and conflicting results for fentanyl. This study investigated whether breastfeeding effectiveness would be less in infants whose mothers received epidural analgesia with hydromorphone compared with those whose mothers received no analgesia, and whether the total amount of drugs given or the presence of multiple stressful events or interventions would be related to the effectiveness of breastfeeding.

Breastfeeding behaviors were studied in 51 infants whose mothers chose epidural analgesia compared with 51 infants whose mothers chose to have no analgesia. Women with epidural analgesia received 1.5% lidocaine with 1:200,000 epinephrine as a test dose and/or 0.25% bupivacaine with 1:200,000 epinephrine as a bolus, and 100 µg hydromorphone followed by continuous infusion of 0.05% bupivacaine with 3 µg/mL hydromorphone at 14 mL/hour. The hospital setting strongly supported breastfeeding. Effectiveness of breastfeeding was measured with the LATCH Breastfeeding Assessment Tool at 3, 12, and 24 hours after birth.

LATCH scores did not differ significantly between groups at any time point and were not related to total amount of drugs administered. The presence of multiple stressful events and interventions, e.g., long duration of labor, large amount of IV fluids, oxytocin administration, induction of labor, and meconium staining/suctioning of the baby, did not significantly affect breastfeeding behavior in the overall study population (n=102), altogether contributing not more than 8% of the variability of LATCH scores in the regression model. The group receiving epidural analgesia (n=51) had significantly longer duration of labor, higher rates of oxytocin administration and induction of labor, and larger amounts of IV fluid administration. These factors contributed approximately 30% of the variability of LATCH scores at 3 and 24 hours. However, this finding was not significant.

Although the study was limited by its nonrandomized nature, these data indicate that, by itself, epidural analgesia with hydromorphone does not decrease effectiveness of breastfeeding behaviors. Epidural analgesia increases risk of multiple stressful events or interventions, which may contribute to breastfeeding difficulties and necessitate intensive help from the nurse to achieve success in breastfeeding.

Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and
Breastfeeding Behavior in the First 24 Hours of Life

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Doctor of Philosophy
at the
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2015

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APPROVAL PAGE

Doctor of Philosophy Dissertation

Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and
Breastfeeding Behavior in the First 24 Hours of Life

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DEDICATION

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Chapter 1: Introduction

Chapter one provides background information on the importance of breastfeeding and the nurse's role in supporting mothers who breastfeed. The chapter describes the problem presented by potential negative effects of epidural analgesia on breastfeeding and discusses the significance and rationale for studying the effects of labor epidural analgesia with hydromorphone. The chapter also defines key terms; discusses the theoretical framework, assumptions of the researcher, study purpose, and specific research questions; and gives an overview of the study methods.

The benefits of breastfeeding to mother and neonate in both the short- and long-term are significant. Infants who are breastfed have a lower risk of respiratory tract infections, necrotizing enterocolitis, sudden infant death, asthma, diabetes, leukemia, and lymphoma, as well as improved neurodevelopment outcomes (Eidelman, 2012). Maternal benefits of breastfeeding in the short term include decreased postpartum blood loss and more rapid involution of the uterus. Long-term maternal benefits include decreased risk of hypertension, diabetes, and ovarian and breast cancer (Eidelman, 2012). The American Academy of Pediatrics (AAP) recommends exclusive breastfeeding for about 6 months, with continuation up to 1 year or more (Eidelman, 2012). The American College of Obstetrics and Gynecologists (ACOG) also supports this recommendation (American College of Obstetricians and Gynecologists, 2007).

Because the benefits of breastfeeding are well known, the rates in the United States continue to rise. According to the 2014 Breastfeeding Report Card issued by the Centers for Disease Control and Prevention, 79% of infants born in the United States started to breastfeed (Centers for Disease Control, 2014). Yet the duration of breastfeeding was not as long as

recommended by the AAP and ACOG: According to the 2014 report card, 49% of infants were breastfeeding at 6 months and 27% at 12 months (Centers for Disease Control, 2014). The reasons cited in the literature for early cessation of breastfeeding are varied. However, it has been consistently reported that mothers who perceive breastfeeding initiation as problematic are more likely to wean than those who perceived breastfeeding as non-problematic (Leff, Gagne, & Jefferis, 1994; Matthews, 1991). The goal of Healthy People 2020 is to increase the proportion of infants who start to breastfeed to 81.9%, continue to breastfeed at 6 months, 60.6%; and at 1 year, 34.1% (CDC BF Report Card 2014).

The literature identifies multiple factors affecting the initiation of breastfeeding, including milk insufficiency, sore nipples, discontented crying baby, socioeconomic status, social support, social norms, and hospital practices (American College of Obstetricians and Gynecologists, 2013). One consistent factor is that women who perceive breastfeeding as difficult, no matter the reason, are more likely to stop breastfeeding during the first week postpartum than women who perceive no problems (Leff et al., 1994). If breastfeeding is established in the first hours after delivery, many of these factors can be overcome to improve breastfeeding success and duration.

The Nurse's Role in Supporting Breastfeeding

In the US, 98% of all births occur in a hospital where nurses are the primary caregiver supporting women through labor, birth and discharge home (AWHONN, 2015). Nurses have a crucial role in preparing, educating supporting women to breastfeed and are instrumental in facilitating the initiation and continuation of breastfeeding.

Nurses are in a unique position to provide an environment conducive to breastfeeding initiation in the immediate postpartum period. The profession of nursing has always had the goal of using knowledge to advance the goals of the health of people in their environment.

Breastfeeding places the mother and infant in the best possible situation of health. Given the benefits of breastfeeding and the recommendations for its promotion, nurses should help nature by providing an environment that is conducive to breastfeeding success. The nurse's knowledge and attitude are crucial. To succeed at providing an optimal environment for nature to act on breastfeeding, nurses must know which factors are beneficial and which factors are detrimental to establishing effective breastfeeding. Thus, nurses and other health care providers who care for mother/infant dyads should acquire the knowledge and competence to provide evidence-based breastfeeding information and support throughout the preconception, prenatal, and postpartum periods.

Statement of the Problem

One factor that may affect the success of early breastfeeding is the administration of pain medicine during labor. The advent of labor epidural analgesia allowed small amounts of narcotics to be placed directly into the epidural space instead of high doses of opioids administered systemically, thus providing intense pain relief without depression of the central nervous system (CNS). Epidural analgesia has been shown to provide more effective pain relief during labor than other types of pain medication (Anim-Somuah, Smyth, & Jones, 2011), and its use during labor has increased exponentially over the past few decades. It was estimated that in 2001, 77% of infants born in the United States were exposed to epidural analgesia during labor and birth, a rise from 21% in 1981 (Bucklin, Hawkins, Anderson, & Ullrich, 2005). However, epidural analgesia may be a barrier to breastfeeding success.

The most common drugs used for epidural analgesia contain a combination of local anesthetics with an opioid, which may affect neonatal behavior. To establish lactation, the neonate must be awake, alert, and able to latch on to the breast and suck, swallow, and breathe in

a coordinated pattern in order to express milk from the breast (Auerbach, 1988; Kuhnert, Linn, & Kuhnert, 1985; L'Esperance & Frantz, 1985; Lawrence & Lawrence, 2011; Marmet & Shell, 1984; Neifert & Seacat, 1986; Shrager & Bocar, 1989). Epidural opioids and local anesthetics are known to readily cross the placenta (Reynolds, 1991) and may depress these reflexes (Chang & Heaman, 2005), thus decreasing the likelihood of breastfeeding success. However, despite 35 years of research, scientists still cannot unequivocally answer the question of whether maternal use of labor epidural analgesia affects the success of breastfeeding (French, Cong, & Chung, in press). Therefore, it is imperative to continue to investigate whether maternal epidural analgesia affects early establishment of breastfeeding behaviors.

Rationale and Significance of the Study

Bupivacaine is the standard local anesthetic used for labor epidural analgesia and is commonly combined with fentanyl. The dosage frequently used in this setting for continuous labor epidural infusions is 0.125% bupivacaine with 2-3 µg/mL fentanyl. The results of research on effects of epidural analgesia with these drugs on breastfeeding so far remain inconclusive. For example, two studies have shown an adverse effect of increasing doses of fentanyl on the success of breastfeeding (Beilin et al., 2005; Jordan, Emery, Bradshaw, Watkins, & Friswell, 2005), although another study showed no effect (Wieczorek, Guest, Balki, Shah, & Carvalho, 2010).

At Yale New Haven Hospital, the standard protocol for otherwise healthy parturients who request epidural analgesia for vaginal delivery calls for continuous infusion of 0.05% bupivacaine with 3 µg/mL hydromorphone instead of fentanyl. Hydromorphone has not been widely accepted in the management of pain in the obstetric setting. However, clinical evidence suggests its safety and efficacy in management of labor pain (Sinatra et al., 2002; Sinatra, Levin, & Ocampo, 2000). Hydromorphone has been used at Yale New Haven Hospital in continuous

labor epidurals since the 1990s and is believed to exhibit the pharmacodynamics necessary to promote analgesia without the clinically significant adverse effects—such as excessive maternal sedation, profound hypotension, respiratory depression, sensory motor blockade, and severe fetal bradycardia—that are seen with traditional opioid infusions (Sinatra et al., 2000). The use of hydromorphone as the narcotic in the epidural infusion appears to represent a promising alternative to fentanyl and may deliver acceptable analgesia without the unintended side effects seen with traditional opioid infusions. If so, neonates whose mothers received labor epidural analgesia with hydromorphone and those whose mothers did not receive labor analgesia may show similar breastfeeding behaviors and neurobehavior. No data on hydromorphone and breastfeeding are available. Thus, a study comparing infants whose mothers received labor epidural analgesia containing hydromorphone with infants whose mothers received no labor analgesia would provide valuable information needed to decide whether to use epidural analgesia during labor.

Definition of Key Terms

The key terms used in the study are defined as follows:

Breastfeeding

The failure of many studies to define terms relating to breastfeeding has led to misinterpretation of data and difficulty of comparisons across studies. In an attempt to provide consistent terminology for researchers and agencies involved in breastfeeding, Labbok and Krasovec recommended the terms *full*, *partial*, and *token* to describe the types of breastfeeding behaviors (Labbok & Krasovec, 1990). For this study *breastfeeding* was defined as the process by which milk is expressed from the lactiferous sinuses in the nipple of the breast, by the compression of the soft palate by rhythmic pulsations of the infants tongue (Weber, Woolridge,

& Baum, 1986). *Exclusive breastfeeding* was defined as the infant taking all nourishment from the breast, with no other liquid or solid consumed.

Breastfeeding Behaviors

Breastfeeding behaviors are a series of suckling behaviors necessary for the infant to draw the nipple into the mouth, remove the milk, and consume the milk. Breastfeeding behaviors include latching on to the breast, sucking, swallowing, and breathing in a coordinated pattern in order to express milk from the breast (Lawrence & Lawrence, 2011). The coordination of tongue movements, swallowing, and breathing was described by Bu'Lock and colleagues (Bu'Lock, Woolridge, & Baum, 1990), based on the historic cineradiographic studies of Ardran and colleagues (Ardran, Kemp, & Lind, 1958), with confirmation by the ultrasound studies of Weber (Weber et al., 1986). “A bolus of fluid is delivered to the pharynx by a phased application of the dorsum of the tongue to the nipple or teat in an anteroposterior peristaltic wave of contraction. Coordinated movement of the mandible and apposition of the gums traps the milk in the lacteal sinuses of the breast or teat of the bottle. Milk is then expressed by the teat, into the pharynx. From the pharynx, a series of reflex muscular contractions and relaxations transfer milk into the oesophagus and onward into the stomach by peristalsis. At the same time milk is prevented from entering the nasal/tracheal airway by elevation of the soft palate and closure of the larynx” (Bu'Lock et al., 1990).

The *LATCH Breastfeeding Assessment Tool* is a charting system that provides a systematic method for measuring breastfeeding behaviors in individual breastfeeding sessions (D. Jensen, Wallace, & Kelsay, 1994).

Epidural Analgesia

Epidural analgesia involves placement of an indwelling catheter placed in the epidural space of the lower lumbar spinal column for pain management. Continuous infusions of local anesthetic and opioids provide pain relief and allow sufficient motor function for labor patients. For this study an infusion of bupivacaine and hydromorphone were used for labor and delivery.

Neonatal Neurobehaviors

Neonatal neurobehaviors are physiologic and behavioral patterns that measure function of the CNS. The *Neurologic and Adaptive Capacity Score (NACS)* is a screening test for full-term neonates to detect CNS depression from drugs and also to differentiate these effects from those found after birth trauma and perinatal asphyxia (Amiel-Tison et al., 1982b).

Theoretical Framework of the Study

The theoretical framework of this study is rooted in Brazelton's theory that neonates exist in six newborn behavioral states and cycle through these states on a continuum at all times (Brazelton & Nugent, 2011). The neonate's skill in organizing these behavior states determines the ability to accomplish developmental tasks such as feeding, as well as forming relationships and learning about the world (Gottesman, 1999). Factors that negatively affect the CNS and lead to a disorganized behavioral state may hinder the effectiveness of breastfeeding (Karl, 2004; Radzysimski, 2005).

Brazelton's Newborn Behavioral States

Brazelton's newborn behavioral states include two sleep states (deep or quiet sleep and light or active sleep), a transitional state (drowsy); and three alert states (quiet alert, active alert, and crying). Each state has identifiable behaviors, and as an infant's state changes, its physiological and behavioral patterns change as well (Brazelton & Nugent, 2011). For instance,

when the baby moves from sleep state to crying, autonomic functions such as respiratory rate and heart rate increase, muscle tone increases, and reflexes become stronger (Brazelton & Nugent, 2011; Karl, 2004). As the neonate moves from alert to crying, smooth movements of the body transition to jerky disorganized movements, often accompanied by tremors. During quiet alert, alertness is at its peak; however, responsiveness diminishes during the active alert state and completely disappears with crying as the neonate is no longer cued into the environment.

The neonate's ability to achieve the quiet alert state is important, because this is when the neonate is able to accomplish new tasks (White, Simon, & Bryan, 2002). The neonate is responsive to environmental stimuli, and more likely to be able to make eye contact and interact with others during the quiet alert state. The neonate may respond to voices or animate objects, letting the parent know the neonate is a capable and willing participant.

Newborns who are unable to experience state organization have greater difficulty with important undertakings such as latching on to the breast and making eye contact with their parent. Neonates who are neurologically intact experience states in defined organizational patterns. The patterns are consistent with developmental success (Brazelton & Nugent, 2011). Each state has a particular purpose, and an infant that is organized uses all the behavioral states. For instance, crying signals for needs, sleep is for rest and recovery and quiet alert is for learning and interacting (Karl, 2004). Active alert and drowsiness are transitional states that signal where the neonate has been and where they are going on the behavioral continuum. Neonates who use all states accomplish tasks with less difficulty than infants who linger in one state with the exclusion of others (Karl, 2004).

CNS Integrity

The neonate's ability to achieve behavioral organization of state, muscle tone, and sucking reflexes depends on CNS integrity. Neonatal behaviors such as sucking represent a measure of CNS function (behavioral organization) and suggest the infant has achieved the level of maturity required for effective oral feeding (Radzysinski, 2005). A delayed CNS response can manifest itself as difficulty latching on or as an uncoordinated suck/swallow reflex.

Breastfeeding behaviors are a series of complex interactive maternal and neonatal behaviors typically involving rooting, sucking, and swallowing by the infant and milk ejection by the mother. Milk production and milk let-down are induced by maternal hormonal changes that occur with labor, birth, and delivery of the placenta. Neonates are born with an instinct to root, latch on to, and suck the breast. When the infant sucks, afferent impulses from sensory stimulation of nerves on the areola travel to the mother's CNS, where they promote the release of oxytocin from the posterior pituitary. In women, oxytocin release is often associated with the sight, sound, or even thought of their infant, indicating a psychological component of the neuroendocrine reflex (Neville, 2001). The mother must have all the functioning anatomical components to allow passage of milk from the alveoli into the ducts and the subareolar sinuses. For the neonate, sucking is a complex motor and behavioral skill. For the infant to successfully suck, the brainstem pathway must be intact and impulses must be transmitted through cranial nerves to healthy musculature of the tongue, mouth, and pharynx. To suck, the lips close around the nipple or breast, and the tongue seals the pharynx posterior forming a closed intraoral cavity. Successful breastfeeding behavior requires coordinated intraoral movements of the rhythm of sucking, breathing, and swallowing in synchronicity, with the mother allowing the pressure to

carry milk into the infant's mouth (Bu'Lock et al., 1990). The sinuses refill as the action of oxytocin continues to force milk from the alveoli to the ducts.

On the one hand, epidural analgesia preserves the beneficial stress response of the fetus to labor and reverses the negative maternal physiological and biochemical changes of labor (Westgren, Lindahl, & Norden, 1986). In this respect, epidural analgesia may exert a positive influence on breastfeeding. On the other hand, epidural analgesia may also negatively affect breastfeeding success. Studies on the impact of labor epidural analgesia have noted subtle changes in the CNS function of neonates whose mothers received continuous epidural infusions containing a narcotic (Beilin et al., 2005; Loftus, Hill, & Cohen, 1995). These changes may influence breastfeeding behaviors. Thus, epidural analgesia may impair the CNS response, decreasing the likelihood of successful breastfeeding.

Various other factors during labor and delivery may affect CNS integrity in the newborn and thus influence the success of breastfeeding. The overwhelming physiologic stress in labor experienced by the mother can cause physiologic stress to the fetus, which may delay the infant's initiation of breastfeeding at birth (Montgomery, Hale, & Academy of Breastfeeding Medicine, 2012). Furthermore, in addition to the direct negative effects of epidural analgesia on neonatal behavior, epidural analgesia may indirectly decrease the success of breastfeeding through its effects on the labor process and maternal condition. A 2011 Cochrane review analyzed 38 of the most rigorous studies on epidural analgesia and concluded that, compared with other methods of pain relief, epidural analgesia was associated with significantly longer second stage of labor, higher rates of instrumental delivery, increased use of oxytocin to augment labor, lower maternal blood pressure, and increased risks of motor blockade and maternal fever (Anim-Somuah et al.,

2011). The combination of these factors may account for at least a portion of any negative effects of epidural analgesia on the success of breastfeeding.

Researcher Assumptions

The premise of the study was that fetal exposure to epidurally administered opioids used for maternal labor pain may affect breastfeeding by interrupting the neonate's CNS. Specifically, the effects of epidural hydromorphone have never been investigated. The neonate may be impaired to the point of being unable to initiate breastfeeding behaviors that are crucial for lactogenesis to occur during the first 24 hours postpartum. The neonate must possess the ability to latch onto the breast and suck in a coordinated matter for breastfeeding to successfully occur.

The underlying assumptions were:

- The defining characteristic of mammals is the provision of milk which is a fluid composition of exactly what the young of the species needs.
- The young of the mammalian species are born with the innate ability to suckle known as breastfeeding behaviors.
- Humans are mammals and lactation is critical to the development, growth and survival of mammalian species.
- In order for the mother to produce milk the neonate must suckle at the breast.
- Many intrapartum and postpartum factors can influence the ability of the neonate to suck at the breast.
- An intact CNS is necessary for the neonate to exhibit breastfeeding behaviors that produce correct suckling for milk removal.
- An impaired CNS with depression of the neonate will interfere with these breastfeeding behaviors.

Purpose of the Study and Research Questions

The primary purpose of this study was to determine whether a relationship exists between labor epidural analgesia containing hydromorphone and breastfeeding behaviors the first 24 hours postpartum. The addition of this knowledge is expected to give healthcare workers the information needed to assist new mothers in making informed decisions related to their care, find effective techniques for managing these issues, and enable provision of breastfeeding support to women who need it postpartum.

Based on current knowledge from review of the literature, the following specific research questions were formulated:

- 1) Does the administration of epidural analgesia with hydromorphone to the mother for labor pain have a negative effect on breastfeeding behaviors in healthy term infants?
- 2) Is the duration of infusion/amount of drug given for epidural analgesia with hydromorphone for labor pain in the mother negatively related to effectiveness of breastfeeding behaviors in healthy term infants?
- 3) During labor or immediately after birth, is the presence of multiple stressful events or interventions that may affect the condition of the mother or infant during labor (e.g., oxytocin administration, induction of labor, ruptured membranes, total amount of intravenous fluids administered, longer long duration of labor, meconium staining, and need for baby suctioning) negatively related to the effectiveness of breastfeeding behaviors in healthy term infants?

Overview of Methodology

A prospective observational cohort study was performed to gather data in answer to these questions. The study assessed breastfeeding behaviors in neonates whose mothers received a

continuous epidural infusion containing bupivacaine (local anesthetic) and hydromorphone (narcotic) for labor pain compared with infants whose mothers received no analgesia during labor and delivery. The neonate's ability to feed was measured at 3, 12, and 24 hours after birth by the LATCH Breastfeeding Assessment Tool (D. Jensen et al., 1994).

Organization of the Dissertation

This dissertation is organized into five chapters. Chapter 1 provided background on the importance of breastfeeding and the nurse's role in fostering its success. The problem to be addressed in this research is that, because of potential effects on the CNS of the neonate, epidural analgesia for labor pain management may be detrimental to the success of breastfeeding. Research on this subject has remained inconclusive; in particular, no data exist regarding the effects of epidural analgesia with hydromorphone. Therefore, the purpose of the study was to determine whether a relationship exists between labor epidural analgesia containing hydromorphone and breastfeeding behaviors the first 24 hours postpartum.

Chapter 2 reviews the literature on the history, physiology, and benefits of breastfeeding and the factors that influence its success, including epidural analgesia during labor and other maternal or neonatal variables that may interfere with breastfeeding initiation. Chapter 3 presents the research design and describe the selection of subjects, the setting of the study, the study procedures and methods used for data collection and analysis, and the methods used to ensure rigor of the study and protection of human subjects. Chapter 4 describes the findings of the study. Chapter 5 discusses the results in relation to the study aims and in the context of the literature review, as well as the study limitations and implications for nurses and other health care providers.

Chapter 2: Review of the Literature

To provide background for the study, Chapter 2 reviews the literature on the history and physiology of breastfeeding, the benefits breastfeeding provides to the infant, the mother, and the public, and factors that influence its success. The chapter also reviews literature on pathophysiology and factors that influence labor pain, analgesia during labor, including epidural analgesia, and other maternal or neonatal variables that may interfere with breastfeeding initiation. It should be noted that in some areas older references were included because of their significance as classics works, or because no more current research on the topic exists.

History of Breastfeeding

Breastfeeding throughout history has been shaped by cultural values, beliefs, and customs. From prehistoric times to the preindustrial period found customs varied little and the likely survival of the infant was related to breastfeeding or by utilizing a wet nurse as a substitute. When a wet nurse was not available, infants were suckled directly on animal udders, given milk using a vessel, or given pre-chewed foods that were poor in nutrients and contaminated, which caused high mortality rates (Diez Castilho & de Azevedo Barros Filho, 2010; Fildes, 1986).

During prehistoric times when humans hunted and gathered their food, if a woman could not breastfeed her child, the child died unless another woman took her place. It is thought at that time the child would breastfeed until they were able to find their own food. Even the Neolithic period, when humans began planting, harvesting and raising livestock, it would still be a long time before animals would be milked (Colon & Colon, 1999; Diez Castilho & de Azevedo Barros Filho, 2010). With the formation of domestic herds, children survived after they were given animal milk with a vessel or directly on the animal udder (Diez Castilho & de Azevedo Barros Filho, 2010; Fildes, 1986; Greenberg, 1980).

From about 1800 BC, regulations on the practice of wet nursing were contained in Hammurabi's Code. Feeding cups were found throughout Europe and Greece in the graves of infants dating from 2000 BC. Even the story of Moses in the Old Testament describes Hebrews and Egyptians utilizing wet nurses for the survival of infants separated from their mothers (Diez Castilho & de Azevedo Barros Filho, 2010). In 200 BC, teachings in the Talmud emphasized that breastfeeding during the first 2 years of life was important to the preservation of life (Fildes, 1986). The people of Mesopotamia, Hebron, and Egypt cared for their children in the same way for millennium despite their cultural differences (Colon & Colon, 1999; Fildes, 1986). Children were considered divine gifts from God. After Egypt was dominated by Rome, the Greco-Roman culture came to prevail and children lost their value. The problem of abandoned children during this time paralleled information about feeding techniques. Families would contract wet nurses, who took the children into their own homes and return them years later. In fact so many infants were abandoned during the time of the early popes in Rome, foundling homes were started. This custom spread through the Greek and Roman Empire and throughout Europe (Lawrence & Lawrence, 2011).

In the 1700's French foundling homes were staffed by carefully selected wet nurses, whose lives were monitored to insure proper nutrition for the abandoned infants (Lawrence & Lawrence, 2011). Infant feeding habits changed when it was discovered that infants fed goat or mule milk in the Foundling Hospitals or who were given substitute foods did not survive as long as infants given breast milk (Fildes, 1986). After "infirmaries" were set up, the relationship was confirmed when mothers breastfed during the first few days immediately after delivery and onwards (Colon & Colon, 1999).

Wealthy Englishwomen did not nurse their infants from A.D. 1500 to 1700 (Fildes, 1986). It was well known in Great Britain during this time that breastfeeding was a means to delay another pregnancy, however these women preferred to have 12-20 babies rather than breastfeed them (Yalom, 1997). They believed breastfeeding aged them and ruined their figures. Wet nurses were soon replaced by cereal or bread gruel fed to infants from a spoon. The death rate was close to 100% in the foundling homes that practiced this feeding technique.

From the 15th through the 18th century, as poor rural women who had breastfed their own children as well as those of wealthy women moved to the city, century-old feeding practices changed. In this era no method for preserving fresh milk had been discovered yet, so other foods were introduced earlier. During this time, mothers started to prefer giving “paps” and “bread sops” rather than having wet nurses (Diez Castilho & de Azevedo Barros Filho, 2010). The first recipes for this were recorded in the 15th century. The recipe called for the use of a liquid, beer, wine, vegetable or meat stock, water, a cereal, bread, rice, wheat or flour, and an additive sugar, meat, eggs, honey, spices, herbs, or meat (Colon & Colon, 1999; Fildes, 1986). Mortality rates of 100% during the first week of life were reported with pap feeding (Radbill, 1981).

The American Industrial revolution saw identical changes in feeding practices. Urbanization changed the way families lived; they needed money for survival because they were no longer farming and raising livestock for sustenance. The living conditions were poor, with people crowded together in slums with little hygiene. Labor was exploited through low wages and women were forced to work. There were few wet nurses and little money to pay for them. Infants were left at home and cared for by elderly women or very young girls who fed them an array of artificial foods, some of which were laced with opiates so the infants would sleep until the mothers returned home (Fildes, 1986). These areas contained the highest rates of infant

malnutrition, morbidity and mortality in the country (Fildes, 1986). Rural areas, which maintained a 90% breastfeeding rate, with duration of breastfeeding 6 months or greater, had the lowest infant mortality (Fildes, 1986).

During the 20th century there were dramatic changes in the way infants were fed (A. L. Wright & Schanler, 2001). In the early 1900s, approximately two-thirds of mothers breastfed (Hirschman & Butler, 1981). Then both the incidence and duration of breastfeeding began to decline, dropping from almost 70% of women in 1911-1915 to about 50% in 1926-1930, and only 25% in 1946-1950 (Hirschman & Butler, 1981). The lowest level was reached in 1972, when only 22% of women breastfed (Eckhardt & Hendersgot, 1984).

The 20th century was a time of unprecedented cultural, technological, and social changes involving the roles of women, their education and income and their childbirth practices. Beginning in the 1920's the emancipation of women was symbolized by short skirts, short hair, birth control, cigarette smoking, and bottle feeding (Lawrence & Lawrence, 2011). The early portion of the 20th century also brought the development of formula milk and the use of milk from other mammals to feed infants, a move away from breastfeeding (Radbill, 1981). Sterilization practices improved which resulted in significant drops in mortality to infants who were not breastfed (Barness, 1987). After WWII there was an increase in commercially prepared infant formula and women were entering the work force.

During the 1930s, medical societies no longer stressed the importance of breastfeeding and came to believe in the healthfulness of formula for infants. Bottle feeding directions for commercial or home use came from the physician or physician surrogate, such as a nurse (Apple, 1994). Women acted on the belief that what the medical community recommended was best for the baby. At the same time, cow's milk was being introduced earlier and earlier, with a further

decrease in breastfeeding rates between 1930 and 1970 (Fomon, 2001; Jelliffe & Jelliffe, 1978) Commercial formula was often used only for a short time because of the expense compared with cow's milk (Fomon, 2001).

In the 1940's formula was made at home mixing water with pasteurized cow's milk or evaporated milk with sucrose or corn syrup. The processed milk was fortified with vitamin D, and children could be given juice which contained vitamin C thereby eliminating the threat of scurvy or rickets. Medical doctors at that time felt there was no difference between breastfeeding and formula regarding safety or satisfaction (Fomon, 2001).

At the start of the 20th century, laboratories were investing in the development of a good substitute for breast milk, producing modified milks or industrial formula. It was becoming increasingly difficult even for physicians to choose an appropriate formula because there were so many options on the market. With WWII causing birth rates to fall, manufacturers wanting to increase profits started a promotion of breast milk substitutes (Rea, 1990). After the war, in response to huge advertising campaigns and with the baby boom sales increased and formula dominated between 1950 and 1960. Interestingly, in 1956, as women who wanted to breastfeed were met with resistance from the medical profession the La Leche League was formed in Chicago to provide mothers with support to breastfeed. Women wanted to be informed and many wanted the right to choose how they would feed their infants.

The feminist movement and the contraceptive pill caused birth rates to fall again in 1960. The attitude of the female breast changed from one of the ability to nurture to the breast as a sex object. Feeding bottles became symbols of women's liberation (Diez Castilho & de Azevedo Barros Filho, 2010). The food industry increased its advertising diversifying even more and expanded into the third world (Rea, 1990). Composition of the formula was also changing based

on new discoveries in nutrition with manufacturers increasing sales by promoting their formulas advantage over similar products at reduced costs (Diez Castilho & de Azevedo Barros Filho, 2010; Fomon, 2001; Jelliffe & Jelliffe, 1978). All these changes caused breastfeeding rates to drop and the increased use of supplementation reaching the nadir in 1972 of only 22% of US women breastfeeding (Eckhardt & Hendersgot, 1984).

In 1978, Dr Derrick Jelliffe coined the term “commerciogenic malnutrition” to refer to the infant starvation caused by the promotion and use of infant formula in areas of poor water supplies and low income, triggering a renewed interest in the promotion and practice of breastfeeding on an international level (Jelliffe & Jelliffe, 1978). Increased awareness of the health consequences of corporate promotion of infant formula led to the “Baby Killers Scandal” and the boycott of Nestle, because of accusations that industry was using aggressive advertising campaigns and interfering with breastfeeding (Joseph, 1981). The prevailing mentality began to change in the 1970s, shifting to support breastfeeding in.

Physiology of Breastfeeding

Anatomy

Complex neuroendocrine reflex responses are involved in mammary gland growth, the production of breast milk, the removal of milk, and the maintenance of lactation. The human breast is composed of glandular (secretory) tissue and fat tissue and is supported by loose connective tissue. The breast is made up of 15-20 lobes that extend from the nipple to the wall of the thorax in a tree like fashion. The lobes are composed of lobules which each contain between 10-100 alveoli. It is thought that 15- 25 ducts drain the alveoli. Alveoli join their ducts (intralobular ducts), forming a distinct lobar duct, which then converges separately to the nipple via lactiferous ducts. The lactiferous ducts open into lactiferous sinuses on the surface of the

nipple that serve as small reservoirs for milk (Buhimschi, 2004). Alveoli are composed of epithelial cells, myoepithelial cells, contractile cells for milk ejection and connective tissue that contains fat and a generous blood supply (Neville, 2001). The interstitial space is where plasma cells are formed which secrete immunoglobulin's into milk during lactation. Milk is constantly secreted into the alveolar lumina and stored, until the let-down reflex causes the myoepithelial cells to contract and milk is ejected (Neville, Morton, & Umemura, 2001). The hormones of pregnancy contribute to complete alveolar-lobular development (mammogenesis) and maturation of the epithelium (lactogenesis).

Lactogenesis

Lactogenesis refers to the evolution of the mammary gland as it develops the ability to secrete milk. Progesterone and prolactin are necessary for the final steps of mammary growth and secretory differentiation which begins with a rise in mRNA for milk proteins and enzymes important for milk formation and secretion (E. Jones & Spencer, 2007; Neville & Morton, 2001). The secretory differentiation is known as stage I lactogenesis and occurs at midpoint of the pregnancy. During this stage the mammary gland has developed extensive lobular clusters and secretes small amounts of milk, the gland continues to grow until parturition, with milk secretion held in place by the high levels of progesterone in the blood (Kuhn, 1969; Neville, McFadden, & Forsyth, 2002).

After delivery of the neonate and the expulsion of the placenta there is a sudden drop in progesterone, estrogen and placental lactogen levels and a simultaneous rise in prolactin levels. The sudden drop in progesterone levels and concurrent rise in prolactin levels prompt lactogenesis II which is the onset of copious milk secretion and occurs at 30-40 hours postpartum. Mothers do not typically notice the sensation of full breasts until 50-73 hours after

birth. The milk composition also changes significantly at this time with a decrease in sodium and chloride concentration and an increase in lactose concentration which is complete usually by 72 hours after delivery (E. Jones & Spencer, 2007; Neville et al., 1991). Immunoglobulin IgA and lactoferrin rise substantially during this period after delivery and despite their concentration decline due to the increased milk production, the secretion rate remains significant the duration of lactation. Lactogenesis II is hormonally driven and milk removal is not necessary during this phase for most women (Kulski, Hartmann, Martin, & Smith, 1978). Nonetheless, the milk must be removed by day 3 for lactation to continue successfully.

Prolactin is crucial to milk synthesis, as shown in a study that intentionally inhibited prolactin using bromocriptine (Peters, Del Pozo, Conti, & Breckwoldt, 1986). Prolactin is found in the lactating breast and in milk and the prolactin in milk originates in the pituitary lactotroph (Buts, 1998; Nolin & Witorsch, 1976). Pituitary lactotrophs have automatic secretory action (M. E. Freeman, Kanyicska, Lerant, & Nagy, 2000), and the pituitary gland functions primarily under a hypothalamic dopamine inhibitory effect. The most important stimuli for prolactin release are high levels of estrogen and suckling stimulus (de Greef, Plotsky, & Neill, 1981; Neill, Freeman, & Tillson, 1971). Estrogen levels decline after delivery of the fetus and placenta, therefore it is necessary for frequent suckling at this time to maintain elevated prolactin levels that are crucial for milk synthesis. Dopamine inhibits prolactin release, but the stimulation of suckling interferes with the inhibitory response (de Greef et al., 1981). Evidence suggests the release of prolactin occurs via a neurogenic pathway from nipple to hypothalamus, with the amount released related to the number of breastfeeding sessions and the strength of the mechanical suckling. Further evidence backs catecholamine and serotonin control on the prolactin release and the

consequences of changes in the hypothalamic dopamine turnover (de Greef et al., 1981; Tyson, 1977).

Oxytocin and Milk Ejection

Removal of milk from the breast is accomplished by contraction of the myoepithelial cells which the processes of form a basket like network around the alveoli where the milk is stored (Neville, 2001). When neonates are suckled, afferent impulses from sensory stimulation of nerve terminals in the areolas travel through the CNS, where they promote release of oxytocin from the posterior pituitary gland (Neville, 2001). Oxytocin release in women has been associated with stimuli such as the thought, sight, or sound of the infant, illustrating a substantial psychological component of the neuroendocrine reflex. The oxytocin travels through the blood stream to the mammary gland, where it interacts with specific receptors on myoepithelial cells, initiating the contraction and the expulsion of milk from the alveoli into the ducts (Neville, 2001). The passage of milk into the ducts is aided by myoepithelial cell possesses which are arranged longitudinally that shorten and widen during contraction and allow the milk to flow freely to the nipple. The process by which the milk is forced through the alveoli is milk ejection or let-down and is necessary for the removal of milk from the lactating breast.

The release of oxytocin is necessary for milk removal and only the mechanical forces of suckling can remove it (Neville, 2001). Removal of the milk is necessary to continued milk secretion. When milk ejection is inhibited, milk cannot be removed from the breast and cells cease milk secretion. The mammary gland loses its ability to secrete milk when milk removal stops completely. Therefore, frequent suckling combined with adequate milk ejection, demonstrates the most crucial stimuli needed for milk production.

Human Milk Composition

It is important to outline the significance of breast milk to infant and mother as part of a review on breastfeeding. The composition of human breast milk is biologically uniquely suited to the nutritional needs of the neonate. Human milk contains both the optimal nutrition composition and non-nutritive bio molecules that contribute to organ development, immune maturation, and healthy microbial colonization and protect against inflammation and infection. Human milk is a dynamic fluid that changes its composition from colostrums to mature milk, and varies with feedings, time of day between mothers and populations.

Stages of Lactation

After delivery, the first fluid produced by the mother is colostrum, which has a unique composition, volume, and appearance (Ballard & Morrow, 2013). The first days after delivery low volumes are produced which contain immunological components such as secretory IgA (sIgA), leukocytes, lactoferrin, and developmental factors such as epidermal growth factor (Castellote et al., 2011; Kulski & Hartmann, 1981; Pang & Hartmann, 2007). Colostrum contains low levels of lactose indicating the function is immunological not nutritional. Colostrum contains higher levels of sodium, magnesium, and chloride and lower levels of potassium and calcium than late milk (Kulski & Hartmann, 1981; Pang & Hartmann, 2007). As mammary epithelial cells change, the sodium to potassium ratio declines and lactose concentration increases, leading to the production of transitional milk.

Transitional milk is the “ramped up” period of milk production, still containing characteristics of colostrum while keeping up with the nutritional and developmental needs of the growing neonate 5-14 days postpartum. After this time, the breast milk is considered relatively mature. Four to six weeks postpartum, breast milk is considered fully matured and

remains relatively fixed in composition, unlike the changing milk composition seen the first weeks of life (Ballard & Morrow, 2013).

Mature human milk is a complex fluid composed of several phases that can be separated either by centrifuge or sitting out for several hours (Neville, 2001). The milk fat globules containing the milk liquids rise to the top forming the cream layer over the skim milk. In human and bovine milk the fat accounts for 4% of milk volume (R. Jensen, 1989) and contains other milk components such as phospholipids, cholesterol, and steroid hormones. Cellular components, of breast milk are primarily sloughed epithelial cells, neutrophils, macrophages, T-cells, stem cells, and lymphocytes (Neville, 2001). The transfer of maternal living cell offers protection against pathogens while stimulating the infant's own immune system.

The composition of mature human milk is reasonably consistent, varying slightly for most components with stage of lactation and for some constituents, such as fatty acids, more with diet (Koletzko & Rodriguez-Palmero, 1999). A few components of milk, such as the B vitamins and selenium, are greatly affected by diet (Neville, 2001). Nutrition received by the fetus through the placenta is completely dependent on maternal metabolism; however, the nutrients the breastfed infant receives are not. For almost all the components of milk, the secretory mechanism is separate from the regulatory mechanism that controls nutritional influx from the mothers making sufficient milk of adequate composition available to the infant regardless of maternal inadequate food intake.

Macronutrients

The major macronutrients of milk are lactose, a disaccharide unique to milk, oligosaccharides, triglycerides, milk fat in the form of proteins, including casein, lactoferrin, α lactalbumin, sIgA, many others that are present in lower concentrations and minerals, including

potassium, chloride, sodium and magnesium. The proteins in breast milk can be divided into two categories—casein and whey—in a ratio of 40:60 (Lonnerdal, 1985). The major casein of human milk is b-casein, which forms micelles of little volume that form soft curds in the infant's stomach. Whey proteins are α lactalbumin, lactoferrin, sIgA, and serum albumin (Lonnerdal, 1985).

Secretory IgA is the principal immunoglobulin of breast milk and the specificity of sIgA antibodies reflects the mother's exposure to infection and is independent of the specific profile of blood borne IgA (Mata, 1986). Many of the proteins in breast milk have multiple functions. For example, lactoferrin transports and promotes iron absorption, is bacteria static to many organisms and acts as a nutritional protein by manufacturing amino acids to be absorbed when digested (Lonnerdal, 1985; Prentice et al., 1987).

More than 98% of the fat in human milk is constructed by the mammary epithelial cells and is in the form of triglycerides. Palmitic acid and oleic acid are the most abundant fatty acids in breast milk triglycerides. Half of the triglycerides molecules in breast milk contain palmitic acid attached to a carbon of the glycerol component making breast milk easier to digest, increasing absorption and mineral balance (Carnielli et al., 1995; R. Jensen, 1989). Long chain polyunsaturated fatty acids, arachidonic acid (AA), and docosahexaenoic acid (DHA) are synthesized from the essential fatty acids linolic acid and linolenic acid respectfully. These fatty acids are the constituents of brain and neural tissue and are needed in early mental and visual development of the neonate (Ballabriga, 1994). The lipid component of human milk provides the transport of fat-soluble micronutrients such as vitamins A, D, E, K and prostaglandins.

The major carbohydrates of human milk are lactose and oligosaccharides. Lactose is the principal sugar of milk and appears to be specific for newborn growth. It has been shown to

increase calcium absorption. Lactose is a source of galactose, which is necessary for the production of galactolipids. Galactolipids are essential for CNS development. For the neonate, human milk oligosaccharides are non-nutritive bioactive factors (Ballard & Morrow, 2013) that are prebiotic in that they enhance the growth of beneficial flora such as *L. bifidus*, indirectly protecting against gastrointestinal tract infections (Lawrence & Lawrence, 2011). They also have a role in defenses against other bacteria, as well as viruses and many toxins. The human milk oligosaccharides are recognized as pathogen-binding inhibitors that function as a “decoy” receptor for pathogens that have an affinity for binding to oligosaccharide receptors on the infant’s intestinal wall (Ballard & Morrow, 2013). Oligosaccharides have demonstrated effects against *Helicobacter pylori*, *E. coli*, *Streptococcus pneumoniae*, and influenza viruses (Lawrence & Lawrence, 2011).

Protection against infection is also provided by other constituents of human milk, such as lactoferrin, an iron-binding glycoprotein belonging to the transferrin family, which has enzyme activity that interferes with microbial function and protects against various bacteria, fungi, and viruses (Ballard & Morrow, 2013; Beljaars et al., 2004; Sherman, Bennett, Hwang, & Yu, 2004). Lactoferrin also functions in cell growth regulation, antitumor activity, and immunologic functions.

Growth Factors

Human milk contains many growth factors that have effects on the intestinal tract, nervous system, and endocrine system of the neonate. Epidermal growth factor is found in early breast milk and is critical to the maturation and healing of the intestinal mucosa (Chailier & Menard, 1999; Hirai et al., 2002; Wagner, Taylor, & Johnson, 2008). The immature gut of the infant includes the enteric nervous system, a branch of the nervous system that governs the function of

the gastrointestinal tract. For its development, the enteric nervous system requires glial cell-line derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF), which are detected in human milk 90 days after birth (Fichter et al., 2011; Li, Xia, Zhang, & Wu, 2011). BDNF enhances peristalsis of the infant intestine and GDNF increases neuron growth and survival (Fichter et al., 2011).

Also found in human milk are insulin-like growth factors (IGF), which increase tissue growth, stimulate erythropoiesis, and increase hematocrit (Kling, Taing, Dvorak, Woodward, & Philipps, 2006; Peterson et al., 2000). Human breast milk contains high amounts of erythropoietin (Epo), which is the main hormone involved in the production of red blood cells.

Hormones

Adiponectin is a hormone found in breast milk that actively regulates metabolism and suppresses inflammation. Adiponectin can cross the intestinal barrier and appears to modify infant metabolism (Martin et al., 2006; Newburg, Woo, & Morrow, 2010). High levels of adiponectin in breast milk have an inverse correlation to infant weight and BMI, leading researchers to speculate that adiponectin in breast milk may reduce the incidence of obesity in later life (Newburg et al., 2010; Woo et al., 2012). Other metabolism-controlling hormones in breast milk are leptin, ghrelin, and resistin which all appear to play a role in energy conservation, appetite control, and body composition (Dundar et al., 2010; Palou, Sanchez, & Pico, 2009; Savino & Liguori, 2008; Savino et al., 2012).

Comparison of Human Milk with Formula

Breast milk is unique in composition when compared to cow's milk, the basis for most formula. The protein in formula contains α -casein and beta lactoglobulin; the ratio of casein to whey protein is 80:20, double that of human milk. The curd formed by casein is hard and

difficult to digest. Formula cannot replicate the hormones, live living cells immunoglobulins, active enzymes, and unique chemical compounds found in human milk (Benson & Masor, 1994). The long chain of fatty acids from breast milk triglycerides, DHA and AA, are not found in cow milk based formula and if added as a supplement is not absorbed completely; furthermore the positional difference of fatty acids on the glycerol molecule is lacking. There is no lactose in some formulas an important carbohydrate for brain development and deficiency in oligosaccharides which promote intestinal health and fight infection. All of these deficiencies may impede normal infant growth and development.

Human milk is very complex. Although the composition of formula may be similar, it cannot duplicate breast milk. The exact composition of breast milk is still unknown, and even though science continues to increase understanding of breast milk and improve formula, it may never find a perfect match. Human breast milk contains at minimum 100 ingredients not found in formula. Breast milk is the perfect food for the growing and developing infant, containing just the right amount of lactose, fatty acids water, and proteins that are easy for the infant to digest. Even when formula contains the same nutrients, such as vitamins and minerals, as in breast milk, they are not absorbed or used in the same way. The differences can affect the infant's ability to digest and absorb nutrients.

Benefits of Breastfeeding

Benefits to Infant

If an infant is breastfed exclusively for more than 4 months the risk of hospitalization for upper respiratory tract infections is reduced by 72% the first year (Ip et al., 2007; Ip, Chung, Raman, Trikalinos, & Lau, 2009). The severity of respiratory syncytial virus bronchiolitis, measured by the oxygen requirement and duration of hospital stay, is reduced by 74% in infants

who breastfed exclusively for 4 months compared with infants who partially or never breastfed (Nishimura, Suzue, & Kaji, 2009). The incidence of otitis media was reduced by 23% if infants had ever been breastfed compared with exclusive formula, and the risk of otitis media was reduced by 50% in exclusive breastfeeding for more than 3 months (Ip et al., 2007). Ear and throat infections and serious colds were reduced 63% in infants exclusively breastfed for 6 months (Duijts, Jaddoe, Hofman, & Moll, 2010). There was a 64% reduction in the incidence of nonspecific gastrointestinal tract infections if an infant had ever been breastfed, with this effect lasting 2 months after breastfeeding stopped (Duijts et al., 2010; Ip et al., 2007; Ip et al., 2009; Quigley, Kelly, & Sacker, 2007). A study of preterm infants noted a 77% reduction in necrotizing enterocolitis in infants exclusively fed breast milk compared to those fed breast milk supplemented by cow's milk-based formula (Sullivan et al., 2010).

There have been consistent differences in neurodevelopmental outcomes between breastfed and formula fed infants reported however outcomes have been confounded by differences in home environment, education of parents intelligence and socioeconomic status (Der, Batty, & Deary, 2006; Ip et al., 2007). In a large open-label cluster-randomized study, the Promotion of Breastfeeding Intervention Trial, hospitals in the Republic of Belarus were randomized to promote and support exclusive breastfeeding (particularly among mothers who had already decided to breastfeed), or to continue their usual institutional policies. The experimental intervention led to a large increase in exclusive breastfeeding at age 3 months (43.3% for the experimental group vs 6.4% for the control group; $p < 0.001$). Cognitive development of the children was tested at age 6.5 years with subtests and IQ scores on the Wechsler Abbreviated Scales of Intelligence and teacher evaluations of academic performance in reading, writing, mathematics, and other subjects. Adjusted outcomes of intelligence scores and teacher's ratings

were significantly higher in children from hospitals which promoted exclusive breastfeeding (Kramer, Aboud, et al., 2008; Kramer et al., 2001; Kramer, Fombonne, et al., 2008). In another study, significant effects of human milk on long-term neurodevelopment were observed in preterm infants, a population more at risk for adverse neurodevelopmental outcomes (Isaacs et al., 2010; Lucas, Morley, & Cole, 1998; Vohr et al., 2007; Vohr et al., 2006).

Maternal Benefits

Mothers who breastfeed have health benefits both long and short term, including more rapid involution of the uterus and decreased postpartum blood loss (American Academy of Pediatrics Section on Breastfeeding, 2012). Continued breastfeeding causes lactational amenorrhea, leading to increased child spacing. Studies on the effects of breastfeeding on postpartum weight loss have been inconclusive, given the large numbers of confounding factors that contribute to weight loss (diet, baseline weight, ethnicity, and activity). In a study of 14,000 women postpartum with covariates adjusted, found women who breastfed more than 6 months weighed 1.38 kg less than those who did not (Krause, Lovelady, Peterson, Chowdhury, & Ostbye, 2010). The Nurse's Health Study found a decreased risk of type 2 diabetes mellitus of 4% to 12% for each year of breastfeeding (Stuebe, Rich-Edwards, Willett, Manson, & Michels, 2005). Another study of 2233 women found that risk of type 2 diabetes increases when term pregnancy is followed by less than 1 month of lactation (Schwarz et al., 2010).

A report by the Women's Health Initiative, a longitudinal study of 139,000 postmenopausal women found an association between cumulative breastfeeding experience and cardiovascular disease (Schwarz et al., 2009). Women who breastfed for 12 to 23 months had significant reductions in hypertension, high cholesterol, diabetes, and heart disease.

Cumulative breastfeeding experience also correlated with a reduction in ovarian and breast cancer (Ip et al., 2007; Ip et al., 2009; Stuebe, Willett, Xue, & Michels, 2009). Breastfeeding for 12 months or longer is associated with a 28% decrease in ovarian and breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). It has been calculated that each year of breastfeeding results in a 4.3% reduction in the risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Lipworth, Bailey, & Trichopoulos, 2000).

Public Benefits

In addition to the health benefits there are financial benefits to the family, society, public and private insurers, government programs, and employers (AWHONN, 2015). A cost analysis of the financial benefits of breastfeeding estimated that if 90% of mothers breastfed exclusively for 6 months, 13 billion health care dollars would be saved (Bartick & Reinhold, 2010). According to the US Surgeon General, the family of a breastfed infant saves approximately \$1500 per year in costs directly related to feeding supplies and formula. Because breastfed infants are less likely to be sick, the family saves indirectly on health care costs because there are fewer medical bills and fewer lost days of work (US Department of Health and Human Services Office of the Surgeon General, 2011). When employers invest in a lactation program and support breastfeeding, they receive \$3 return for every \$1 invested (Tuttle & Slavitt, 2009). This reduced costs for health insurance claims, reduced absenteeism reduced turnover rates leading to cost savings in recruitment and training (US Department of Health and Human Resources Health Resources and Services Administration, Undated).

Because it does not require packaging, a manufacturing plant, storage, refrigeration, or transportation, breastfeeding is also beneficial to the environment (Fairfield, 2012). Researchers have estimated that for every 1 million infants fed formula, 150 million containers used to

package the formula were disposed of, many in landfills (US Department of Health and Human Services Office of the Surgeon General, 2011).

Factors Influencing Breastfeeding in the First Days Postpartum

Maternal Intention to Breastfeed

Maternal intention to breastfeed is the strongest modifiable predictor of breastfeeding duration (Blyth et al., 2002; DiGirolamo, Thompson, Martorell, Fein, & Grummer-Strawn, 2005; Forster, McLachlan, & Lumley, 2006). Often women have made the decision to breastfeed before they became pregnant or in the first trimester before their first prenatal visit (Earle, 2002; J. Henderson & Redshaw, 2011). The influence of the primary care clinician on breastfeeding is significant (Bentley et al., 1999; Guise et al., 2003; Lu, Lange, Slusser, Hamilton, & Halfon, 2001). Responses of 1229 women in a nationally representative sample showed that, in population groups that were least likely to breastfeed, the most significant influence was prenatal encouragement and support (Lu et al., 2001). At office visits during the prenatal period, nurses and midwives have an opportunity to provide guidance and education. During well-child visits, pediatric nurses and nurse practitioners trained and certified in lactation can provide breastfeeding support and discuss a variety of issues (family support, returning to work, sore nipples etc).

Institutional Practices and Breastfeeding Support

For hospital births, the practices of the institution can act as a barrier or facilitator to breastfeeding initiation. Such factors must be considered when collecting and interpreting data from the proposed study. The groundbreaking work by Righard and Alade showed that delivery room routines are strongly associated with the infant's ability to initiate breastfeeding (Righard & Alade, 1990). Of infants placed on the mother's chest immediately after delivery, 63.2%

initiated rooting behaviors within 20 minutes and were breastfeeding successfully within the hour, 10.5% sucked incorrectly, and 26.3%, who were born to women who had narcotic epidural analgesia, did not exhibit rooting behavior. When infants were separated from their mothers for routine weighing and exams, only 20% sucked correctly, and none of these infants had received narcotic epidural analgesia (Righard & Alade, 1990).

Professional breastfeeding support from postpartum nurses and lactation consultants strongly correlates with breastfeeding initiation (Persad & Mensinger, 2008). In the immediate postpartum, mothers require professional guidance and support in breastfeeding initiation. A study in Finland (Tarkka, Paunonen, & Laippala, 1998) used multivariate analysis of predictors related to breastfeeding success and found five variables that contributed to the establishment of breastfeeding: the mother's experience of breastfeeding in the hospital postpartum, the time when breastfeeding was first initiated, the opinions of the mother's significant other and the healthcare staff on her decision to breastfeed, the amount of professional breastfeeding assistance available to her, and whether she was upset while in the hospital (Tarkka et al., 1998). Mothers who had a positive experience breastfeeding and started lactating 2 to 3 days postpartum coped better than those whose experience was not as positive and who did not start lactating until later. In addition, the more emotional support and interactive lactation assistance the mother received from her significant other and healthcare staff the better she coped with breastfeeding. In comparison, the mothers who were upset during their hospitalization did not cope well with breastfeeding.

A 2005 Cochrane review analyzing interventions for promoting initiation of breastfeeding showed that breastfeeding education had a significant effect on increasing breastfeeding initiation compared to standard care (Dyson, McCormick, & Renfrew, 2005). Five studies with a

total of 582 women on low incomes in the USA showed breastfeeding education clearly increased breastfeeding rates compared to providing routine care (Brent, Redd, Dworetz, D'Amico, & Greenberg, 1995; Coombs, Reynolds, Joyner, & Blankson, 1998; Hill, 1987; Ryser, 2004; Serwint, Wilson, Vogelhut, Repke, & Seidel, 1996). One trial with 165 women showed peer support for women considering breastfeeding also increased breastfeeding rates (Chapman, Damio, Young, & Perez-Escamilla, 2004). Needs based, one-to-one, informal education or support sessions, delivered either before or before and after the birth by a trained breastfeeding professional or peer counsellor, was the most effective intervention among women of different ethnicity and feeding intention in three studies.

Breastfeeding usually begins in the hospital so it is reasonable to examine hospital practices and the association to breastfeeding initiation. Because breastfeeding has so many positive health benefits, the United National Children's Fund and World Health Organization launched a program in 1991 called the Baby-Friendly Hospital Initiative (BFHI) to promote exclusive breastfeeding for the first 6 weeks of life. The *Ten Steps to Successful Breastfeeding* were formulated to address the negative impact of maternity care birth practices in hospitals had on the initiation, exclusivity, and maintenance of breastfeeding (World Health Organization & UNICEF, 1989). The 10 steps to successful breastfeeding as stated by the BFHI are to: (1) have a written breastfeeding policy; (2) train staff with skills to implement the breastfeeding policy; (3) inform all pregnant women of the benefits/ management of breastfeeding; (4) help mothers initiate breastfeeding within an half hour of birth; (5) show mothers how to breastfeed, and how to maintain lactation even if they should be separated from their infant; (6) give newborn infants no food or drink other than breast milk unless medically indicated; (7) use proactive rooming-in to allow mothers and infants to remain together 24 hours a day; (8) encourage breastfeeding on

demand; (9) give no artificial teats or pacifiers to breastfeeding infants; (10) Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic. Additionally, procedures that may interfere with breastfeeding are to be limited.

The 10 steps were operational targets for hospitals and became the basis for the BFHI (Brodrigg, Kruske, & Miller, 2013). The implementation of BFHI accreditation brought about increases in the initiation of breastfeeding, any breastfeeding and exclusive breastfeeding the first days postpartum (Braun et al., 2003; Broadfoot, Britten, Tappin, & MacKenzie, 2005; Merewood, Mehta, Chamberlain, Philipp, & Bauchner, 2005; Philipp, Malone, Cimo, & Merewood, 2003; Philipp et al., 2001; Venancio, Saldiva, Escuder, & Giugliani, 2012), and increased duration of breastfeeding (Braun et al., 2003; Duyan Camurdan et al., 2007; Merten, Dratva, & Ackermann-Liebrich, 2005; Venancio et al., 2012), most notably in hospitals with low breastfeeding rates to begin with. However, it was found that, in hospitals with high rates of breastfeeding initiation and where infant-friendly practices are the norm, breastfeeding initiation and duration rates did not increase when BFHI accreditation was achieved (Brodrigg et al., 2013). Women who received at least four of the 10 Baby-Friendly Hospital practices, including implementing skin-to-skin at birth, attempted breastfeeding in the first hour, no formula supplementation, and 24-hour rooming in, had an increased probability of breastfeeding at 1 and 4 months compared with women who experienced fewer than four of these practices (Brodrigg et al., 2013). The authors concluded that baby-friendly, evidence-based practices in the hospital environment were more important than the accreditation.

The Ten Steps are relevant to the research described here because the facility where the study took place (Yale New Haven Hospital) is in the process of achieving the BFH designation

and has initiated these steps. The process requires each nurse to complete 20 hours of formal breastfeeding education and requires that patients receive initial breastfeeding instruction within 6 hours after delivery. A hospital environment strongly supportive of breastfeeding may be able to at least partially offset any potential negative effects of epidurals on breastfeeding (Halpern et al., 1999; Wieczorek et al., 2010).

Literature regarding the steps relevant to the current study will be discussed in the following sections.

Immediate Skin-to-Skin Contact and Immediate Breastfeeding Initiation

The early postpartum period is an important time for mother and infant to develop this synchrony and reciprocity (Kennell, Trause, & Klaus, 1974). Skin-to-skin contact between the neonate and the mother within the first hour postpartum, which is known as the “sensitive period,” enhances the long-term interaction between mother and neonate. When the newborn is placed skin-to-skin between the mother's breasts, oxytocin is released as the newborn exhibits instinctual behavior by rooting, finding the breast, and sucking at approximately 1 hour of age (Matthiesen, Ransjo-Arvidson, Nissen, & Uvnas-Moberg, 2001; Nissen, Gustavsson, Widstrom, & Uvnas-Moberg, 1998). Endogenous oxytocin during labor and birth is necessary for the development of maternal behavior that facilitates the process of breastfeeding. Oxytocin induces the milk ejection reflex and contributes to the release of prolactin, which is linked to milk production (Dawood, Khan-Dawood, Wahi, & Fuchs, 1981).

Oxytocin and prolactin are pivotal to breastfeeding and are associated with behavioral and physiological adaptations in breastfeeding women (Jonas et al., 2009; Nissen et al., 1998; Uvnas-Moberg, Widstrom, Werner, Matthiesen, & Winberg, 1990). When this early contact occurs, mothers are more likely to be breastfeeding at 1 and 4 months or longer after delivery (Bystrova

et al., 2009; E. R. Moore, Anderson, Bergman, & Dowswell, 2012; Salariya, Easton, & Cater, 1978; Wiberg, Humble, & de Chateau, 1989).

Skin-to-skin contact immediately postpartum allows development of innate neonatal behaviors such as temperature regulation, crying, respiration, and nursing behavior. It assists the neonate in the transition to extrauterine life by decreasing the stress of birth through the mother's warmth, touch, and odor, guiding the neonate to her nipple, and triggering release of maternal oxytocin. Unmedicated spontaneous vaginal deliveries with immediate maternal-infant skin-to-skin contact have an increased likelihood of successful baby-led breastfeeding (E. R. Moore et al., 2012; Righard & Alade, 1990; Widstrom, Liilja, & Aaltomaa, 2011). The timing of the first breastfeed is associated with duration of breastfeeding. Bramson and colleagues analyzed data from a prospective cohort of 21,842 mother-infant pairs and determined that the longer the mother experienced skin-to-skin contact with the infant in the first 3 hours after delivery, the more likely she was to be exclusively breastfeeding during her hospital stay (Bramson et al., 2010). A systemic review of 59 studies found increased breastfeeding initiation rates in hospitals that promoted early mother-neonate contact as part of their initiatives (Fairbank et al., 2000). The earlier the initiation of the first breastfeed and/or mother-neonate contact, the longer the duration of breastfeeding with decreased incidence of early postpartum breastfeeding cessation (Berra et al., 2003; Buxton et al., 1991; Salariya et al., 1978). Step 4 of the 10 steps encourages that neonates be placed near the breast immediately after birth to initiate a latch-and-feed response, preferably within the first hour of delivery (DiGirolamo, Grummer-Strawn, & Fein, 2008; Hung & Berg, 2011; Mahmood, Jamal, & Khan, 2011; E. R. Moore et al., 2012; Murray, Ricketts, & Dellaport, 2007; Thukral et al., 2012).

Neonatal-Maternal Interaction and Infant Neurobehavior

Early contact between mother and neonate establishes the interaction necessary for breastfeeding. Lower neurobehavior scores at birth are associated with slower initiation of optimal sucking behavior (Beilin et al., 2005; Chang & Heaman, 2005; Radzysinski, 2005). Persistence of neurobehavior disorganization can interfere with development of optimal mother-infant synchrony necessary for the establishment of sucking and feeding (A. D. Murray, R. M. Dolby, R. L. Nation, & D. B. Thomas, 1981; A.D. Murray, R.M. Dolby, R.L. Nation, & D.B. Thomas, 1981). If mothers identify their neonate as being too sleepy and unable to latch onto the nipple and suck during the first day of life, mothers may perceive their neonate's disorganized behavior as difficult to care for and behave in ways to reinforce and confirm the behavior (A.D. Murray et al., 1981). Such factors may result in a vicious circle, preventing good feeding behaviors in the first 24 hours of life, which may prompt the mother to quit breastfeeding too soon.

Use of Infant Formula in the Hospital

Step 6 of the 10 steps says that unless medically necessary no food or drink other than breast milk should be given to the newborn. Despite this recommendation, recent data from the US Centers for Disease Control and Prevention found that 42% of infants breastfed in US hospitals were given supplemental formula (Grummer-Strawn, Scanlon, & Fein, 2008). Many birth facilities give formula, water or glucose water as a first feed or as a supplement to breast milk (World Health Organization, 1998). In-hospital supplementation has been associated with fewer breastfeeds, lower maternal milk supply, and shorter breastfeeding duration (DiGirolamo et al., 2008; Grummer-Strawn et al., 2008; Nylander, Lindemann, Helsing, & et al., 1991; Semenik, Loiselle, & Gottlieb, 2008). Research has found infants were most likely to receive

supplemental formula between 7 pm and 9 am, regardless of time of delivery (Gagnon, Leduc, Waghorn, Yang, & Platt, 2005). This study also found that the infants who had a breastfeed on the maternity unit were 'protected' from the use of formula up to 10 hours of age (Gagnon et al., 2005). Despite an early meta-analysis showing the use of infant formula not having a statistically significant effect on breastfeeding outcomes (Bernard-Bonnin, Stachtchenko, Girard, & Rousseau, 1989), recent studies from the United States, Turkey, and Italy found the use of formula during the postpartum hospital period had a negative affect after adjusting for confounding factors (Alikasifoglu et al., 2001; DiGirolamo, Grummer-Strawn, & Fein, 2001; Riva et al., 1999).

For US hospitals, the most challenging aspect of fulfilling step 6 is that the BFHI requires certified hospitals to abide by provisions of the International Code of Marketing of Breastmilk Substitutes to not distribute any commercial materials from formula manufacturers and to pay fair market value for formula. Almost all hospitals in the US receive heavily discounted or no-cost formula directly from manufacturers. Although the practice is decreasing, many hospitals also receive formula promotional materials in the form of a “diaper bag” gift to new mothers (Sadacharan, Grossman, Sanchez, & Merewood, 2011). These promotional gift packs have been shown to lead to decreased rates of exclusive breastfeeding (Howard et al., 2000; Rosenberg, Eastham, Kasehagen, & Sandoval, 2008).

Rooming In

Neonates who room-in with their mothers have a greater likelihood to be put at the breast to suck, leading to more continual breastfeeding and less supplementation. Mothers were able to identify feeding cues sooner, and the infants cried less and weighed more after the first week. When an infant stayed with the mother 24 hours a day, she produced more milk and her

confidence in both parenting and bonding with her infant increased (Bystrova et al., 2007; Keefe, 1987; Yamauchi & Yamanouchi, 1990b). Infants have a better quality of sleep when they room-in compared to those in the nursery, and interestingly mothers sleep the same amount of time whether they room-in or not, with rooming-in mothers reporting higher scores measuring quality of sleep (Keefe, 1987, 1988).

Studies conducted on rooming-in have not been rigorous in their methods; however the practice has been shown to have a positive association with breastfeeding outcomes (Perez-Escamilla, Segura-Millan, Pollitt, & Dewey, 1992; Scott, Landers, Hughes, & Binns, 2001) with even partial rooming-in having a positive influence (Buxton et al., 1991).

Breastfeeding on Demand

It is now accepted that fixed or set breastfeeding schedules lead to insufficient milk supply and breastfeeding problems. BFHI acknowledges that breastfeeding does not occur at scheduled time points and places no restriction on the amount or duration of breastfeeding. Allowing a neonate unrestricted breastfeeding allows them to self-regulate their own feedings by indicating their readiness. A recent study examined the volume and fat content of breast milk over a 24 hour period and found there is variation in feeding patterns between infants and from day to day (Kent et al., 2006). Unrestricted breastfeeding increased volume of milk intake on day 3, lactogenesis occurred earlier, meconium passed earlier, neonates glucose levels stabilized, higher weight nadir day 3-4 with increases in the rate of weight gain, less supplementation, and lower rates of hyperbilirubinemia (De Carvalho, Klaus, & Merkatz, 1982; De Carvalho, Robertson, Friedman, & Klaus, 1983; Hawdon, Ward Platt, & Aynsley-Green, 1992; Yamauchi & Yamanouchi, 1990a). Increased breastfeeding frequency was also shown to decrease breast soreness, nipple pain, and engorgement (Hill & Humenick, 1996).

Rooming-in from birth enables and encourages mothers to pursue a baby-led demand feeding schedule and allow them to successfully initiate breastfeeding.

Breastfeeding Support

Women may need breastfeeding support from healthcare providers in the immediate postpartum in assisting the mother to position and attach their babies at the breast. In a study using focus groups to determine factors mothers felt contributed to their decision to wean early, the dominant themes that emerged were overworked nurses or lack of nurses, lack of skill of nursing staff to assist with breastfeeding and getting the infant to latch on, conflicting advice, lack of privacy, and noise (Vogel & Mitchell, 1998). The main problem the women identified was that the infant was unable to latch on and suck. The mothers attributed this to the lack of nurse's skill.

Another study reported five variables associated with breastfeeding success and duration. They included the time of breastfeeding initiation, the mother's experience of breastfeeding during her hospitalization, whether the mother was upset with her hospital stay, the attitudes of the professional staff and her significant other about her decision to breastfeed, and the availability of help from the nursing staff to breastfeed (Tarkka et al., 1998). The main source of the mother's unhappiness was the infant's inability to latch on and feed. When the staff was unable or unavailable to remedy the situation, her ability to cope decreased and she became unhappy with her hospital care. She was more likely to quit breastfeeding if she was coping poorly.

The primary cause of sore nipples is thought to be due to incorrect breastfeeding mechanics, such as improper positioning, dysfunctional or disorganized sucking, improper latch or failure of the infant to form a teat, i.e., the ability of the infant to draw the nipple and part of

the areola into the mouth (Righard, 1998; Righard & Alade, 1992; Tait, 2000; Walker, 2007). Limiting the time at breast has no effect on nipple soreness, but correct latch and position are crucial. It is important to address the nipple pain and implement corrective action as up to a third of these mothers will switch to formula feeding postpartum (Briggs, 2003). Many women are surprised and the intensity and extent of the pain they experience which can result in unwanted rejection toward the infant, inability to trust their body and early cessation of breastfeeding (Kelleher, 2006).

Maternal Satisfaction with Breastfeeding

Maternal dissatisfaction with breastfeeding may lead to early cessation. The top reasons that a mother stops breastfeeding in the early postpartum is her perception that her infant is not satisfied by her breast milk alone (Li, Fein, Chen, & Grummer-Strawn, 2008; Murray et al., 2007), concern she is not producing enough milk (Murray et al., 2007), and nipple pain (Morland-Schultz & Hill, 2005). In another study (O'Leary, Kopsell, & Haller, 1997), the main reasons for formula supplementation was the mother's perception that she did not have enough milk, and the formula was easier to give. A further study similarly reported that the main reasons mothers supplemented with formula was the perceived inadequacy of their milk supply, sore nipples, frequency of night feedings, and the baby's preference for formula (Chapman & Perez-Escamilla, 1999). Upon further analysis of these themes, the mothers determined that lack of milk supply was related to infant behaviors such as fussiness, slow weight gain, rashes, and the infant's rapid consumption of formula with sound sleep afterwards, whereas when breastfed, the infants were fussy and discontented.

Consistently reported as a reason of early of weaning is insufficient milk supply (Meedya, Fahy, & Kable, 2010; Thulier & Mercer, 2009). Despite the fact 50% of women report they

perceive their milk supply to be insufficient, only 5% actually suffer from a physiological insufficient milk supply (Meedya et al., 2010; Thulier & Mercer, 2009). Many women supplement with infant formula in response to their perception of having insufficient milk supply. The reduction in demand for the breast milk decreases the maternal supply, multiplying the problem. There is a strong psychological component to this biological factor as perception of insufficient milk supply is associated with low maternal self-efficacy for breastfeeding (Meedya et al., 2010).

Specific infant behaviors valued by the mother have been linked to maternal satisfaction (Vandiver, 1997). Fifty primigravida who had given birth to term healthy infants completed questionnaires on infant temperament, caregiver flexibility, and their perception of breastfeeding in their third trimester and then again when their infants were 12 weeks old. Thirty of the mothers were additionally watched in their homes for 2 hours while interacting with their infants at 2, 6, and 12 weeks postpartum. Significantly longer duration of breastfeeding was correlated with higher rates of mothers' interactive behaviors with their infants and their perception that the infants had an easy temperament.

This led researchers to examine the relationship between infant fussiness, discontent behavior and poor weight gain, and the mother's perception of poor milk supply and sore nipples. Two researchers independently concluded that it was correct infant position and sucking of the breast that avoided the majority of problems that led to early breastfeeding cessation (Fisher, 1981; K. B. Frantz & Fleiss, 1980). They determined that the infant had an oral search reflex which is stimulated when the lips are close to the nipple. The reflex allows correct sucking at the breast which they defined as the infant's mouth is wide open, tongue under the areola with the milk expressing in slow deep sucks. They determined manipulation of the nipple into the

infant's mouth led to faulty sucking, and once the infant learned faulty sucking, it was problematic to retrain the infant to suck correctly at the breast. The introduction of artificial nipples on formula supplement bottles or pacifiers contributed to the infant learning faulty sucking technique (Fisher, 1981; K. B. Frantz & Fleiss, 1980).

Maternal self-efficacy in the prenatal period has been examined in relation to breastfeeding outcomes. A longitudinal study conducted in the United States evaluated 64 minority women 2 months postpartum (Ertem, Votto, & Leventhal, 2001). The women who during the prenatal period were not confident about breastfeeding were 12 times more likely to stop breastfeeding than those who were confident. Lack of confidence in breastfeeding was associated with mothers' perception of insufficient milk supply, which led to a decrease in breastfeeding and an increase in formula supplementation (Dennis, 2002). In another study, lower breastfeeding rates were found at 6 weeks postpartum in women who perceived their milk production to be insufficient who also scored lower on maternal confidence (Hill & Humenick, 1996).

Maternal Perception of Infant Behavior

Breastfeeding requires mother and infant fully participate in an interactive process each learning to fulfill their new roles. The maternal task of initiating and facilitating breastfeeding has been recognized. However, it has only recently been acknowledged that the infant plays a part in this process. Research in past decades established that newborns are interactive, proactive and individualized in their reaction to the world (Klaus & Klaus, 1998).

Studies of mother-infant interaction have highlighted the role of infants perceptual, communicative, and interactive competency (Brazelton, Cramer, Kreisler, Schappi, & Soule, 1983). The bi-directionality of the mother-infant interaction is characterized by synchrony and reciprocity (Tronick & Cohn, 1989). The infant's behavior is not only influenced by the mother

but it may also affect the mother's behavior. In this way, the infant's signals may affect the quantity and quality of caregiver exchanges (Mazet & Stoleru, 1993). If this interaction is interrupted due to the direct effects of epidural medication, and the baby is less alert, less able to orient, and less able to show organized movement, this may interfere with the mother-infant relationship (A.D. Murray et al., 1981; Sepkoski, Lester, Ostheimer, & Brazelton, 1992).

Research has demonstrated how these infant behaviors are useful for breastfeeding. Mothers appear to associate certain infant behaviors with satisfaction with breastfeeding. In one study (Lothian, 1995), a group of mothers who—regardless of support, motivation or intent—continued breastfeeding only if they believed their newborn was satisfied and “attached easily, sucked well and appeared content” (p.333). In related studies, maternal satisfaction with breastfeeding was associated with competent infant feeding behaviors (Matthews, 1991), and an infant demonstrating attachment behaviors (Brandt, Andrews, & Kvale, 1998). Both of these studies established satisfied infants breastfed longer than an infant perceived to be unsatisfied.

Descriptions of their newborn's satisfaction by the mother were related to behavioral state organization. The behaviors described included the infants' ability to come to a quiet alert state (Brandt et al., 1998), calm themselves (Leff et al., 1994; Lothian, 1995), make eye contact and maintain a mutual gaze with the mother (Lavelli & Poli, 1998) and exhibit cuddliness and consolability without irritability (R. B. Hughes, Townsend, & Branum, 1988; Karl, 2004). Infants who were able to organize their behavioral states breastfed more effectively and for a longer duration than those who were not (R. B. Hughes et al., 1988; Lothian, 1995). The early infant behaviors at the breast may affect the mother's decision to continue to breastfeed based on the mother's perception of whether or not her infant enjoys breastfeeding.

Demographic and Socioeconomic Factors

A number of demographic and socioeconomic factors may decrease incidence and duration of breastfeeding. Such factors include returning to work (Brand, Kothari, & Stark, 2011; Johnston & Esposito, 2007), lack of social support (Brand et al., 2011), racial minority, level of education high school or less (Chin, Myers, & Magnus, 2008), low socioeconomic status (Chin et al., 2008), parity (Lind, Perrine, & Ruowei, 2014), marital status (Lind et al., 2014), biological and physiological conditions (Chin et al., 2008), and smoking (Lind et al., 2014). Research has shown that mothers who are married (Avery, Duckett, Dodgson, Savik, & Henly, 1998), are older than age 30 years (Bolton, Chow, Benton, & Olson, 2009; Brand et al., 2011), have a high income (Avery et al., 1998; Dennis, 2002), and are well educated (Avery et al., 1998; Haas et al., 2006; Wen, Baur, Rissel, Alperstein, & Simpson, 2009) had higher incidence of breastfeeding initiation and duration. Elevated maternal body mass index was also found to negatively influence the initiation, intention, and duration of breastfeeding significantly (Guelinckx, Devlieger, Bogaerts, Pauwels, & Vansant, 2012).

Infant's Ability to Latch and Suck

In order for the infant to effectively breastfeed, the infant must be correctly positioned at the breast to stimulate the neonate's oral searching reflex. While mothers must develop the skills for successful breastfeeding, the infant is born with two specific innate reflexes to assist him in taking in the nutrients required for survival. The first of these is the rooting reflex, which is initiated by the mother. The rooting reflex has two components (1) tactile stimulation of the skin around the infant's mouth will cause the infant to turn his head in that direction and (2) his mouth gapes in preparation of the nipple (Woolridge, 1986). When the infant's mouth gapes, the mother must take the initiative to bring infant and breast together so that the second reflex—the

sucking reflex—can be elicited (Woolridge, 1986). The infant should be supported to open the tongue wide, thrust the tongue forward to take the breast, then with the tongue under the areola express milk from the breast with deep slow sucks (Righard, 1998; Righard & Alade, 1992). The nipple and surrounding breast tissue is drawn into a teat by suction created in the infant's mouth. The teat is 3 times as long as the nipple is at rest, and extends back into the infant's mouth to the junction between the soft and hard palates (Ardran et al., 1958). At its base it is held between the upper gum and the tongue, which covers the lower tongue (Woolridge, 1986). The lateral margins of the tongue cup around the nipple creating a central trough in which the nipple lies (Weber et al., 1986). Milk is expressed from lactiferous sinuses and is propelled toward the back of the mouth by a posterior directed peristaltic action of the tongue (Ardran et al., 1958; Weber et al., 1986). The cycle of sucking is initiated by an upward curving of the anterior tongue, followed closely by pressure from the lower gum caused by elevation of the jaw (Woolridge, 1986). The raising of the tongue continues to move the milk into the pharynx. If the volume of milk is sufficient to trigger swallowing, the soft palate rises and closes off the nasal cavity. The larynx, which separates the trachea from the esophagus, moves up to close the trachea, which is aided by a downward movement of the epiglottis resulting from pressure from the fluid bolus and rear portion of the tongue (Woolridge, 1986). The pharyngeal space is progressively reduced until it is obliterated propelling the milk into the esophagus (Logan & Bosma, 1967).

There are two features of normal sucking that deserve a closer look because their disturbance can lead to sore nipples. The first is that normal sucking is devoid of frictional movement. If a significant amount of breast tissue has been formed into a "teat," then there should be very little movement of the teat in and out of the infant's mouth; there should be a unidirectional exchange of milk into the infant's mouth (Woolridge, 1986). Thus, there should be

minimal friction from the tongue and gums against the skin of the breast. This picture is consistent with reports made by cineradiographic and ultrasound observation (Ardran et al., 1958; W. Smith, Erenbery, Nowak, & Franken, 1985; Weber et al., 1986). The second feature is that the application of positive pressure on the nipple by the tongue surface is the primary force in evacuating milk from the nipple and into the esophagus.

The infant also generates a negative pressure in his mouth during the process of milk removal. The role of negative pressure has not been determined, but the two most likely functions are 1) to retain the nipple and breast in the mouth in the correct position (countering the natural retractile nature of the tissue), thereby retaining the teat shape of the nipple and breast tissue; and 2) to aid in the refilling of the nipple by sinuses and ducts (Woolridge, 1986). Evidence for the former suggestion can be seen in Ardran's cineradiographic films (Ardran et al., 1958).

Survival of the newborn is reliant on establishing effective feeding. Effective and efficient feeding requires coordination of breathing with sucking and swallowing and involves the functional interaction of lips, jaw, palate, tongue, larynx, pharynx, and esophagus (Bu'Lock et al., 1990; A. Miller, 1982). To accomplish this, the neonate uses cerebral and brainstem structures, 6 of the 12 cranial nerves (V, VII, IX, X, XI, and XII), 22 bones connecting at 34 sutures, and 60 voluntary and involuntary muscles in a process that occurs at 40 to 60 cycles/per minute, 10-30 minutes at a time, 8-16 times a day (Smyth, Alldred, & Markham, 2007). Newborns must have oropharyngeal muscle patterns with the coordination and strength to obtain milk from the breast, as well as the psychomotor ability to cue that they are ready to feed (L. Smith, 2010). The muscles that control the sucking, opening and closing of the mouth during breastfeeding are innervated by motor fibers. If compromised, this may interfere with the

neonate's ability to root, latch, and suck adequately (L. Smith, 2010). An intact CNS is essential for the infant to physiologically latch and feed (Radzynski, 2005).

Methods for Assessment of Breastfeeding

Very few studies have used an objective breastfeeding assessment scoring tool (J. J. Henderson, Dickinson, Evans, McDonald, & Paech, 2003; Volmanen, Valanne, & Alahuhta, 2004; Wiklund, Norman, Uvnas-Moberg, Ransjo-Arvidson, & Andolf, 2009; Wilson et al., 2010). There is no standardized method to assess the breastfeeding encounter, but several tools have been developed for breastfeeding assessment. These include the LATCH scoring system, Infant Breastfeeding Assessment Tool (IBFAT), and the Mother Baby Assessment Tool (MBA). The LATCH scoring system (D. Jensen et al., 1994) is used extensively by nurses at birthing centers and hospitals and is the breastfeeding assessment tool used at Yale New Haven Hospital (YNHH). It has been used by researchers (Baumgardner, Muehl, Fischer, & Pribbenow, 2003b; Chang & Heaman, 2005) in their assessment of the effects of labor analgesia on breastfeeding and was used for the current study. LATCH is a breastfeeding charting system that assesses individual breastfeeding sessions using a systemic model to gather information (D. Jensen et al., 1994). The LATCH score includes all aspects of latching behavior by providing a score of 0, 1, or 2 for key components of breastfeeding. L= is the infants ability to latch onto the breast, A= is the audible sound of swallowing, T=Type of nipple the mother has, C= Comfort of the mothers breast and nipple, H=Holding which is the amount of assistance the mother needs to hold the neonate. To obtain the score all the areas of assessment are added to get a total for that breastfeeding session. For example a mother with previous breastfeeding experience, everted nipple, and an alert and vigorous infant could get a score of 9 or 10 (D. Jensen et al., 1994).

Successful breastfeeding defined by LATCH is a score >7 at two feeds in 24 hours (Baumgardner et al., 2003b; Bramson et al., 2010).

The interrater reliability of the LATCH tool was high and ranged from 85.7%-100% and strong construct validity (Adams & Hewell, 1997; J. M. Riordan & Koehn, 1997). Riorden and Koehn (1997) found a significant correlation between nurses' and mothers' assessment scores, and both assessment scores positively correlated with duration of breastfeeding. These findings support previous research that assessed the validity and reliability of LATCH tool (Adams & Hewell, 1997; Matthews, 1988). Matthews (1988) found interrater reliability between raters' scores and mothers' scores to be 91%. A more recent study (Altuntas et al., 2014) found positive and significant correlations between researchers' scores for 46 observations using the IBFAT, MBA, and LATCH. They reported that all three assessment tools were compatible in the assessment of breastfeeding performance.

Methods for Assessing Infant Well-being

One of the primary concerns of obstetrical anesthesia is neonatal well-being. The greatest challenge for researchers has been how to accurately measure neurobehavior. Clinical and laboratory measurement scales, including Apgar scores (Apgar, 1953), umbilical blood venous and arterial acid-base balance analysis (Bax & Nelson, 1993), and neonatal neurobehavioral testing scales have been developed to assess neonatal well-being (Als, Tronick, Lester, & Brazelton, 1977).

Apgar Scores

Early studies used Apgar scores at 1 and 5 minutes, cord blood pH, and respiratory depression to evaluate the effects of epidural analgesia on the neonate. Whereas these tests evaluate depression of vital function, they are not sensitive to the subtle differences in neonatal

neurobehavior, such as variation in muscle tone, motor movements, and sleep cycles, which may be differentially influenced by narcotics, resulting in impairment of the neonate's ability to breastfeed effectively.

Nearly every infant born in the developed world is assigned an Apgar at 1 and 5 minutes with virtually all studies on epidural analgesia and neonatal outcomes including Apgar scores. Dr Virginia Apgar, an anesthesiologist, developed a scoring system in 1952 to rapidly assess the status of the newborn after delivery and the need for prompt intervention to establish breathing (Apgar, 1953). The Apgar score is comprised of five components: Heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0, 1, or 2. The score is reported at 1 and 5 minutes after birth, and higher scores indicate optimal condition of the neonate in the transition to extrauterine life.

Apgar and her team established the relationship between blood gas data and Apgar scores, verifying that newborns with low scores were acidotic and hypoxic and needed treatment. Once the mechanism of low Apgar scores was understood, she then applied them to assess labor, delivery, and the effects of anesthetics given to the mother on the baby. She and her colleagues demonstrated that cyclopropane, which was commonly used for cesarean and vaginal deliveries at that time, caused depression of babies and low Apgar scores when given to the mother. On the basis of their data, they concluded that epidural analgesia provided the best outcomes for mother and newborn (Apgar, Holaday, James, Prince, & Weisbrot, 1957), starting the trend toward regional anesthesia in obstetrics.

The 5 minute Apgar score has been shown to be more predictive of survival than the 1 minute score (Apgar, 1966; Drage, Kennedy, & Schwarz, 1964). A report from the Collaborative Study of Cerebral Palsy, which involved 17,221 babies at 13 institutions, showed that the Apgar

score, especially the 5-minute score could predict neonatal survival and neurologic development (Drage et al., 1964). Several large cohort studies since then have documented that a 5-minute score <7 is associated with increased risk of neonatal death (Casey, McIntire, & Leveno, 2001; Moster, Lie, Irgens, Bjerkedal, & Markestad, 2001; Nelson & Ellenberg, 1981; Thorngren-Jerneck & Herbst, 2001) and cerebral palsy in term infants (Drage, Kennedy, Berendes, Schwarz, & Weiss, 1966; Thorngren-Jerneck & Herbst, 2001). This is significant because labor epidural analgesia administered to the mother has been shown to produce a mild but significant decrease in Apgar scores at 1 and 5 minutes (Greenwell et al., 2012; Herrera-Gomez et al., 2015). In a population study of 1 million term births in Sweden (Thorngren-Jerneck & Herbst, 2001), epidural analgesia was found to be a risk factor for Apgar scores <7 , along with several other obstetric risk factors. The authors concluded that 5-minute Apgar scores <7 are associated with an increased risk of neonatal morbidity, infant mortality, and neurologic impairment (Thorngren-Jerneck & Herbst, 2001).

Neonatal Neurobehavior Tests

Neonatal neurobehavior scales describe the individual infants' autonomic, motor, state, and social-attentional systems as they interact with each other and become integrated, how the neonate is affected by environmental factors, and what the neonate contributes to the development of the emerging parent-child relationship (Brazelton & Nugent, 2011). Such tests can assess the neonatal depressant effects of drugs given to the mother intrapartum. Various neurobehavioral tests have been designed to capture these subtle aspects the Apgar score cannot detect. Three assessment tools have been used to examine the association between epidural analgesia and neonatal behavior: the Brazelton Neonatal Assessment Scale (NBAS) (Brazelton,

1973), the Scanlon Early Neonatal Neurobehavioral Scale (ENNS) (Scanlon, Brown, Weiss, & Alper, 1974), and the NACS (Amiel-Tison et al., 1982b).

The NBAS, which takes the longest to administer (30-45 min) and requires significant training to carry out, has been described as the most comprehensive neonatal neurobehavior examination (Kuhnert, Linn, et al., 1985).

The ENNS was developed by an anesthesiologist to examine neurobehavioral changes that occur with anesthetic drugs. The test takes 10 minutes to perform and places more emphasis on muscle tone, reflexes and decrement to stimulation than the NBAS because it is believed these would be most affected by anesthesia drugs (Kuhnert, Linn, et al., 1985). It covers many of the same areas as the NBAS, including assessment of state and interaction so it provides a general evaluation.

The NACS was specifically designed to detect CNS depression of the neonate from drugs and to differentiate those effects from birth trauma and perinatal asphyxia (Amiel-Tison et al., 1982a, 1982b). This test does not specifically assess breastfeeding but uses 20 criteria to assess 5 general areas: adaptive capacity, passive tone, active tone, primary reflexes, and general neurologic status (Amiel-Tison et al., 1982b). The NACS was proposed as a simple, noninvasive, 5 minute neurobehavior exam to assess subtle effects of drugs and distinguish drug effects from birth trauma. No special training is required to perform the NACS. It has been widely embraced by the obstetrical anesthesia community and is used worldwide, despite criticism of its reliability and validity (Brockhurst, Littleford, Halpern, & Fisher, 2000; M. D. W. Camann & Brazelton, 2000) and its ability to differentiate effects among different drugs (Kuhnert, Linn, et al., 1985).

Labor Pain

Pathophysiology of Childbirth Pain

To understand the nature of labor pain it starts with understanding how nociceptive stimuli that is centrally received by the parturient called pain. During the first stage of labor (dilation) visceral pain predominates, with pain (nociceptive) stimuli arising from mechanical distention of the lower uterine segment and cervical dilation (McDonald, 2001; Ward, 1997). High-threshold mechanoreceptors in the myometrium may also generate nociceptive stimuli in response to uterine contractions, particularly in long protracted labors (Faure, 1991). The increasing intensity of pain commonly observed in the progression of dilation may be partially attributed to lower activation threshold in the mechanoreceptors, and to chemoreceptor stimulation produced by the repeated stimulation of uterine contractions (Bonica & McDonald, 1990; Brownridge, 1995). These nociceptive stimuli of the dilation phase are predominately transmitted to the posterior root ganglia at T 10 through L1 (McDonald, 2001; Ward, 1997). Similar to other types of visceral pain, labor pain may be progressively referred to the abdominal wall, lumbosacral region, iliac crests, gluteal areas and thighs (McDonald, 2001). Although virtually all laboring women experience lower abdominal pain during contractions, 15-74% may also experience contraction-related low back pain, which for some is continuous even between contractions (Labrecque, Nouwen, Bergeron, & Rancourt, 1999; Melzack & Schaffelberg, 1987). Some women experience very widespread and diffuse pain sensations, whereas others feel very localized pain in specific well defined areas (Melzack, Kinch, Dobkin, Lebrun, & Taenzer, 1984). As the pelvic or descent phase of labor advances (first stage and second stage), somatic pain predominates from distention and traction on pelvic structures surrounding the vaginal vault and from distention of the pelvic floor and perineum. Sharp and generally well localized, these

stimuli are transmitted via the pudendal nerve through the anterior rami of S2 through S4 (McDonald, 2001; Ward, 1997).

In the dorsal horn of the spinal cord, the nociceptive stimuli are processed and transmitted via the spinothalamic tract to the thalamus, brain stem, and cerebellum, where spatial and temporal analysis occurs, and to the hypothalamic and limbic systems where emotion (affect) and autonomic responses originate (Terman & Bonica, 2000). At the level of the dorsal horn, motor and sympathetic relax activity is stimulated, and modulation of nociceptive impulse transmission may occur through several complex inhibitory systems activated at many supraspinal levels of the CNS.

Knowledge of the anatomy of labor pain defines the current treatments of labor pain with epidural analgesia. The visceral pain of the first stage of labor and sacral somatic pain caused by descent of the fetus in the birth canal can be completely blocked by epidural analgesia, resulting in decreased maternal stress response.

The local anesthetics widely used in labor epidurals work by blocking voltage-gated sodium channels preventing conduction of an action potential in afferent C and A delta fibers (Lirk, Picardi, & Hollmann, 2014). During the first stage of labor unmyelinated C fibers transmit slow, dull, poorly localized, visceral pain. Myelinated A delta fibers transmit the rapid, sharp well localized somatic pain seen in the second stage of labor. Spinal opioid receptors are positioned to modulate noxious afferent input in the central/spinal axis. Opioids work on the dorsal horn of the spinal cord, binding with mu, delta, and kappa opioid receptors, causing G-coupled proteins to activate, and inhibiting the release of Ca⁺⁺, and K channels. Activation of the kappa receptor directly inhibits the release of substance P, by blocking Ca⁺⁺ influx required for transmitter release at primary afferent terminals. Mu and delta receptors are coupled to

voltage-dependent K channels and inhibit depolarization of the nerve. Central/ spinal pain modulation occurs by inhibiting excitatory neurotransmitters such as glutamate and substance P, from presynaptic afferent nerve terminals that ascend the spinal cord to the brain.

Physical and Psychological Factors Affecting Perception of Pain

The severity and duration of labor pain and suffering are influenced by a number of physical and psychological factors. Physical factors such as maternal age and parity, maternal condition, condition of the cervix at the onset of labor, and the relationship of the size and position of the fetus to the size of the birth canal (Sheiner, Sheiner, & Shoham-Vardi, 1998). Many of these factors are interrelated. Generally, older nulliparas experience longer and more painful labors than younger nulliparas (Melzack et al., 1984). The parous cervix begins to soften before the onset of labor and is less sensitive than the nullipara cervix. The intensity of uterine contractions in early labor tends to be greater in nulliparas than parous women, whereas the reverse is true as labor progresses (Wong, 2009). Dystocia caused by a contracted pelvis, a large baby, or abnormal presentation or position is likely to cause more pain. Women who go on to have a cesarean delivery after labor have more breakthrough pain during epidural analgesia and require higher opioid doses during systemic analgesia than women who deliver vaginally (Alexander, McIntire, & Leveno, 2001; Hess, Pratt, Soni, Sarna, & Oriol, 2000). A history of dysmenorrhea, maternal fatigue, and general debility are associated with higher levels of pain (Melzack, 1984).

Psychological factors, including fear, apprehension, and anxiety, and the presence of family members or birthing companions, also influence pain and suffering during childbirth (Henneborn & Cogan, 1975; Kennell, Klaus, McGrath, Robertson, & Hinkley, 1991; Lang, Sorrell, Rodgers, & Lebeck, 2006). Education, intense motivation, and cultural factors influence

the affective and behavioral dimensions of pain, although they probably affect actual pain sensation minimally. For example, Bonica observed that women who had predelivery training in psychoprophylaxis manifested little or no pain behavior during childbirth, although when questioned the next day, most of them indicated the process had been quite painful (Bonica, 1969).

Labor Pain and Its Effects on Mother and Fetus

During the first stage of unmodified labor, maternal respiration increases by 75-100% (Hagerdal, Morgan, Sumner, & Gutsche, 1983). Maternal hyperventilation in response to pain has long been known to have negative effects on the fetus (Huch, 1986; Motoyama, Rivard, Acheson, & Cook, 1966). This leads to hypocarbia and respiratory alkalosis, which can disrupt placental transfer of oxygen (Reynolds, 2010). A compensatory metabolic acidosis becomes progressively more severe as labor advances, and is conveyed to the fetus (Thalme, Belfrage, & Raabe, 1974). Episodes of hypoventilation that occur between contractions lead to oxygen desaturation (Minnich, Brown, Clark, Miller, & Thompson, 1990). Maternal hyperventilation causes vasoconstriction which affect the uterine arteries (Huch, 1986). There is a shift in the oxygen disassociation curve. It was demonstrated years ago in sheep that maternal hyperventilation resulted in reduced oxygen content in umbilical venous blood, and restoring the carbon dioxide to normal reversed this effect (Levinson, Shnider, DeLorimier, & Steffenson, 1974). The adverse effects of hypocarbia at first were harder to demonstrate in humans (Huch, 1986). However, a reversal of this phenomenon could explain the reduction of metabolic acidosis seen in regional anesthesia. Maternal hyperventilation lowers the partial pressure of carbon dioxide ($p\text{CO}_2$) of the umbilical artery, but as labor progresses this change is overcome by an

increased severity of metabolic acidosis to the extent that the longer the second stage of labor (pushing to delivery) the lower the cord pH will be at birth (Pearson & Davies, 1974b).

Maternal stress and pain adversely affect the fetus. The stress of labor also leads to the release of maternal cortisol and catecholamines and prolongs labor (Lederman, Lederman, Work, & McCann, 1978; J. Moore, 1993; Myers, 1975). Painful labor activates the stress response with release of β lipotropin and ACTH thus β endorphin and cortisol with the β endorphin having very little analgesic effect. The increased sympathetic/ adrenal activity can lead to uncoordinated uterine movement and decreased uteroplacental perfusion (Loo & Irestedt, 2000). The metabolic outcome of the stress response is hyperglycemia with poor insulin response, lipolysis with release of free fatty acids, ketones and lactate (Reynolds, 2010). Catecholamines, along with the metabolic acids, readily cross the placenta, increasing the oxygen requirement of the fetus, another outcome of maternal metabolic acidosis compounded in the fetus (Thalme et al., 1974).

Although the maternal stress response is relatively counterproductive, it can be suppressed by epidural analgesia. In contrast, the fetal stress response is beneficial for adaptation to extrauterine life and is not suppressed by maternal epidural analgesia (Irestedt, 1993; Westgren et al., 1986). Particularly during the second stage (complete cervical dilation to delivery of neonate), labor induces a massive catecholamine (epinephrine and norepinephrine) surge in the fetus, which helps to preserve blood flow to brain, heart, and adrenals and to promote postnatal adaptive circulatory changes and surfactant release (Reynolds, 2010).

The amount of pain a woman feels when she is in labor is influenced by a number of physical factors, including oxytocin augmentation, dysfunction of labor, and the duration and progress of the labor. Women experience pain in a variety of ways, and the way a woman copes with the pain is influenced by psychological and environmental factors, the circumstance of her

labor, her cultural background, the support available to her, and her preparation for labor (Anim-Somuah et al., 2011). Suffering during labor can have a negative effect on her psychologically, lead to labor dysfunction and postpartum depression which all can influence breastfeeding negatively (Montgomery et al., 2012). The overwhelming physiologic stress in labor experienced by the mother can cause physiologic stress to the fetus which may affect breastfeeding initiation at birth (Montgomery et al., 2012).

Labor induces a massive catecholamine (epinephrine and norepinephrine) surge in the fetus, particularly in the second stage, which helps to preserve blood flow to brain, heart, and adrenals and to promote postnatal adaptive circulatory changes and surfactant release (Reynolds, 2010). Although this stress response is advantageous to the fetus, unmedicated labor produces maternal physiological changes that can affect the fetus adversely. Maternal hyperventilation in response to pain has long been known to have negative effects on the fetus (Hutch, 1986; Motoyama et al., 1966). This leads to respiratory alkalosis and a left shift in the oxygen dissociation curve which can disrupt placental transfer of oxygen (Reynolds, 2010). A compensatory metabolic acidosis, which becomes progressively more severe as labor advances and is conveyed to the fetus (Thalme et al., 1974), episodes of hypoventilation between contractions leading to oxygen desaturation (Minnich et al., 1990) and uterine vasoconstriction (Hutch, 1986). Additionally the stress of labor also leads to the release of maternal cortisol and catecholamine's, which may prolong labor and impair placental flow (Lederman et al., 1978; Ohno et al., 1986; Segal & Wang, 2008). Stress hormones also bring about lipolysis (with release of free fatty acids that readily cross the placenta) and hyperglycemia, which exacerbate fetal hypoxia (Reynolds, 2010). All these changes tend to intensify fetal metabolic acidosis which becomes progressively worse as labor progresses (Thalme et al., 1974).

History of Labor Analgesia

On January 19, 1847, James Young Simpson used diethyl ether to anesthetize a woman with a deformed pelvis for delivery of her child. The era of obstetrical anesthesia had begun. Simpson was highly criticized for his etherization of childbirth. The medical community, including obstetricians, believed that uterine pain was inseparable from contractions, and any drug that abolishes pain would alter contractions (Caton, 2014). Clergy argued that childbirth pain is God's punishment to Eve and her descendents for disobedience in the garden of Eden, and it was wrong to avoid the pain of divine punishment (Caton, 2014). The controversies continued until 1853 when John Snow administered chloroform to Queen Victoria during the birth of her 8th child, Prince Leopold. Queen Victoria's decision to use an anesthetic during labor shattered the clergy's argument and empowered women. Women lost their skepticism, announced they wanted anesthesia, and essentially forced their physicians to provide it to them. By 1860, because of the demands of women, anesthesia for childbirth became part of medical practice. Physicians used obstetric anesthesia sparingly until the early twentieth century, when suffragettes recognized that they could not participate fully in the economic and political life of the country unless they were healthy. For this reason they made obstetric care, including anesthesia, part of their campaign for political party (Caton, 2014).

Early feminists had a good reason to be concerned about obstetric care. Despite many improvements to medicine, maternal morbidity and mortality hardly changed between 1830 and 1930. Women were debilitated by the sequelae of poorly managed deliveries and exhausted by frequent pregnancies and management of large families. Accordingly feminists sought care by obstetricians rather than midwives, deliveries in hospitals rather than at home, and adequate time for recuperation before returning to their normal responsibilities (Caton, 2014).

They also campaigned for obstetric anesthesia. Feminists and physicians alike believed that the pain of childbirth, in and of itself, contributed to the disability of women later in life. To improve the quality and availability of anesthesia, feminists founded two organizations. The National Twilight Sleep Association began in the US just before the beginning of World War I, and The National Birthday Trust Fund started in Great Britain in 1928. Both organizations influenced the practice of obstetric anesthesia. Physicians explored new ways to manage labor pain, including use of rectal ether and intravenous opioids. They also performed many important studies on the use of regional anesthesia (Caton, 2014).

A major development in obstetric anesthesia occurred around 1910 with the development of *Dämmerschlafl* or “twilight sleep.” It combined opioids and scopolamine to make women amnestic and provide some comfort during labor while they remained awake. However, it left the women disoriented and uncoordinated where they were no longer actively involved in the birth of their infant. Recovery was long after these medications, preventing mothers from caring for their infants. Hence, they were taken to the nursery and cared for by nurses. The infants would subsequently be fed formula. The period from 1860 through 1940 was referred to as the “dark ages of obstetric anesthesia and analgesia,” with minimal progress in obstetric analgesia and anesthesia (Bonica, 1995). The introduction of regional anesthesia would be the next major change in obstetric anesthesia.

In 1885, Leonard Corning, a New York neurologist inadvertently performed the first epidural analgesia by injecting cocaine in the lower back of a gentleman with the intention to cure him of his complaint of masturbation (Corning, 1885). Based on the description of the results and the manner of onset of analgesia, there is little doubt that this was an epidural. In addition, it was a “walking epidural”; the man experienced dizziness but his motor function was

intact, and he displayed no observable uncoordinated movements. He left an hour after his injection. After this account, Corning introduced the term “spinal anesthesia” (Brill, Gurman, & Fisher, 2003).

The first papers describing obstetric applications of spinal and lumbar epidural appeared between 1900 and 1930 (Caton, 2014). The origin of epidural analgesia began with Jean Enthuse Sicard, a neurologist who treated sciatica and tabes by injecting cocaine through the sacral hiatus. Known as caudal anesthesia, this method was used to provide surgical anesthesia. Fidel Pages-Mirave, a Spanish surgeon, first used the lumbar approach to the epidural space for surgical anesthesia in 1921. He introduced the idea of “segmental anesthesia,” where loss of sensation is limited to an area supplied by one or two spinal nerves. This was a huge contribution to the field because it eliminated the side effects of complete spinal anesthesia blocks. Sadly, Pages-Mirave died in a motor vehicle collision before he could publish his findings. In 1931, Achille Dogliotti independently identified the epidural space and described its anatomy and physiology in detail. Dogliotti developed the modern “loss of resistance” technique used to find the epidural space. He also published a report on the introduction of local anesthetics into the epidural space. The technique at this time involved a single bolus of local anesthetic, limiting the duration of anesthesia provided by epidural anesthesia (Dogliotti, 1931). This dilemma was solved in 1947, when Manuel Martinez Curbelo of Cuba used a Tuohy needle and a small ureteral catheter to provide “continuous lumbar epidural infusion for analgesia” (Curbelo, 1949).

Major change in obstetric anesthesia and analgesia came when John Bonica, who later became the first chairman of the Department of Anesthesiology at the University of Washington, took over his wife’s pain management during her labor in 1943. She had a close to fatal complication with open-drop ether, and his management of her anesthesia probably saved her

life. From the moment he intervened to save his wife's life, he devoted his career to pain management and advancing anesthesia care of the mother and fetus (Chadwick, 2005).

Caudal anesthesia was the primary means of providing labor pain relief when Bonica was chief of anesthesia. In 1943, Hingson and Edwards published a method for continuous caudal analgesia for labor in which a malleable needle remained in the sacral canal throughout labor and tetracaine (Pontocaine) was introduced (Hingson & Edwards, 1943). In 1970, small flexible catheters replaced the needles. Only when commercially produced catheters became readily available in the 1970s did labor epidural analgesia become more popular (H. S. Chadwick, 2005).

For obstetricians, regional anesthesia had many advantages. First, it appeared safe and easy to manage, which was important because qualified anesthesia providers were in short supply. Second, regional anesthesia allowed obstetricians to make more liberal use of operative techniques for vaginal delivery (e.g., episiotomy, use of forceps), which were just coming into vogue. No less important, regional anesthesia appeared to satisfy the desires of women who wanted more comfortable deliveries. These motives prompted the use of more regional blocks, including presacral, paravertebral, spinal lumbar epidural, and caudal epidural anesthesia.

In 1967, the first volume of Bonica's classic textbook *Principles and Practice of Obstetric Analgesia and Anesthesia* was published (Bonica, 1967). The book was a comprehensive discourse on almost everything known in obstetric anesthesia. It examined the anatomy and physiology of uterine function and childbirth pain, including the neurologic pathways involved in the perception of childbirth pain. It brought together studies of placental structures and function pointed to the transmission of drugs and the effects the drugs may have on the infant.

The studies of the anatomy and physiology of the uterus worked to identify the effects of inhalation and regional anesthesia on the labor process.

In 1978, Philip Bromage published the book *Epidural Analgesia*, which took the practice of epidural analgesia to the modern era and played an essential role in the acceptance and use of epidural analgesia in obstetrics and pain management (Bromage, 1978). Subsequent problems with the use of epidurals during labor stimulated detailed and accurate studies of the effects of anesthesia with modifications of techniques. The introduction of opioids to either the spinal or epidural space was a significant development in obstetric anesthesia, making labor and delivery even less painful. This stirred practitioners in the 1980s and 90s to reexamine the effects of drugs on the fetus, neonate, mother, and the labor process. As a result of these studies, a number of modifications were made to minimize adverse effects.

Systemic Analgesia

Systemic opioids are still the most widely used medication for labor analgesia worldwide (Pandya, 2010). Systemic analgesia is dependent upon an effective concentration of drug in maternal circulation and any drug that affects the maternal CNS crosses the blood-brain barrier and also the placenta. Drugs given systemically over time affect the mother as well as the fetus. Because of the effects the doses of these medications are limited and pain relief is insufficient to reduce any of the adverse effects of labor pain.

The most common parenteral opioids used for labor pain relief are morphine and pethidine (Demerol), administered IV or intramuscularly (IM). Respiratory depression of the neonate is a common and the most serious adverse effect of intrapartum opioid administration (B. A. Lieberman et al., 1979; Schnider & Moya, 1964; Wiener, Hogg, & Rosen, 1979). Studies have demonstrated systemic opioids decreased neonatal alertness (Belsey et al., 1981), lower neonatal

neurobehavior scores (Hodgkinson, Bhatt, & Wang, 1978), impairing mother-infant interaction (Moreau & Birch, 1974; Richards & Bernal, 1972; Scanlon et al., 1974; Standley, Soule, Copans, & Duchowny, 1974), inhibition of sucking (Kron, Stein, & Goddard, 1966; Nissen et al., 1995; Righard & Alade, 1990), and a delay in effective feeding (Crowell, Hill, & Humenick, 1994; Matthews, 1989). The neonatal behavior variables measured at delivery and found to be affected were reduced alertness, more likely to cry when handled, and decreased measures of consolability which is the ease with which the tester could quiet the infant (Belsey et al., 1981). CNS depression affects the infant's tone, with fewer and less well directed movements, less spontaneous motor activity when awake, impaired success in the infants ability to move the hand to mouth all impairing the infants ability to breastfeed (Belsey et al., 1981; Kraemer, Korner, & Thoman, 1972). Drug exposure reduced the infant's ability to quiet himself after arousal, with frequent state changes from sleep through wakefulness to crying (Belsey et al., 1981; Emde, Swedborg, & Suzuki, 1975).

The majority of studies on maternal systemic opioid and its effects on the fetus/neonate have focused on pethidine (meperidine) because it has been in frequent use worldwide for a long time. Detrimental effects could last up to 72 hours postpartum due to the accumulation of norpethidine (normeperidine) (Kuhnert, Kuhnert, Philipson, & Syracuse, 1985). Maximal fetal exposure of respiratory depression (Belfrage, Boreus, Hartvig, Irestedt, & Raabe, 1981; Hamza et al., 1992), and metabolic acidosis (Sosa et al., 2006) were seen when pethidine was given 3 to 5 hours before delivery; however, if administration was 1 hour before delivery, effects were barely noticeable. Infants whose mothers received pethidine during labor sucked at significantly lower pressures and rates and consumed less milk than those whose mothers received no medication (Kuhnert, Kuhnert, et al., 1985).

In summary, the adverse effects on the neonate of parenteral opioids given during labor are well documented, and there is no evidence to support their continued use.

Epidural Medications

The most common drugs used for epidural analgesia contain combinations of local anesthetics with an opioid and are set on a continuous infusion, often for many hours.

Bupivacaine is the mainstay local anesthetic used and is commonly combined with fentanyl. The dosage frequently used in this setting for continuous labor epidural infusions is 0.125% bupivacaine with 2-3 µg/mL fentanyl. At Yale New Haven Hospital, the standard protocol for otherwise healthy parturients who request epidural analgesia for vaginal delivery calls for a continuous infusion of 0.05% bupivacaine with 3 µg/mL hydromorphone instead of fentanyl.

Low-Dose Local Anesthetic Epidurals

In the early years of labor epidurals, bupivacaine doses of 0.2-0.25% were used to maintain labor pain relief by blocking both somatic and visceral pain. The high concentration of local anesthetics produced very dense pain relief but also caused many unwanted side effects, such as motor block, hypotension, extreme sensory deficit, and rarely toxicities to the fetus. The discovery of opioid receptors on the dorsal horn of the spinal cord changed epidural analgesia. Opioids administered in the epidural space bind directly on the opioid receptors on the spinal cord without the effects seen when administered intravascular. Intrathecal opiates could relieve the visceral pain of the first stage of labor but to relieve the somatic pain of the late first stage to second stage of labor a local anesthetic needed to be combined.

When combined, epidurally administered local anesthetics and lipid-soluble opioids work together to provide analgesia (Lyons, Columb, Hawthorne, & Dresner, 1997; Polley, Columb, Wagner, & Naughton, 1998; Vercauteren & Meert, 1997). During the past 10 years,

concentrations of local anesthetics have decreased to 0.0625 %- 0.125%, lowering the total amount of local anesthetic used and eliminating many of the side effects, such as motor blockade, associated with the higher doses of local anesthetics. In addition, the lower doses of opioid needed for analgesia reduce the side effects seen with systemic absorption of high doses of opioids. An important aspect of labor analgesia is latency. The supplement of a lipid-soluble opioid to long acting/long latency local anesthetics shortens latency (Justins, Francis, Houlton, & Reynolds, 1982). Hence, present day labor epidural analgesia usually combines a low-dose long acting local anesthetic with an opioid. Bupivacaine is the mainstay local anesthetic used and is commonly combined with fentanyl. Bupivacaine is highly protein bound, so placental transfer is low with a duration of analgesia of 2 hours.

Ropivacaine is a homologue of bupivacaine with a latency and duration similar to that of bupivacaine (J. A. Katz, Bridenbaugh, Knarr, Helton, & Denson, 1990) without the cardio toxicity bupivacaine. Studies on potency have suggested that ropivacaine is 40% less potent than bupivacaine (Polley, Columb, Naughton, Wagner, & van de Ven, 1999). However, clinical studies have shown no difference in terms of sensory blockade between low-concentration epidural infusions of ropivacaine and bupivacaine (Beilin et al., 2007; Lee, Ngan Kee, Ng, Lau, & Wong, 2004). When equal potent sensory doses were compared ropivacaine may be associated with less motor blockade than bupivacaine (Beilin et al., 2007; Lacassie, Habib, Lacassie, & Columb, 2007). This characteristic is probably not clinically significant when low doses of bupivacaine are used (Wong, 2009).

A 2013 meta-analysis (Sultan, Murphy, Halpern, & Carvalho, 2013) that included 15 articles involving 1,997 patients compared the effect of low-concentration epidural bupivacaine ($\leq 0.1\%$) or ropivacaine ($\leq 0.17\%$) versus high concentration of local anesthetics on obstetric and

anesthetic outcomes. Although 1-minute Apgar scores <7 favored the high concentration group, low concentrations of labor epidural solutions improved obstetric outcomes (decrease in frequency of assisted vaginal delivery, shorter duration of second stage of labor) and reduced maternal side effects (less motor blockade, better ambulation, and decreased urinary retention) without compromising analgesia. The authors recommended the use of low concentrations of local anesthetics for epidural analgesia to optimize obstetric outcome.

Properties of Epidural Opioid Analgesia

Lipid solubility of an opioid is one of the most important factors in determining its individual effects (Wagemans, Zuurmond, & de Lange, 1997). Lipid solubility determines how the drug is absorbed into local tissue, traverse the dura and gain access to the cerebral spinal fluid (CSF) or be absorbed systemically (Brose, Tanelian, Brodsky, Mark, & Cousins, 1991). Once the drug is administered in the epidural space, the pharmacology and pharmacodynamics of the drug allocate its unique profile of analgesia and side effects.

Pharmacokinetic studies have shown that highly lipophilic opioids such as fentanyl and sufentanil diffuse freely from the epidural space into the maternal blood and across the placenta (de Barros Duarte et al., 2009; Desprats et al., 1991). Because fentanyl is so frequently used in this setting, it has been well researched and its effects documented. The side effects of fentanyl, such as sedation, vomiting, pruritus, and, although rare, neonatal respiratory depression, are known (Carrie, O'Sullivan, & Seegobin, 1981; M. Kumar, Chandra, Ijaz, & Senthilselvan, 2014; M. Kumar & Paes, 2003; Noble, Morrison, Brockway, & McClure, 1991, 1994). Most studies have focused on neonatal outcomes in the delivery room, ignoring the possibility of late-occurring side effects that can arise up to several hours after exposure because of the longer terminal half-life of fentanyl in neonates. Because it is bound principally to albumin and

becomes unbound during the first day of life, increasing the free concentration of fentanyl, secondary peaks in plasma drug concentration can occur (R. Katz & Kelly, 1993; Koehntop, Rodman, Brundage, Hegland, & Buckley, 1986; Leighton & Halpern, 2002; E. Lieberman & O'Donoghue, 2002; McClain & Hug, 1980; Reynolds, 2011). A 2014 case-control study showed a positive association between exposure to traditional fentanyl-bupivacaine infusate in maternal epidural analgesia and respiratory distress in neonates at ≥ 34 weeks gestation within 24 hours of life who required supplemental oxygen ≥ 2 hours and/or positive pressure in the neonatal intensive care unit (M. Kumar et al., 2014).

Neonatal Drug Exposure After Epidural Analgesia During Labor

Placental Drug Transfer by Diffusion

Most drugs, including those used for analgesia and anesthesia cross the placenta by passive diffusion. Diffusion is dependent on a concentration gradient across the placenta with drugs passively moving from areas of high concentration to low. The placenta is a lipid membrane and lipophilic molecules diffuse readily across lipid membranes. Drugs with a molecular weight of <500 Da readily diffuse across the placenta. Most drugs used in anesthesia, including opioids and local anesthetics have molecular weights <500 Da.

Only the non-ionized portion of a partially ionized drug crosses the placenta (Griffiths & Campbell, 2014). The pH of maternal blood and the pKa of the drug determine the degree to which the drug is ionized. Most drugs used in anesthesia are poorly ionized in blood therefore un-ionized unbound drug readily crosses the placenta. If the pH of maternal blood changes, such as in labor, then changes in the degree of ionization of the drug and placental transfer can occur.

The transplacental distribution of lipophilic substances whose unbound and un-ionized particles readily cross the placenta is influenced by the transplacental gradient for protein

binding and pH. Fetal pH is lower than maternal pH, therefore free bases tend to stay on the fetal side due to ion trapping, and weak acids to the reverse (Reynolds, 2010). If the fetus becomes acidotic basic drugs such as local anesthetics and opioids can accumulate in the fetus called “ion trapping” (Griffiths & Campbell, 2014). Ion trapping occurs when the lower pH of the fetus produces an increased portion of ionized drug, which is then unable to cross the placenta increasing the exposure to the drugs.

Acidic drugs bound mainly to albumin do not diffuse across the placenta. Only the unbound portion of the drug is free to cross the placenta. For most basic drugs, the major binding protein is α_1 -acid glycoprotein, the concentration which is always higher in maternal than fetal plasma (Krauer, Dayer, & Anner, 1984). For drugs that are mainly bound to α_1 -acid glycoprotein, higher maternal than fetal binding reduces the equilibrium fetal/maternal ration (Reynolds, 2010).

Placental Transfer of Epidural Medications

Bupivacaine, the local anesthetic most frequently used in labor epidural analgesia has a high degree of protein binding in maternal and fetal circulation. It has been established there is excessive bupivacaine binding to maternal α_1 -acid glycoprotein (90%) compared to fetal protein binding (50%) and that the difference in protein binding affects placental transfer of bupivacaine (R. F. Johnson et al., 1995; Mather, Long, & Thomas, 1971). When both maternal and fetal plasma have normal physiologic serum protein levels, the maternal-to-fetal bupivacaine transfer ratio decreased and the fetal-to-maternal transfer increased (R. F. Johnson et al., 1995). This difference in transfer is due to the amount of free (un-ionized) drug available for placental transfer. It has been definitely established in these studies that drugs that are demonstrate more protein binding potentials express these elements in the maternal-fetal gradient. For example

placental bupivacaine transfer increased as the amount of protein in the receiving perfusate was increased (Hanshaaw-Thomas & Reynolds, 1985). Increased bupivacaine clearance across the placenta is also related to the maternal-fetal gradient of unionized bupivacaine. This is clinically significant under pathological conditions when maternal and fetal plasma levels of protein are not normal. For instance, in severe pre-eclampsia maternal protein binding is reduced leading to greater transfer of bupivacaine across the placenta to the fetus.

Using pregnant rabbit (Gaylard, Carson, & Reynolds, 1990) and ewe (Biehl, Shnider, Levinson, & Callender, 1978; Pickering, Biehl, & Meatherall, 1981) models, researchers found increased bupivacaine concentration in the umbilical vein related to lower pH of fetal circulation. It has been proposed decreased fetal pH results in ion trapping leading to the higher fetal bupivacaine concentration. It has further been determined that the increases in fetal bupivacaine concentration may also be due to the decreased ability of the fetus to clear the drug and changes in tissue distribution (Finster, Ralston, & Pedersen, 1993). Regardless this information is extremely important to the safety of the fetus. Researchers have established increased sensitivity of the fetus during times of hypoxia and fetal acidosis to the harmful effects of bupivacaine (R. F. Johnson et al., 1995; Morishima & Covino, 1981; Morishima et al., 1989). During fetal acidosis, bupivacaine transfer may be increased by a large factor.

The transfer of lipophilic drugs by diffusion across the placenta and equilibrium takes longer in fetal than maternal tissue because the fetal compartment is deep. Fetal exposure is dependent on blood flow on both sides of the placenta (flow-dependent transfer), duration of exposure and equilibrium ratios (Reynolds, 2010). The immediate effect of the drug is related to the concentration of free unbound drug however a large albumin-bound portion is a storehouse for the neonate (Reynolds, 2010). During the first days after delivery, albumin binding declines,

increasing free concentrations of drugs such as fentanyl and diazepam (Nau, Luck, Kuhnz, & Wegener, 1983).

Bader et al. (1995) evaluated umbilical vein and maternal vein concentrations of fentanyl and bupivacaine after continuous epidural infusion during labor (Bader et al., 1995). In their study, 21 parturients received 0.125% bupivacaine and 2 µg/mL fentanyl at a constant rate of 10 mL/h (12.5 mg/h bupivacaine and 20 µg/h fentanyl). Maternal vein (MV) and umbilical vein (UV) concentrations were measured at birth. Length of infusion ranged from 1 to 15 hours. The mean value of bupivacaine in MV was 0.50 ± 0.16 and UV 0.15 ± 0.06 with an UV/MV ratio 0.03. Bader et al. (1995) did not find a statistically significant relationship between duration of infusion and accumulation of either drug but did suggest rapid placental transfer and equilibration of fentanyl between maternal and neonatal blood and a maternal-neonatal gradient for bupivacaine concentration, attributed to placental deposition and protein binding (Bader et al., 1995).

Data from the study by Bader et al (1995) are consistent with those of Abboud and colleagues (Abboud et al., 1984), who observed patients receiving 0.125% bupivacaine at a rate of 14 mL/h. Their data showed a MV bupivacaine concentration of 0.54 ± 0.10 and a UV concentration of 0.18 ± 0.04 , with a UV/MV ratio of 0.33. The low UV/MV ratio is reflective of bupivacaine high protein binding and lipid solubility. *In vitro* studies examining isolated human placental cotyledons support these theories, showing a fetomaternal concentration gradient mean of 0.58 (Ala-Kokko, Plenimaki, Hollmen, & et al., 1993). Although bupivacaine rapidly crossed from the MV to the fetal reservoir, the fetomaternal concentration was low, suggesting placental deposition of this extremely lipid-soluble drug. These two studies showed no correlation with cord blood level of bupivacaine and duration of infusion. Radzysinski did

find a significant correlation between bupivacaine concentration in cord blood and length of infusion time (Radzyminski, 2005). The dose of bupivacaine in that study was 0.044% at a continuous infusion of 14 mL/h. The longer the epidural infusion ran, the greater the concentration of bupivacaine in cord blood at delivery. However, the levels of bupivacaine were low when compared to the amount of drug infused, and she found no difference in breastfeeding or neurobehavior between the epidural group and the nonmedicated group.

Fentanyl is also detectable in the cord blood after birth. Bader and colleagues reported MV concentration of 0.17 ± 0.10 ng/mL, UV concentration 0.16 ± 0.09 ng/mL, and a UV/MV ratio of 0.94 (Bader et al., 1995). The UV/MV ratio was quite high, suggesting placental transfer was rapid, and UV concentration quickly reached equivalence with MV concentration. Fentanyl is highly lipid soluble and it would be expected to cross the placenta rapidly. Animal studies support this theory. An early animal study examined maternal and fetal fentanyl concentrations 1-60 minutes after a bolus of medication was given (Craft et al., 1983). There was a rapid decline in maternal concentration, demonstrating rapid redistribution and uptake in maternal tissue, with the fetal concentration profile running parallel to maternal decline. The UV/MV ratio in both studies remained equal over time not changing with longer infusion times. In addition, an *in vitro* human placental study that examined uptake and distribution of fentanyl reported equal M→F, F→M clearance of fentanyl (Zakowski, Schlesinger, Dumbroff, & et al., 1993). They found that the transfer of fentanyl reached a plateau within 40-80 minutes of continuous infusion, alluding to passive transfer of fentanyl across the placenta. They also found a high amount of fentanyl in placental tissue, suggesting the placenta serves as a storehouse for fentanyl. To date there have been no studies that have examined whether there is an interaction between bupivacaine and fentanyl facilitating or inhibiting transfer of either drug. The results of these three studies show

MV and UV fentanyl concentrations are low and fentanyl levels did not correlate with infusion time.

Fetal Tissue Uptake

UV samples do not mirror fetal tissue uptake. In animal studies fentanyl showed a large distribution to all tissue and a clearance rate dependent on dose (Murphy, Hug, & McClain, 1983). Clearance rate for the neonate is slow due to immature liver enzymes, and may at first distribute to the brain or heart (Gauntlett et al., 1988). Maternal half-life of fentanyl is approximately 8 hours (Moises et al., 2005); however, fetal half-life is difficult to measure quantitatively after exposure to maternal epidural analgesia because of the fetal tissue uptake (Desprats et al., 1991; Paech, Westmore, & Speirs, 1990). Therefore, because of the unknown amount of fentanyl accumulation in fetal tissue of this highly lipophilic drug, UV measurements of fentanyl may not be accurate (Capogna & Camorcia, 2004).

The importance of fetal tissue accumulation of bupivacaine is unknown. Tissue uptake by the nonvital organs of the fetus may impede increased bupivacaine levels in fetal heart and brain. It has been suggested that the fetus metabolizes and excrete bupivacaine like an adult (Mango, Berlin, Karlsson, & et al., 1976). Small amounts of bupivacaine metabolites have been found in neonatal urine 36 hours after delivery (Kuhnert, Zuspan, Kuhnert, Syracuse, & Brown, 1987). In the absence of observable neurobehavioral deficits, it would convey that there is not enough bupivacaine accumulation to impair CNS function in the neonate.

Epinephrine

Epinephrine is frequently added to the local anesthetic to slow the vascular uptake of the local anesthetic and opioids from the spinal space. The addition of epinephrine to bupivacaine has been shown to reduce plasma levels of bupivacaine by approximately 17% in the fetus and

30% in maternal circulation (Abboud et al., 1989). Some studies suggest the effects of epinephrine on fetal drug levels were smaller than the effect on maternal plasma levels; therefore, the fetal/maternal concentration gradients were higher for bupivacaine plus epinephrine than for bupivacaine alone (Beazley, Taylor, & Reynolds, 1972; Belfrage, Berlin, Raabe, & Thalme, 1975; Belfrage, Raabe, Thalme, & Berlin, 1975; Reynolds & Taylor, 1971). Other studies did not confirm the increased fetal/maternal ratios following co-administration of epinephrine. Hence, most authors regard the addition of epinephrine to the local anesthetic as unnecessary, especially since the duration of anesthesia was not prolonged (Jouppila et al., 1978; Nesheim, 1983), and epinephrine can alter uterine blood flow leading to uteroplacental insufficiency and prolong labor (Nesheim, 1983).

Epidural Hydromorphone

Hydromorphone is a mu receptor agonist with pharmacokinetic properties intermediate between highly hydrophilic morphine and highly lipophilic opioids such as fentanyl and sufentanil (Reisine & Pasternak, 1996). After epidural administration, the amount of drug that penetrates dura and pia-arachnoid to enter the CSF and spinal compartments is inversely proportional to its lipid solubility and polarity (Chrubasik, Chrubasik, & Martin, 1993; Herz & Teschemacher, 1971; Plummer, Cmielewski, Reynolds, Gourlay, & Cherry, 1990; Sinatra et al., 2000; Yaksh, Al-Rodhan, & Jensen, 1988). For example, high lipid solubility increases systemic absorption and reduces availability of the drug in the dorsal horn of the spinal cord thereby continually needing more drug to extend their limited duration of action (Bernards et al., 2003; Sinatra et al., 2000). Hydrophilic opioids have more difficulty traversing neural and vascular membranes, staying in the spinal compartment, increasing the availability of drug on the dorsal horn of the spinal cord, and ensuring lower concentration of drug needed for continued receptor

site activity (Sinatra et al., 2000). Placental transfer of hydrophilic opioids is impeded and they therefore diffuse across slowly and are unlikely to attain effective concentration in the fetus (Reynolds, 2011; Syme, Paxton, & Keelan, 2004).

This gain in opioid-mediated analgesic effect provides a local anesthetic dose-sparing effect, allowing the use of bupivacaine as an adjunct rather than primary analgesic where infusions are 2-2.5 times as dilute as those traditionally seen in continuous labor epidural infusions (Sinatra et al., 2000).

Quality of pain relief for continuous epidural infusion containing 0.05% bupivacaine plus 3 µg/mL hydromorphone was evaluated in 1830 parturients requesting analgesia during labor and delivery (Sinatra et al., 2002). The infusion provided rapid and effective analgesia and minimal adverse events for patients whom differed in parity and at varying stages of labor. Pain relief was maintained in most patients without need for epidural reinforcement (Sinatra et al., 2002). Clinically significant adverse events including excessive maternal sedation, profound hypotension, respiratory depression, clinically significant motor blockade, and severe fetal bradycardia were not observed (Sinatra et al., 2002). The fact that patients report highly effective pain control with epidural doses comparable to fentanyl is significant, considering that intravenous doses of fentanyl are 10-12 times more potent than hydromorphone.

The author of this dissertation and colleagues conducted a prospective observational study in 2012 at Yale New Haven Hospital to determine neonatal and maternal exposure to hydromorphone and bupivacaine in the epidural solution (Shah, French, Dai, & Snegovskikh, unpublished data, 2012). Ten healthy parturients with uncomplicated pregnancies received an initial bolus of 100 µg hydromorphone and 9 mL 0.25% bupivacaine, followed by continuous infusion of 0.05% bupivacaine and 3 µg/mL hydromorphone at 14 mL/h (0.7 mg/h bupivacaine

and 42 µg/h hydromorphone), which is the standard protocol at Yale New Haven Hospital. If necessary, additional boluses of 0.25% bupivacaine were given to maintain analgesia. As mentioned above, Sinatra and colleagues (Sinatra et al., 2002) had previously found that this protocol achieved a level of analgesic efficacy comparable to that with 0.125% bupivacaine 2 µg/mL fentanyl, despite earlier findings that the IV potency of hydromorphone is only 1/10 to 1/12 that of fentanyl (Reisine & Pasternak, 1996). Umbilical vein and maternal vein blood samples were obtained within 15 minutes of delivery to determine hydromorphone and bupivacaine concentrations. The umbilical/maternal vein ratio was calculated for each sample.

Table 1 compares the results of our study with those of Bader et al. (1995) and with those of another study by Abboud et al., who observed patients receiving 0.125% bupivacaine at a rate of 14 mL/h (Abboud et al., 1984).

Table 1. Drug Concentration Data in Maternal Vein (MV) and Umbilical Vein (UV)

	MV concentration	UV concentration	UV/MV ratio
Shah et al (unpublished data)			
Bupivacaine, µg/mL	0.23±0.18	0 (0-0) ^a	0 (0-0.06)
Hydromorphone, ng/mL	0.26±0.09	0.23±0.09	0.88±0.11
Bader et al. (1995)			
Bupivacaine, µg/mL	0.50±0.16	0.15±0.06	0.30
Fentanyl, ng/mL	0.17±0.10	0.16±0.09	0.94
Abboud et al. (1984)			
Bupivacaine, µg/mL	0.54±0.10	0.18±0.04	0.33

MV = maternal vein; UV = umbilical vein.

Data are expressed as mean ± SD unless otherwise noted.

^aMedian (interquartile range). The UV concentration was 0 µg/ml in 8 of 10 neonates, 0.10 in one, and 0.16 µg/ml in one.

Consistent with the results of the Bader et al. study, we found that maternal and umbilical vein concentrations were independent of duration of epidural infusion/total amount of infusate. Maternal venous concentrations of hydromorphone and bupivacaine were highly correlated, consistent with maternal vascular absorption of the infusate from the epidural space. The overall concentration of bupivacaine needed to achieve efficacy was much lower when bupivacaine was combined with hydromorphone rather than fentanyl, resulting in lower maternal vein concentrations of bupivacaine in our study than in the other two studies. Furthermore, whereas all 21 UV samples in the Bader et al. study had detectable levels of bupivacaine in the umbilical vein, only two umbilical vein samples had detectable levels of bupivacaine in our study, and these were from patients who had required more than one additional bolus.

The infusion concentration and total amounts of hydromorphone infused in our patients were higher than those of fentanyl in the Bader et al (1995) study: 3 µg/mL hydromorphone (42 µg/h) versus 2 µg/mL fentanyl (20 µg/h). However, the overall concentration of hydromorphone in the umbilical vein was comparable to that of fentanyl, possibly because of the greater hydrophilicity of hydromorphone compared with fentanyl. This is significant because other studies have found incidences of neonatal respiratory depression with the fentanyl umbilical vein concentrations that were found in the Bader et al. study (Carrie et al., 1981; M. Kumar et al., 2014; M. Kumar & Paes, 2003; Nikkola, Ekblad, Kero, Alihanka, & Salonen, 1997; Noble et al., 1994). Thus, although the potency of hydromorphone is only 1/10 to 1/12 that of fentanyl, the fetus is exposed to a lower opioid dose while achieving comparable pain relief. The use of hydromorphone in the epidural solution may therefore be more favorable with respect to limiting neonatal exposure to foreign substances.

Effects of Epidural Analgesia on Mother and Neonate

The effects of epidural analgesia on the fetus may be *direct* by placental transfer and fetal uptake with CNS depression or *indirect* as a result of a change in maternal homeostasis that results in a change to the fetal intrauterine environment or both (Bonica & McDonald, 1990). The direct effects are potentially more important for drugs that act systemically, where it is dependent on the presence of the drug in maternal circulation to exert its effects and placental transfer more relevant. Epidurally administered drugs do not require presence in maternal blood to work effectively. Therefore, indirect effects of epidural analgesia may be more prominent than direct placental transfer.

Positive Effects

Epidural analgesia preserves the beneficial stress response of the fetus to labor and reverses the negative maternal physiological and biochemical changes of labor. Analgesia reduces stress hormones such as epinephrine, cortisol, ACTH, peptide hormones and angiotensin II (Shnider et al., 1983) (Cascio, Pygon, Bernett, & Ramanathan, 1997; Eberle, Kinsella, & Arrison, 1995; Westgren et al., 1986), reduces hyperventilation (Thalme et al., 1974), maintains uterine dilation due to sympathetic blockade (Hollmen, Jouppila, Jouppila, Koivula, & Vierola, 1982), reduces episodes of hemoglobin oxygen desaturation (Arfeen, Armstrong, & Whitfield, 1994; Deckardt, Fembacher, Schneider, & Graeff, 1987; R. P. Griffin & Reynolds, 1995), and provides better quality pain relief and higher maternal satisfaction than systemic opioids or nitrous oxide (L. Jones et al., 2012).

Neonatal Acid-Base Status

Three studies published in the 1970s examined intrapartum acid-base changes with or without epidural analgesia (Pearson & Davies, 1973a, 1973b, 1974a, 1974b; Thalme et al., 1974;

Zador & Nilsson, 1974), one of which was randomized (Thalme et al., 1974). The studies demonstrated that labor epidural analgesia reduced maternal hypocarbia and maternal and fetal metabolic acidosis and lactate (Zador & Nilsson, 1974), while notably reducing the drop in fetal pH that normally occurs during stage 2 of labor (Reynolds, 2011).

These findings were confirmed by the end 1990's, when the epidural cesarean and backache controversies prompted a number of randomized studies comparing epidural analgesia with systemic opioids, allowing for a meta-analysis of acid-base status in over 2000 babies in 12 studies (Reynolds, Sharma, & Seed, 2002). This confirmed that umbilical artery pH and base excess were significantly better in babies born to mothers who received epidural analgesia for labor. A Canadian study comparing Apgar scores and need for neonatal resuscitation between PCEA (Patient-Controlled Epidural Analgesia) containing bupivacaine and fentanyl with PCIA (Patient-Controlled Intravenous Analgesia) showed an improvement in neonatal pH and base excess in the epidural group (Halpern et al., 2004). To show that the differences between the groups were not simply due to adverse effects of systemic opioids, Schocket and colleagues conducted a case-controlled study comparing umbilical artery acid-base status in 110 matched pairs of women who had either received epidural analgesia or no analgesia (Schocket, Garrison, Wiley, & Sharma, 2005). There were no differences in umbilical artery pH, but both pCO₂ and base excess were significantly higher in the epidural group suggesting epidural analgesia had a beneficial effect on metabolic acidosis rather than an adverse effect of systemic opioids.

Maternal Stress Reduction

It has been hypothesized the stress of labor can have long-term behavioral effects on the neonate (Taylor, Fisk, & Glover, 2000). Studies in animal models also found an association between peripartum stress and long-term behavioral outcomes (W. C. Griffin, 3rd, Skinner,

Salm, & Birkle, 2003; Hayashi et al., 1998; Kapoor & Matthews, 2005; Schneider, Roughton, Koehler, & Lubach, 1999). Prolonged antepartum maternal stress has been linked to adverse neurobehavioral outcomes in children (Van den Bergh, Mulder, Mennes, & Glover, 2005; Weinstock, 2005). It is uncertain whether a single stress episode such as one that occurs during labor and delivery can lead to long-term neurobehavioral consequences. It is unknown at this time if peripartum stress has a role in the development of learning disabilities. Epidural analgesia administered for labor decreases markers of both maternal and fetal stress such as cortisol (Abboud, Sarkis, Hung, et al., 1983; N. M. Miller, Fisk, Modi, & Glover, 2005; Taddio, Katz, Ilersich, & Koren, 1997). If fetal stress has a role in decreased neurobehavioral outcomes, it could be that neuraxial analgesia might also affect long-term outcomes after vaginal delivery.

Negative Effects of Maternal Labor Analgesia on Neonatal Neurobehavior

Neurobehavior tests have been used in various studies of the effects of maternal analgesia on the neonate. These studies introduced the clinical importance of neonatal neurobehavior on breastfeeding initiation. However, failure to provide information and inconsistencies in medication regimens, definition of variables, sample sizes, and research methods make it difficult to draw conclusions.

Morikawa and colleagues reported a significant relationship between bupivacaine dose and neonatal neurobehavior as assessed with the NACS (Morikawa et al., 1990). Abboud and colleagues found no relationship between epidural bupivacaine and NACS scores (Abboud et al., 1984). In a study by Radzysinski and colleagues, infants born to mothers who received epidural analgesia with low-dose bupivacaine and fentanyl showed no differences in NACS scores compared to infants of mothers who received no pain medication for labor (Radzysinski, 2003).

In a second study, the same author found a relationship between bupivacaine passive tone, active tone, and total score on the NACS at 1 hour but not at 24 hours (Radzyminski, 2005).

Abboud and colleagues used the ENNS to compare neurobehaviors differences in 170 infants; 50 mothers received 2% epidural 2-chloroprocaine, 50 with 0.5% epidural bupivacaine, 50 with 1.5% lidocaine and 20 in an unmedicated control group (Abboud, Khoo, Miller, Doan, & Henriksen, 1982). Patients were randomly assigned to local anesthetic groups. Analysis of variance showed no differences in ENNS scores among the groups. In another study, Abboud and colleagues found no adverse effects of lidocaine on the early neurobehavioral status of the neonate as assessed with the ENNS (Abboud, Sarkis, Blikian, et al., 1983).

In one study using the NBAS exam, neonatal behavior in a group of infants whose mothers received pethidine during labor was assessed at delivery and during the first six weeks of life by means of the NBAS. Higher cord blood levels of pethidine were associated with depressed attention and social responsiveness, but the changes observed were relatively subtle, and comparison of these infants with a control groups whose mothers had received no drugs revealed no between-group differences in behavior (Belsey et al., 1981). In another study, the same authors found that visual skills and alertness decreased significantly with increases in the cord blood concentration of bupivacaine, particularly on the first day of life but also throughout the next six weeks. Adverse effects of bupivacaine levels on the infants' motor organization, ability to control their own state of consciousness, and physiological response to stress were also observed (Rosenblatt et al., 1981).

Three studies using the NBAS exam found a marked difference between the groups (B. A. Lieberman et al., 1979; A.D. Murray et al., 1981; Sepkoski et al., 1992). Lieberman and colleagues described the fewest differences between the groups, finding that the epidural-

exposed infants responded less to human voice in the delivery room (B. A. Lieberman et al., 1979). Murray and colleagues compared 15 control infants whose mothers received no analgesia for pain relief, 20 infants exposed to bupivacaine 0.25%, and 20 infants exposed to bupivacaine and oxytocin (A.D. Murray et al., 1981). The infants in the epidural groups had lower NBAS scores at 1 and 5 days and identified marked differences in motor control, response to stress and state control. The largest differences were in state control; only 13% of nonmedicated infants had poor state control compared with 50% of the epidural-exposed infants. The difference remained despite controlling for forceps delivery and there was no dose-response effect seen. Even on day 5 the state control scale remained significantly different. There were no differences in NBAS scores between the groups after 1 month. However, at 1 month, mothers who had had epidural analgesia viewed their infants less favorably and in general found them more difficult to care for compared with unmedicated mothers (E. Lieberman & O'Donoghue, 2002). Sepkoski and colleagues compared 38 epidural-exposed (bupivacaine 0.5%) infants to 20 nonmedicated infants using the NBAS at 3 hours, and on day 3, 7, and 28 (Sepkoski et al., 1992). The infants were matched for potentially confounding factors such as maternal ponderal index, parity, the number of maternal and fetal non-optimal conditions and induction of labor. The epidural group received significantly more oxytocin, had longer labors and more forceps deliveries. The infants that were exposed to epidural were less alert, had difficulty orienting, and exhibited poor motor function in the first month of life. Multivariate analysis examining the dose of bupivacaine demonstrated a dose response for both orientation and motor effects similar to those reported by Murray et al. (1981).

The early bupivacaine studies were performed when high concentrations of local anesthetic solutions were common. Although the higher concentration of local anesthetic provided dense

pain relief, it created many of the unwanted side effects such as motor blockade, hypotension, excessive sensory loss, and toxicities (Hess, Pratt, & Oriol, 2006). With the addition of opioids to the epidural infusions, the local anesthetic concentration can be decreased, still providing effective analgesia with fewer side effects (Breen, Shapiro, Glass, Foster-Payne, & Oriol, 1993; S. E. Cohen, Tan, Albright, & Halpern, 1987; Cousins & Mather, 1984).

It is difficult to determine why there is so much variability in study conclusions. Early differences in infant behavior might be attributed to a direct effect of the medication on the infant (A.D. Murray et al., 1981; Sepkoski et al., 1992). This explanation can be supported by the dose-response effect, which only one study was able to establish (Sepkoski et al., 1992). However, differences up to 1 month later cannot be attributed to a direct effect of the drugs. Brazelton hypothesized that early interactions with a baby who is less alert, less able to orient, and less able to show organized movement may interfere with the development of the mother-infant relationship (Brazelton, 1973; A.D. Murray et al., 1981; Sepkoski et al., 1992). There may be individual characteristics of the mother that determine both how she will interact with her infant and what she will choose for pain relief when in labor.

Indirect Negative Effects of Labor Epidural Analgesia

Effects of Physical Changes in the Mother

If the mother develops respiratory depression with hypoxemia from systemic absorption of epidurally administered opioids, fetal hypoxemia and hypoxia will follow (Ferouz, Norris, & Leighton, 1997). Hypotension in the mother caused by epidural medications may reduce uteroplacental perfusion and oxygenation of the fetus (Wong, 2009). Fetal bradycardia can occur without maternal hypotension 15-45 minutes after epidural initiation. There is an acute drop in maternal plasma epinephrine associated with the onset of analgesia (Shnider et al., 1983).

Epinephrine is a tocolytic and it has been postulated that the acute drop in epinephrine results in a short term imbalance of uterine tocolytic/tocodynamic forces that result in uterine hypertonus, decreased uterine perfusion and subsequently fetal bradycardia (Clark, Smiley, & Finster, 1994; Wong, 2009). Although the bradycardia usually resolves by fluid bolus, ephedrine, and/or suspension of oxytocin infusion, it still has potential to disrupt the labor process.

Effects of Epidural-Related Maternal Fever on Neonatal Outcomes

Intrapartum maternal fever complicates one-third of all deliveries and is defined as a maternal temperature increase of 37.5-38°C. Women develop fever during labor for various reasons, with the most common causes related to infection such as chorioamnionitis. However, epidural analgesia has been consistently associated maternal fever or temperature increase in a number of prospective and observational studies in the absence of infection (W. R. Camann, Hortvet, Hughes, Bader, & Datta, 1991; Fusi, Steer, Maresh, & Beard, 1989; E. Lieberman et al., 1997; Macaulay, Bond, & Steer, 1992; Philip et al., 1999; Ramin et al., 1995; Yancey, Zhang, Schwarz, Dietrich, & Klebanoff, 2001). The exact cause of epidural-related fever is unknown, but it thought to be associated with an inflammatory state or altered thermoregulation and not due to an infectious process (de Orange, Passini, Amorim, Almeida, & Barros, 2011; Fusi et al., 1989; Goetzl, Evans, Rivers, Suresh, & Lieberman, 2002; Negishi et al., 2001; Yancey et al., 2001).

Even when the fever is not related to infection, it can still have significant consequences to the neonate which may ultimately affect the success of breastfeeding. As maternal temperature increases, the transfer of heat can cause fetal hyperthermia. Primate studies conducted in the 1970s assessed the effects of maternal fever without infection by artificially warming pregnant baboons to 42°C to evaluate fetal outcomes (Morishima, Glaser, Niemann, & James, 1975). The

extreme increase in temperature was associated directly with fetal hypoxia, hypotension, and metabolic acidosis. However, because this level of elevation in temperature is rarely seen in clinical practice, the relevance to practice remains uncertain.

Although no data are available on the specific effects of increased maternal temperature on breastfeeding, the many studies showing a negative effect of maternal fever on neonatal outcomes make it logical to assume a negative effect on breastfeeding. Therefore, early identification of maternal fever is imperative to prevent neonatal consequences. Furthermore, maternal fever is related to other factors, such as separation of mother and infant, which may compound the effect. For example, in one study (E. Lieberman et al., 1997), although no difference in the actual rate of sepsis was observed, neonates born to mothers with epidural-related fever were more frequently evaluated for sepsis (34%) than neonates of mothers who did not receive epidural analgesia (10%) and who had a much lower rate of fever. Another study of 1100 women showed that evaluations for sepsis were more frequent when the mother had epidural analgesia even when the mother was afebrile (Goetzl et al., 2001). The immediate postpartum period is a crucial time to initiate breastfeeding, and each minute of skin-to-skin contact during the first 3 hours after delivery increases the likelihood of exclusive breastfeeding (Bramson et al., 2010). Because the neonate is often separated from the mother for an extended period of time during such evaluations, this separation may increase the negative effect on initiation of breastfeeding.

Epidural Analgesia and Oxytocin Regulation in Relation to Breastfeeding

Oxytocin Mechanism During Labor and After Birth.

Endogenous oxytocin during labor and birth is necessary for the development of maternal behavior that facilitates the process of breastfeeding. Large amounts of oxytocin are released

during labor and delivery, leading to more forceful contractions, which are necessary for delivery of the neonate, detachment of the placenta, and keeping the uterus contracted to prevent postpartum hemorrhage. Additionally, as noted in the section on skin-to-skin contact above, maternal oxytocin is released by skin-skin contact as the infant exhibits the instinctual behavior by rooting, finding the breast, and sucking at approximately 1 hour of age (Nissen et al., 1998), and this results in milk ejection and the release of prolactin, which is linked to milk production (Dawood et al., 1981).

Oxytocin and prolactin are also pivotal to breastfeeding and are associated with behavioral and physiological adaptations in breastfeeding women (Jonas et al., 2009; Jonas, Nissen, Ransjo-Arvidson, Matthiesen, & Uvnas-Moberg, 2008; Nissen et al., 1998; Uvnas-Moberg, Widstrom, & Nissen, 1990). Animal studies show that oxytocin levels immediately after birth may be integral to the development of maternal behavior and the interaction between the mother and infant (Jonas et al., 2008; Keverne & Kendrick, 1994). Oxytocin promoted maternal behavior and mother/newborn interaction in animal experiments (Keverne & Kendrick, 1994; Pedersen, Ascher, Monroe, & Prange, 1982; Williams, Gazal, Leshin, Stanko, & Anderson, 2001) and promoted maternal behavior adaptations in human experiments (A. G. Frantz, 1978; Jonas et al., 2009; A. Levine, Zagoory-Sharon, Feldman, & Weller, 2007; Pedersen et al., 1982; Poulain & Wakerley, 1982; Richard, Moos, & Freund-Mercier, 1991; Theodosis, Poulain, & Vincent, 1981). Thus, it can be concluded that the mother's endogenous oxytocin facilitates the mother/infant interaction and breastfeeding.

Effects of Synthetic Oxytocin on Breastfeeding.

The physiology of labor and onset of lactation is clearly understood, but little research has been conducted on the effects of synthetic oxytocin on breastfeeding or newborn neurobehavior,

although induction and augmentation of labor with synthetic oxytocin is used in the majority of births in the United States and is the most frequent medical intervention in childbirth (R. K. Freeman & Nageotte, 2007). Another study found a previously unsuspected association between reduction in breastfeeding rates and oxytocin administered either alone or combined with ergometrine (Jordan et al., 2009). Synthetic oxytocin used during labor was found to disturb onset and duration of breastfeeding in women who received higher doses of oxytocin experiencing difficulties with neonatal reflexes necessary for breastfeeding (Garcia-Forte et al., 2014; Olza Fernández et al., 2012). Oxytocin infusions cause serum levels of oxytocin to be much higher than seen naturally. This may interfere with the mother's endogenous oxytocin release and/or sensitivity of oxytocin receptors, which could interfere with maternal/infant bonding postpartum (Garcia-Forte et al., 2014; Jordan et al., 2009).

Newborn neurobehavior feeding cues in 47 healthy term infants exposed to synthetic oxytocin demonstrated a low level of feeding organization, significant for brief and sustained hand-to-mouth cues compared to an unexposed group (Bell, White-Traut, & Medoff-Cooper, 2010). In another study, the administration of oxytocin was associated with delayed initiation of breastfeeding and increased use of formula during the hospital stay (Wiklund et al., 2009).

Synthetic oxytocin crosses the placenta and reaches the fetus (Melek, Blann, & Mattison, 1996; M. R. Odent, 2013). Approximately 80% of the blood traveling from the umbilical vein to the fetus bypasses the liver, going directly to the vena cava through the patent ductus venosus and quickly to the brain. The fetal blood-brain barrier is very immature and permeable. The developing brain is exposed to a large amount of oxytocin during labor infusions. Oxytocin receptor desensitization induced by oxytocin is well documented (M. Odent, 2010; Phaneuf, Rodriguez Linares, TambyRaja, MacKenzie, & Lopez Bernal, 2000; C. Robinson, Schumann,

Zhang, & Young, 2003). It seems plausible that interfering with the oxytocin system in the developing brain of the fetus at this critical phase may alter neonatal behavior and contribute to difficulties with breastfeeding (M. R. Odent, 2013). Furthermore, oxytocin administration causes uterine contractions that are much stronger and more painful than natural contractions. Oxytocin can cause hyperstimulation of the uterus, producing fetal distress and hypoxia (Simpson & James, 2008; Wei, Luo, Xu, & Fraser, 2009).

Epidural Analgesia and Oxytocin Regulation.

There is no evidence that oxytocin administration increases epidural use (Bugg, Siddiqui, & Thornton, 2011; S. Wei et al., 2009), although in one study, women in whom labor was augmented or induced with oxytocin requested an epidural earlier than women who went into spontaneous labor (A. R. Moore, Shan, & Hatzakorjian, 2013). When oxytocin infusions and amniotomy were implemented together, the rate of epidural use did increase, and this occurred earlier in labor (S. Wei et al., 2009). This finding is significant because epidural analgesia combined with oxytocin for labor has been associated with negative birth outcomes (Roberts, Algert, Douglas, Tracy, & Peat, 2002; Tracy, Sullivan, Wang, Black, & Tracy, 2007).

Women who receive epidural analgesia for labor pain have higher rates of oxytocin augmentation than those who do not receive epidural analgesia (Anim-Somuah et al., 2011; Chang & Heaman, 2005; Wiklund et al., 2009). Circulating maternal plasma levels of endogenous oxytocin decrease with the use of epidural analgesia during labor (Goodfellow, Hull, Swaab, Dogterom, & Buijs, 1983; Rahm, Hallgren, Hogberg, Hurtig, & Odlind, 2002). Research with sheep and heifers showed that epidural analgesia inhibited maternal oxytocin immediately postpartum in the blood and the brain, leading to hindered acceptance and recognition by the mother (Krehbiel, Poindron, Levy, & Prud'Homme, 1987; Williams et al., 2001). Epidural

analgesia impedes the binding of oxytocin to receptors located on the uterus, which leads to desensitization of the uterine oxytocin receptors, reducing uterine contractility (Phaneuf et al., 2000; C. Robinson et al., 2003). Subsequently, augmentation with synthetic oxytocin (Pitocin, Syntocinon) is required in increasing amounts to maintain labor in women who have received epidural analgesia (Anim-Somuah et al., 2011; Chang & Heaman, 2005; E. Lieberman & O'Donoghue, 2002; Wiklund et al., 2009). As the concentration of the exogenous oxytocin infusions continue to rise, it interferes with the mother's endogenous oxytocin release and uptake via a negative feedback mechanism (Goodfellow et al., 1983; Rahm et al., 2002). Women who had both an epidural and an oxytocin infusion for labor had significantly lower mean endogenous serum oxytocin levels in response to sucking on the second day postpartum in a dose-dependent fashion (Jonas et al., 2009). The shortened breastfeeding duration shown in women who received epidural analgesia (Beilin et al., 2005; J. J. Henderson et al., 2003; Torvaldsen, Roberts, Simpson, Thompson, & Ellwood, 2006) may be a result of decreased maternal milk production due to low levels of maternal oxytocin at birth, which may interfere with the pattern of oxytocin secretion for milk production and impact maternal-infant bonding at birth (Jordan et al., 2009).

Although more than 70% of women in the United States use epidural analgesia during labor (Cambic & Wong, 2010), and almost all labors use oxytocin infusions to increase labor contractions (R. K. Freeman & Nageotte, 2007), the long-term consequences of these two interventions are largely unknown. Animal research has demonstrated perinatal manipulation of the oxytocinergic system can have enduring effects on feeding, attachment, and social and sexual behavior (Carter, 2003; Olza Fernández et al., 2012). Further research in this area is needed to ascertain the effects of intrapartum oxytocin combined with epidural analgesia on breastfeeding success and maternal and neonatal behavior.

Epidural Analgesia with Instrumental Vaginal Delivery and Breastfeeding

Epidural analgesia is associated with a significantly higher rate of instrumental vaginal delivery (forceps and vacuum) (Anim-Somuah et al., 2011; Nyuyen et al., 2010). Two large cohort studies found that the use of epidural analgesia in nulliparous women was associated with a 4-fold increase in instrumental vaginal deliveries (Hawkins, Hess, Kubicek, Joyce, & Morrow, 1995; Paterson, Saunders, & Wadsworth, 1992). Instrumented vaginal delivery can have serious ramifications for the neonate and mother. It has been associated with an increase in severe maternal perineal lacerations (J. N. Robinson, Norwitz, Cohen, McElrath, & Lieberman, 1999) and neonatal birth injuries (L. M. Chadwick, Pemberton, & Kurinczuk, 1996; Gebremariam, 1999; Gilbert, Nesbitt, & Danielsen, 1999; C. A. Hughes, Harley, Milmo, Bala, & Martorella, 1999; M. G. Levine et al., 1984). Women who had epidural analgesia, forceps delivery, and episiotomy have been reported to have a 40% higher incidence of anal sphincter tears (Fitzgerald et al., 2007). In another study (J. H. Johnson, Figueroa, Garry, Elimian, & Maulik, 2004), neonates delivered by forceps showed a significantly greater risk for marks and bruising, whereas neonates delivered by vacuum showed significantly more cephalohematoma and caput and molding. Epidural analgesia was used frequently in both groups, with more in the forceps group, but the study classified according to delivery mode and not epidural use. This study also found a statistical significance with epidural and pudendal analgesia and episiotomy, vaginal lacerations, and third- and fourth-degree perineal lacerations with forceps, whereas in vacuum-assisted deliveries periurethral lacerations were most significant (J. H. Johnson et al., 2004).

A retrospective case-control study was designed to evaluate the relationship between epidural analgesia, labor length, and perinatal outcomes in 350 women who received epidural compared with 1400 patients without epidural. Epidural analgesia was associated with longer

labors and increased rates of vacuum deliveries due to dystocia or fetal distress was higher than the control (Hasegawa et al., 2013). The results also demonstrated that Apgar scores and umbilical artery pH were significantly lower in the neonates delivered by vacuum, whether they had an epidural or not. The instrument delivery adversely affected the neonate more than the epidural.

Lieberman and colleagues evaluated 1233 nulliparous women in spontaneous labor who were afebrile at admission to investigate whether there was an association between intrapartum temperature elevation and assisted vaginal delivery (E. Lieberman, Cohen, Lang, Frigoletto, & Goetzl, 1999). They found that women who had a temperature $>37.5^{\circ}\text{C}$ were three times more likely to experience an assisted vaginal delivery (25.2 % vs. 8.5%) in both epidural users and nonusers. Even after adjusting for potentially confounding factors such as length of labor, women who had an elevated temperature intrapartum were still two times as likely to require an assisted vaginal delivery. With more frequent intrapartum temperature elevations in women who receive epidural analgesia, perhaps this may be one factor to explain the higher assisted vaginal delivery rates in women who use epidural analgesia

Epidural analgesia causes a longer stage 2 labor (Anim-Somuah et al., 2011) and a four-fold increase in the risk of fetal occiput position (E. Lieberman, Davidson, Lee-Parritz, & Shearer, 2005). This combination can expose the fetal vertex to excessive molding (*caput succedaneum*) (Akmal & Paterson-Brown, 2009; Tamagawa & Weaver, 2012). The extra tension and stretch of the cranial nerves caused by the increased molding on the fetal vertex can cause hemorrhage when tension is added during instrumental delivery. This substantially increases the risk of postpartum complications.

Instrument deliveries cause pain during delivery from the episiotomy and perineal lacerations. When a repair is needed with stitches, this can create even more discomfort for the mother. The tissue damage caused by episiotomies and lacerations can take a long time to repair, and this can delay immediate skin-to-skin contact between the infant and mother. During early skin-to-skin contact, the neonate initiates breastfeeding, inducing the production of maternal oxytocin necessary for milk production, uterine contraction, and maternal and neonatal behaviors. When delivery is difficult, the baby may need medical assessment, thereby delaying immediate skin-to-skin contact during the crucial time. Being in pain may prevent the mother from getting breastfeeding off to a good start. The baby may have pain from bruising and facial injury caused by the forceps or vacuum delivery which inhibits movements of the baby's head and neck, making it difficult for the baby to get into the breastfeeding position and to latch on effectively. Longer stage 2 labor caused by epidural analgesia tires mothers and stresses babies, making breastfeeding even more difficult. The delay in breastfeeding that this cascade of events creates requires extra support and postpartum follow-up for the mother and neonate.

Instrument-assisted delivery, longer labor, and maternal-infant separation after delivery may lead to increased difficulties in breastfeeding (Rajan, 1994) (Patel, Liebling, & Murphy, 2003; Tamminen, Verronen, Saarikoski, Goransson, & Tuomiranta, 1983). Labor epidural analgesia affects these labor and delivery outcomes, thereby secondarily affecting breastfeeding initiation in conjunction with the direct effects of the medications (Anim-Somuah et al., 2011; Montgomery et al., 2012).

Effects of Epidural Medications on Breastfeeding

It has been theorized that labor analgesia reduces a mother's probability of successfully breastfeeding her child. One proposed mechanism by which intrapartum labor analgesia may decrease breastfeeding success is that women who remain unmedicated during labor experience a higher acute stress level, which subsequently prompts their neonate to organize neurobehavior including those tied to feeding, more rapidly and effectively during the immediate postpartum period (Bell et al., 2010). Those infants who feed most vigorously during the first few days of life are more likely to still be breastfeeding at 3 or 6 months (Mizuno, Fujimaki, & Sawada, 2004). Epidural opioids are known to cross the placenta potentially depressing neonatal CNS function (Loftus et al., 1995). The neonatal depression may prevent development of good feeding behavior in the initial hours of life predisposing the mother to quit breastfeeding prematurely (Wieczorek et al., 2010).

Empirical Studies on Labor Epidural Analgesia and Breastfeeding

A review of the literature found 23 empirical studies that were specific to labor epidural analgesia and measured a breastfeeding outcome (French et al., in press). Results were conflicting: 11 studies found that epidural analgesia was not implicated in adverse breastfeeding outcomes (10 found no effect and 1 found a positive effect) and 12 studies showed negative associations between epidural analgesia and breastfeeding success.

Of the 11 studies showing epidural analgesia was not implicated in adverse breastfeeding outcomes, 10 showed no effect (Albani et al., 1999; Armani et al., 2013; Bell et al., 2010; Chang & Heaman, 2005; Chen, Li, Wang, & Wang, 2008; Halpern et al., 1999; Radzynski, 2003; Rajan, 1994; Wang, Li, & Hu, 2005; Wieczorek et al., 2010; Wilson et al., 2010), and only one

reported positive results on initiation of breastfeeding and quantity of milk in a comparison of continuous epidural with no analgesia (Wang et al., 2005).

One study (Wieczorek et al., 2010) recruited 87 multiparas who had previously breastfed and who delivered vaginally after receiving continuous labor epidural infusion with various doses of fentanyl. A telephone questionnaire was administered during the immediate postpartum period and at 1 week and 6 weeks postpartum by an investigator blinded to the total fentanyl dose. No dose-response relationship was found. However, because of the high rate of breastfeeding (95.4% at week 6), the study did not have sufficient power to detect a difference between high and low doses of fentanyl. Another study (Radzynski, 2003) evaluated breastfeeding behaviors using the Preterm Infant Breastfeeding Behavior Scale in 56 healthy mother-infant pairs and found no difference in neonatal rooting, latching, or sucking at 1 hour and at 24 hours after delivery between neonates born to mothers who received epidural analgesia and those whose mothers had no analgesia. They also measured the levels of bupivacaine and fentanyl in cord blood and found no significant effects on breastfeeding variables.

In addition, no dose-response effect was found in a secondary analysis of data from a randomized trial in the United Kingdom that assessed the effect of epidural analgesia on mode of delivery. A total of 1054 primiparas were randomized to receive high-dose epidural analgesia with bupivacaine alone or one of two mobile epidural techniques with low-dose bupivacaine and fentanyl, either a combined spinal epidural with a mean fentanyl dose of 107 μg , or a low-dose infusion with a mean fentanyl dose of 163 μg (Wilson et al., 2010). A matched comparison group of women who did not receive regional analgesia was also recruited. The women were interviewed postpartum and mailed a postal questionnaire 12 months after delivery. The authors found no differences among the groups with regard to initiation rates or duration of

breastfeeding. However, the breastfeeding initiation rate was significantly lower in a subset of women in the non-epidural group who received pethidine than in the other groups.

In a study reported in Chinese with an English abstract, 124 women with vaginal delivery were randomly divided into labor analgesia group ($n = 75$) and control group ($n = 49$). No significant differences in the initial time of lactation, the rate of abundant lactation, or newborn weight reduction between mothers receiving epidural analgesia and a control group (Chen et al., 2008). In another study reported in Chinese with an English abstract, healthy women hospitalized for vaginal delivery without obstetric complications were observed, and 96 women who received continuous epidural anesthesia were compared with 74 women who did not (Wang et al., 2005). The epidural group had a shorter starting time of lactation, a larger quantity of milk secretion, and higher prolactin level 48 h after delivery. The women in the epidural group also reported better analgesia and postpartum mental state than the control group.

Twelve studies found adverse effects of epidural analgesia on breastfeeding, either in comparisons of women with and those without epidural analgesia (Baumgarder et al., 2003b; Dozier et al., 2013; Gizzo et al., 2012; J. J. Henderson et al., 2003; Jordan et al., 2009; Ransjö-Arvidson et al., 2001; J. Riordan, Gross, Angeron, Krumwiede, & Melin, 2000; Torvaldsen et al., 2006; Volmanen et al., 2004; Wiklund et al., 2009) or in analyses of dose-response relationships of epidural medications and breastfeeding (Beilin et al., 2005; Jordan et al., 2005).

In contrast to the three studies finding no effects of fentanyl dose level, a retrospective cohort study in the UK, in which midwife and obstetric case notes were analyzed in a random sample of 425 healthy primiparas identified from a birth registry (Jordan et al., 2005), found a dose-response relationship between fentanyl and bottle feeding. Higher fentanyl doses decreased breastfeeding rates even after demographic confounders of breastfeeding had been accounted for.

However, women who had decided antenatally to bottle feed did so regardless of fentanyl dose. In addition, a randomized double-blind study (Beilin et al., 2005) found an adverse effect of fentanyl dose on neurologic variables at 24 hours after birth but not on breastfeeding behavior observed by a lactation consultant. At 6 weeks, more women with high-dose than with low-dose fentanyl had discontinued breastfeeding.

In a prospective cohort study of 1280 women in Australia who responded to mailed questionnaires regarding breastfeeding at 1, 8, 16, and 24 weeks postpartum (Torvaldsen et al., 2006), women with epidural analgesia had an increased likelihood of breastfeeding difficulties and partial breastfeeding in the first week postpartum and were more likely to stop breastfeeding in the first 24 weeks compared with women who had no analgesia. In another prospective observational study conducted in Australia (J. J. Henderson et al., 2003), 992 primiparas were enrolled to investigate effects of labor epidural analgesia ($n = 690$) on breastfeeding duration by a self-reported postal questionnaire at 2 and 6 months. Women with labor epidural analgesia had a shorter breastfeeding duration and a 1.4-times greater risk of breastfeeding cessation in the first 6 months postpartum when compared to women who had no analgesia. Similar results were found in a retrospective study of 164 primiparas with spontaneous vaginal delivery in Finland (Volmanen et al., 2004). Questionnaires were mailed a median of 2.4 years after delivery. Women who had epidural analgesia were more likely to report problems of “not having enough milk,” and reported more partial breastfeeding or formula feeding during the first 6 months postpartum than women who had no epidural.

A retrospective cohort study was performed in a large obstetric data set from Wales to investigate the associations between drugs given routinely in labor and breastfeeding at 48 hours (Jordan et al., 2009). Regression analysis confirmed the association between epidural analgesia

and lower breastfeeding rates, even after accounting for confounding variables such as age, parity, and social class. The authors did not name the epidural medications used.

A prospective study assessed the effects of different types of analgesia during labor on spontaneous breastfeeding movements and behavior (Ransjo-Arvidson et al., 2001). The authors videotaped 28 neonates placed skin-to-skin with the mother immediately after birth. Analysis of the video tapes blinded to type of analgesia or no analgesia showed that neonates whose mothers had received labor analgesia had less frequent infant hand massage-like movements and sucking at the breast than infants whose mothers had received no analgesia, with almost half of the infants in the analgesia group not breastfeeding within the first 2.5 hours after birth. However, some patients receiving epidural analgesia also had parenteral pethidine or multiple types of analgesia, and only two patients had only epidural analgesia. Another prospective study of 129 women in the United States examined labor analgesia and its effect on neonatal sucking and breastfeeding duration (J. Riordan et al., 2000). The researchers measured suckling using the IBFAT and found reduced neonatal suckling scores in women who had labor analgesia, although there was no difference in duration of breastfeeding through 6 weeks postpartum compared to women who had no analgesia. Similarly, a study in the United States of 52 mixed-parity healthy women with spontaneous vaginal delivery found that epidural analgesia ($n = 34$) was associated with reduced sucking among the female neonates during their first feed compared with the nonmedicated group (Armani et al., 2013; Bell et al., 2010).

In a retrospective comparative study carried out in Sweden (Wiklund et al., 2009), all maternity records of women who received epidural analgesia for labor between January 2000 and April 2000 were assessed. After exclusions, 351 charts were included. Each epidural chart was matched to a control record similar in age, parity, and gestational age. Compared to matched

controls, neonates born to mothers who had epidural analgesia during labor had significantly lower rates of suckling at the breast during the first 4 hours after delivery, were given formula more often while in the hospital, and fewer were fully breastfeeding at discharge.

Discussion of Studies on the Effects of Epidural Analgesia on Breastfeeding

Studies on the relationship between epidural analgesia and breastfeeding success yielded conflicting results, with 1 study showing a positive association, 12 studies yielding negative associations, and 10 studies finding no effect of epidural analgesia on breastfeeding. The level of evidence was evaluated using the criteria shown in Table 2.

Table 2. Criteria for Evaluating Levels of Evidence

Therapeutic Studies—Investigating the Results of Treatment	
Level I	<ol style="list-style-type: none"> 1. Randomized controlled trial <ol style="list-style-type: none"> a. Significant difference b. No significant difference but narrow confidence intervals, 2. Systematic review of Level I randomized controlled trials (studies were homogeneous)
Level II	<ol style="list-style-type: none"> 1. Prospective cohort study, 2. Poor-quality randomized controlled trial (e.g., <80% follow-up) 3. Systematic review <ol style="list-style-type: none"> a. Level II studies b. Nonhomogeneous Level I studies
Level III	<ol style="list-style-type: none"> 1. Case-control study 2. Retrospective cohort study 3. Systematic review of Level III studies
Level IV	Case series (no, or historical, control group)
Level V	Expert opinion

Source: Wright, J. G., Swiontkowski, M. F., & Heckman, J. D. (2003). Introducing levels of evidence to the journal. *The Journal of Bone and Joint Surgery. American volume*, 85-A(1), 1-3.

The studies are summarized in Table 3. The level of evidence ranged from II to IV.

Table 3. Studies on the Effects of Epidural Analgesia on Breastfeeding

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Rajan, 1994	Retrospective study – secondary analysis of UK survey of pain relief in labor (n = 1064)	Lignocaine (Lido)	No EDA	Questionnaire mailed at 6 weeks asked whether mother was breastfeeding	No negative effects of EDA, but breastfeeding rate decreased when mothers received pethidine	Retrospective study; not able to separate use of lignocaine in EDA from use as local anesthetic; doses unknown; pethidine used in some EDA patients; chi-square analyses	III
Albani et al., 1999	Prospective cohort study; vaginal delivery (n = 1920); mixed parity	Drugs unknown	No analgesia	Recorded feeding modality at discharge	No difference in breastfeeding rate between EDA and no analgesia in women with vaginal delivery	Article in Italian, only abstract in English; unknown medication and doses; chi-square analyses	II
Halpern et al., 1999	Prospective cohort study, mixed parity (n = 189)	Combined spinal/EDA (Bupi + Suf) (n = 79) or pure EDA (Lido or Bupi) (n = 34); maintained with Bupi or Fent if needed. Total EDA n = 113	No EDA (n = 76)	Breastfeeding assessment at 6 weeks by structured telephone interview; multivariate logistic regression analysis (n = 171)	No significant effect of EDA or other types of labor analgesia on breastfeeding when leaving hospital or 6 weeks later; 74% were fully breastfeeding at 6-8 weeks	Study included only women intending to breastfeed; EDA was combined with spinal and/or IM opioid in some patients	II

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Riordan et al., 2000	Prospective multisite cohort study; unknown parity	Assorted drugs, usually Bupi + Fent or Suf (n=27) in varied doses	No medication (n=37); IV opioids (n=52); both IV opioids and EDA (n=13)	Sucking (IBFAT) during hospital stay; duration of breastfeeding assessed by telephone at 6 weeks; ANCOVA	Significant negative effect of medication vs no medication on IBFAT (suck scores, LATCH. No difference between EDA and IV opioids but mothers with both had significantly lower scores. Medication diminished sucking but not duration of breastfeeding, although duration shorter with low IBFAT scores	Multiple medication and doses; unclear whether IBFAT assessment was properly blinded; post hoc analysis of EDA vs IV opioids	II
Ransjo-Arvidson et al., 2001	Prospective cohort study; parity unknown	Bupi via EDA or parenteral pethidine or 2-3 types of analgesia (n=12)	Pudendal block with mepivacaine (n=6) or no analgesia (n=10)	Video recordings of immediate PP skin-to-skin (assessed blindly) - rooting, latch on, sucking, swallowing, activity state, and neurobehavior. Age at and duration of first suck and number of sucks	Negative effect of EDA: Medicated babies had less frequent hand movements than nonmedicated babies. Nearly half of the medicated group did not feed in the first 2.5 hours of life, had higher temps ($p = 0.03$) and cried more ($p=0.05$)	Small sample size, some patients with EDA had parenteral pethidine or multiple types of analgesia; only 2 patients had EDA alone	II
Radzyminski 2003, 2005	Randomized trial	Bupi + Fent + Epinephrine in an ultralow-dose infusion (n=28)	No analgesia (n=28)	PIBBS/NACS at birth and 24 hours; high NACS = increased breastfeeding success. Measured duration of epidural infusion and amount of drug in cord blood at birth	No significant difference between EDA and no analgesia in PIBBS/NACS scores. No significant relation between levels of bupivacaine or fentanyl in cord blood and breastfeeding variables	Small sample size, randomization method not truly random	II

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Henderson et al., 2003	Prospective observational (cohort) study; primiparas	CSE with PCEA Bupi + Fent (n=690)	Continuous midwifery support group, N ₂ O and/or pethidine (n=302)	Time and quality of first breastfeed and self-report at 2 and 6 months	Negative effect of EDA: EDA associated with shorter duration of breastfeeding. Factors that favored longer breastfeeding were higher education, older mothers, non-smokers and no EDA	Intended as a randomized clinical trial, but analyzed as a prospective observational study because of high crossover rates (43.4%), pethidine used in some EDA patients; self-report biased and unreliable	II
Baumgardner et al., 2003	Prospective cohort study (consecutive breastfeeding mothers receiving EDA compared with next breastfeeding mother without EDA); mixed parity	Drugs not specified (n=115)	No analgesia (n=116)	2 successful breastfeeding sessions in 24 hours as defined by LATCH	Negative effect of EDA, with 69.6% of mothers with EDA and 81% of nonmedicated mothers achieved successful breastfeeding in 24 hours; OR 0.53; $p=0.04$ by LATCH	Medications used not stated	II
Volmanen et al., 2004	Retrospective survey, primiparas, vaginal delivery	Bupi + occasional Fent (n=30)	No EDA (n=34)	Mailed questionnaire 2-3 years after delivery asking about breastfeeding success or failure in the first 12 weeks	Negative effect of EDA. Full breastfeeding: 33% with EDA, 71% with no EDA; “not enough milk” was reported as reason more often with EDA	Doesn't address breastfeeding in immediate PP, recall after 2-3 years may be faulty, failed to control for confounding variables after discharge	III

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Chang & Heaman, 2005	Prospective cohort study; mixed parity	Bupi or Ropi with Fent or occasionally epinephrine; no other analgesia (n=52)	No analgesia (n=63)	Assessed at 8-12 hours PP LATCH and NACS telephone; phone interview at 4 weeks PP	No differences between EDA and no analgesia regarding LATCH and NACS. Positive correlation between infant neurobehavior and breastfeeding effectiveness ($p=0.01$)	No mention of breastfeeding hospital practices, no definition of exclusive breastfeeding, no mention of total EDA infusion time	II
Jordan et al., 2005	Retrospective sample from birth register, primiparas	Neuraxial analgesia (n=232) containing opioid (n=158) or local anesthetic (n=74)	Nitrous oxide or IM opioid (n=570)	Infant feeding at discharge as recorded in case notes: proportion with exclusive bottle feeding or breastfeeding (total or partial)	Possible negative effect of EDA: Bottle feed: N ₂ O+O ₂ (32%); IM opioids + N ₂ O+O ₂ (42%); Neuraxial LA (44%); neuraxial +opioid (54%) with Fent (55%) and morphine (64%). Main determinants of bottle feed: maternal age, occupation, feed intention, cesarean, and Fent in a dose-response relationship	IM pethidine used in some EDA patients; No formal breastfeeding assessment in discharge summary; exclusive breastfeeding not separately analyzed, no neurobehavior assessment	III
Beilin et al., 2005	Randomized double-blinded study of different doses of Fent in EDA; multiparas who had previously breastfed	Bupi with intermediate-dose Fent (n=59) or high-dose Fent (n=58)	EDA with Bupi only (no Fent) (n=60)	PP day 1, mother and lactation consultant each assessed breastfeeding separately using "B-R-E-A-S-T" feeding observation form, NACS and 6 weeks PP telephone interview	Negative effect of high-dose Fent at 24 h on NACS scores but no difference in consultant assessment. Negative effect of increasing Fent dose at 6 weeks, 17% of PP women in the high-dose Fent group, 5% with the interim dose, and 2% with no Fent reported stopping breastfeeding ($p=0.005$). High-dose Fent group reported significantly more difficulty with breastfeeding than other groups	No control group without EDA, breastfeeding assessed at 6 weeks	II (for dose comparison)

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Wang et al., 2005	Prospective observational study; unknown parity	Continuous EDA, drug unknown (n=96)	No EDA anesthesia or postpartum analgesia	Starting time of lactation, milk quantity, feeding times in 24 h, prolactin level 48 h after delivery	Positive effects of EDA: EDA group had earlier starting time of lactation, larger quantity of milk secretion, higher prolactin levels 48 h after delivery, better analgesia and PP mental state than control	Article in Chinese –only abstract available in English	II
Torvaldsen et al., 2006	Prospective cohort, primiparas and multiparas either intending or not intending to breastfeed (not differentiated)	Bupi + Fent PCEA ± IM pethidine or N2O (n=416)	No analgesia, N ₂ O, pethidine (with or without N ₂ O), or general anesthesia (n=762)	Questionnaire on day 4 and mailed at 8, 16, and 24 weeks PP. Breastfeeding categorized as full, partial or not breastfeeding	Possible negative effect of EDA: at week 1, EDA ± pethidine group had higher risk of partial instead of full breastfeeding compared with N ₂ O, pethidine, and no analgesia groups. At 24 weeks, both EDA and pethidine groups had higher risk of breastfeeding cessation than no analgesia group ($p = <0.0001$)	Not possible to determine effects of EDA alone because no EDA patient had vaginal birth without pethidine (all EDA patients without pethidine had cesarean birth)	III
Chen et al., 2008	Randomized study	Ropi PCEA (n=75)	No analgesia (n=49)	Starting time of lactation, rate of abundant lactation, newborn weight reduction, and prolactin were recorded during first 24 hours	No differences between EDA and no analgesia in starting time of lactation, rate of abundant lactation, or newborn weight reduction	Article in Chinese – only abstract available in English	Not clear if I or II

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Jordan et al., 2009	Retrospective analysis of survey data; (n=48,366)	EDA drugs not specified, with or without IM opioid or spinal	No analgesia	Breastfeeding or not at 48 hours PP; as recorded in maternal notes. Regression analyses	Negative effect of EDA: Regression analysis showed breastfeeding rate was significantly lower with EDA than with no EDA ($p<0.001$), even when adjusted for parity	Drugs and doses not specified; incomplete coding for social class. Retrospective design cannot separate effects of confounding variables	III
Wiklund et al., 2009	Retrospective matched case-controlled study	Bupi+Suf ± pudendal or paracervical block (n=351)	No analgesia +/- pudendal or paracervical block (n=351)	Breastfeeding assessed at 1 and 4 hrs after birth, bottle-fed in hosp, breastfeeding at discharge; as recorded in maternity record	Negative effect of EDA: Fewer babies of mothers who received EDAs suckled breast within first 4 hours ($p<0.0004$); babies with EDAs were more likely to receive supplement ($p<0.0012$), and fewer had exclusive breastfeeding at discharge ($p<0.0430$)	Retrospective study	III
Wilson et al., 2010	Prospective cohort study – secondary outcome measure from randomized trial comparing different types of EDA (COMET trial)	High-dose Bupi (n=353); CSE with low-dose Bupi+Fent (n=351); low-dose Bupi and Fent infusion (n=350)	Nonrandomized matched comparison group with no EDA (n=351); pethidine (n=151)	Interviewed 24-48 hrs PP. Postal questionnaire 12 months PP asked duration of breastfeeding	No difference between EDA and non-EDA groups in breastfeeding initiation; women with pethidine in non-EDA group reported lower breastfeeding initiation rates ($p=0.002$). Older age ($p<0.001$) and non-white ethnicity ($p<0.026$) predicted breastfeeding. Duration of breastfeeding similar across all EDA groups	Maternal report of breastfeeding may not be accurate, sample size estimates not determined by breastfeeding initiation or duration, and no data on additional breastfeeding support women may have had	II

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Bell et al., 2010	Prospective cohort study	EDA Bupi+Fent (n=34)	No medication (n=18)	Neonatal neurobehavior organization measured within 1 hour after birth with sucking apparatus	No difference in number of sucks; sucking pressure not related to EDA exposure overall, but unmedicated girls had more sucks ($p=0.027$) than girls in EDA group. Overall girls had stronger suck pressure than boys ($p=0.042$)	Groups were self-selected. Missing data on 4 neonates due to video recorder problems/ and 1 infant needing observation, no racial/ethnic diversity, and small sample size	II
Wieczorek et al., 2010	Prospective observational cohort study; multiparas who had previously breastfeeding successfully	Bupi+Fent (n=87). Compared high-dose Fent ($>150\text{ }\mu\text{g}$, n=47) vs low-dose Fent ($<150\text{ }\mu\text{g}$, n = 40)	No control without EDA	Immediate PP questionnaire and telephone interview at 1 and 6 weeks with degree of breastfeeding classified	No significant correlation between Fent dose and breastfeeding success. Breastfeeding success rate of $>95\%$ PP; cessation rate at 6 weeks PP was much lower than in previously quoted literature	Comparison was only high vs low dose of Fent. High breastfeeding rates resulted in insufficient power to detect a true difference between doses if one existed	II (for dose comparison)
Gizzo et al., 2012	Prospective cohort study; primiparas	Bolus Fent+Ropi, booster boluses as need (n=64)	No medication (n=64). Controls randomly selected from larger group who met inclusion criteria but did not receive EDA	Within 2 hours of birth midwife completed grid follow-up and recorded data	Negative effect of EDA: Duration of first breastfeeding was significantly shorter in the EDA group than in the nonmedicated group ($p<0.001$), and length of labor was longer in epid vs. nonmedicated ($p<0.001$)	Abstract states “randomized” but assignment to study group was not random; narrow patient selection (patients with potential confounding factors excluded)	II

	Type of Study	EDA (n)	Comparison Group (n)	Assessment Methods	Findings	Limitations	Evidence Level
Armani et al., 2013	Retrospective case-control study	Bupi or Ropi combined with opiates administered as EDA top-up (n=287)	No analgesia (n=1676)	Gathered data on neonatal and obstetric outcomes, rates of breastfeeding, supplemental formula, and full formula	No difference between EDA and no analgesia in breastfeeding rate or supplementation. EDA had higher rates of instrument deliveries ($p<0.01$; occiput post position ($p<0.05$, neonatal cephalohematoma ($p=0.01$) and lower 1 minute Apgar ($p=0.016$); more women with EDA had fever ($p=0.003$)	Retrospective design; not possible to draw conclusions about duration of breastfeeding	III
Dozier et al., 2013	Retrospective analysis of data from 2 cohort studies of breastfeeding support: 1 prospective in-hospital and 1 retrospective perinatal; primi- and multiparas	EDA (any type, drugs not specified, excluded local, spinal, or general anesthesia) (n=437)	No EDA (n=290)	Data abstracted from birth certificate + EMR; breastfeeding cessation within first month assessed by maternal self-report (mailed survey)	Negative effect of EDA: Mothers with EDA more likely to discontinue breastfeeding during first 30 days (Kaplan-Meier analysis with log-rank test), even considering BFH status and other factors ($p<0.04$ for BFH; $p<0.01$ for non-BFH) (Cox proportional hazards). Mothers with EDA + oxytocin most likely to stop	Medications not specified; breastfeeding data relied on maternal self-report; results applicable only to vaginal deliveries, full-term singleton infants; secondary analysis – data not available for certain relevant variables; different data sources may introduce bias	II-III

ANCOVA = analysis of covariance; BFH = Baby-Friendly Hospital; Bupi = bupivacaine; CSE = combined spinal epidural; EDA = epidural analgesia; EMR = electronic medical record; Fent = fentanyl; IBFAT = Infant Breastfeeding Assessment Tool; IM = intramuscular; LATCH = breastfeeding assessment tool; Lido = lidocaine; NACS = Neonatal Neurologic and Adaptive Capacity Score; PCEA = patient-controlled epidural analgesia; PIBBS = Preterm Infant Breastfeeding Behavior Scale; PP = postpartum; Ropi = ropivacaine; Suf = sufentanil.

Only two randomized studies comparing epidural analgesia to no analgesia were found, and neither study justified classification at level I. One of these (Radzysinski, 2003; J. G. Wright, Swiontkowski, & Heckman, 2003) showed no difference in breastfeeding behaviors between infants of women who received epidural analgesia and those whose mothers received no analgesia, but the method of treatment allocation was not truly random. The second randomized trial (Chen et al., 2008) showed no difference between epidural analgesia and no pain-relieving measures. However, the number of patients in the two groups differed, and it was not possible to evaluate the study design because only the abstract was available in English. One problem with studies that find no differences between groups is that they are not always powered to detect a true difference, even if one did indeed exist.

Another study (J. J. Henderson et al., 2003) was intended as a randomized trial, but breastfeeding outcomes were analyzed as a prospective observational study because of high crossover rates (43.4%). This study found an association between epidural analgesia and shortened duration of breastfeeding. A further randomized study compared different doses of epidural fentanyl without a non-epidural group and found a negative effect of increasing doses (Beilin et al., 2005).

If epidural medications have a physiological effect on breastfeeding, and the half-life of epidural fentanyl in the maternal circulation is 2 to 2.5 hours, then breastfeeding should be studied the first few hours after delivery, before the drugs are cleared. However, breastfeeding was measured at time points ranging from immediate postpartum to 6 months, or assessed retrospectively through questionnaires mailed up to 2 or 3 years after delivery. Especially after so much time has elapsed, maternal self-report carries the risk of recall bias. After hospital

discharge, many new factors may confound the picture of breastfeeding success; for example, lack of social support, presence of siblings, or the mother's need to return to work or school. In addition, studies did not always take into account maternal factors that may influence breastfeeding, such as the mother's intention to breastfeed, level of education, marital status, BMI, and smoking behavior.

Numerous differences among studies make it difficult to draw conclusions. Different definitions of breastfeeding success were used. In some studies, breastfeeding was considered successful only if exclusive, whereas other studies grouped partial and full breastfeeding together. Many of the studies did not consider other factors that may influence breastfeeding success, such as hospital practices in regard to provision of breastfeeding support, availability of supplemental formula, and the timing of breastfeeding initiation after delivery. A hospital environment strongly supportive of breastfeeding may be able to at least partially offset the potential negative effects of epidurals on breastfeeding (Halpern et al., 1999; Wieczorek et al., 2010).

To assess reflexes needed for rooting and swallowing, standardized breastfeeding assessment tools such as LATCH (D. Jensen et al., 1994), the IBFAT (Matthews, 1988), or the Preterm Infant Breastfeeding Behavior Scale (PIBBS) (Nyqvist, Rubertsson, Ewald, & Sjoden, 1996) should be used. However, only a few studies reported such measures (Baumgarder et al., 2003b; Beilin et al., 2005; Chang & Heaman, 2005; Radzynski, 2003; J. Riordan et al., 2000).

The drugs and doses used in labor epidural analgesia varied among study sites, but all contained a local anesthetic (usually bupivacaine) and an opioid (generally fentanyl or sufentanil). However, some studies failed to mention the exact name and/or dose of the medications used in the epidural. Furthermore, in several studies, women in the epidural

analgesia groups also received other medications, including pethidine, which has been shown to have an adverse effect on breastfeeding (Rajan, 1994; Wilson et al., 2010). This makes it very difficult to determine whether the observed breastfeeding outcome was associated with the pharmacokinetics of a specific epidurally administered drug given at a specific dose at a certain time or with some other variable related to the epidural.

It is unclear whether and to what extent epidural medications exert a direct or indirect effect on breastfeeding. For example, epidurally administered local anesthetic and opioid drug combinations readily cross the placenta and fetal blood-brain barrier and may depress necessary neonatal reflexes needed for rooting, swallowing, or sucking (Chang & Heaman, 2005). A depressed neonate not responsive to sucking may prompt the mother to quit breastfeeding too soon. Because an intact and functioning central nervous system is necessary for an infant to latch on and feed, several studies have used the NACS (Amiel-Tison et al., 1982b) to address the association between epidural opioids and neonatal neurobehavior. Infants who score high on breastfeeding behaviors tend to have high NACS scores (Chang & Heaman, 2005; Radzysinski, 2005). For example, Beilin et al. randomized 177 multiparas who had previously breastfed into three groups, with epidural bupivacaine and either no fentanyl, or fentanyl at $<150\text{ }\mu\text{g}$ or $>150\text{ }\mu\text{g}$ (Beilin et al., 2005). More than $150\text{ }\mu\text{g}$ of fentanyl was associated with significantly lower NACS scores compared to bupivacaine without fentanyl. Thus, it can be concluded that depression of the neonate's tone by epidural opiates impedes the neonate's ability to latch on to the breast. Such factors may result in a vicious circle, preventing good feeding behaviors in the first 24 hours of life, which may prompt the mother to quit breastfeeding too soon.

Epidural analgesia has been consistently associated with maternal fever or temperature elevation. This may also affect breastfeeding, because the transfer of heat can cause fetal

hyperthermia. In one study (Greenwell et al., 2012), when the temperature of all women who received epidural analgesia was evaluated, a significant linear correlation was found between maximum maternal temperature and the infant's Apgar scores, hypotonia, early-onset seizures, and need for assisted ventilation. Infants born to women with maternal fever $>38.3^{\circ}\text{C}$ had a two- to six-fold increase in all the neonatal outcomes evaluated. Although no data are available on the specific effects of increased maternal temperature on breastfeeding, the many studies showing a negative effect of maternal fever on neonatal outcomes make it logical to postulate a negative effect on breastfeeding.

Furthermore, it is not clear to what extent the combination of epidural analgesia with other intrapartum interventions has an indirect effect on breastfeeding (Montgomery et al., 2012). Recent emphasis has been placed on research involving the potential lowering effect of epidural analgesia on oxytocin levels in the maternal plasma during labor and birth and the relationship of epidural analgesia to the mother's endogenous release of oxytocin. Oxytocin use has been associated with delayed initiation of breastfeeding (Wiklund et al., 2009), and combined administration of epidural analgesia and oxytocin during labor has been negatively associated with breastfeeding success. The shortened breastfeeding duration shown in women who received epidural analgesia (Beilin et al., 2005; J. J. Henderson et al., 2003; Torvaldsen et al., 2006) may be a result of decreased maternal milk production due to low levels of maternal oxytocin at birth, which may interfere with the pattern of oxytocin secretion for milk production and impact maternal-infant bonding at birth (Jordan et al., 2009). Further research in this area is needed to ascertain the effects of intrapartum oxytocin combined with epidural analgesia on breastfeeding success.

Epidural analgesia is also associated with a significantly higher rate of instrumental vaginal delivery (Anim-Somuah et al., 2011; Nguyen et al., 2010). Two large cohort studies found that the use of epidural analgesia in nulliparous women was associated with a 4-fold increase in instrumental vaginal deliveries (Hawkins et al., 1995; Paterson et al., 1992). Instrumental vaginal delivery can have serious ramifications for the neonate and mother. A retrospective case-control study was designed to evaluate the relationship between epidural analgesia, labor length, and perinatal outcomes in 350 women who received epidural analgesia compared with 1400 patients without epidural. Epidural analgesia was associated with longer labors and increased rates of vacuum deliveries due to dystocia or fetal distress was higher than the control (Hasegawa et al., 2013).

The tissue damage caused by episiotomies and lacerations due to instrumental delivery can take time to repair, which can delay immediate skin-to skin contact between the infant and mother. During early skin-to-skin contact, the neonate initiates breastfeeding, inducing the release of maternal oxytocin necessary for milk production and maternal and neonatal behaviors. When delivery is difficult, the baby may need medical assessment, thereby delaying immediate skin-to-skin contact during the crucial time. Being in pain may prevent the mother from getting breastfeeding off to a good start. The baby may have pain from bruising and facial injury caused by the forceps or vacuum delivery which inhibits movements of the baby's head and neck, making it difficult for the baby to get into the breastfeeding position and to latch on effectively. Longer stage 2 labor caused by epidural analgesia tires mothers and stresses babies, making breastfeeding even more difficult. The delay in breastfeeding that this cascade of events creates requires extra support and postpartum follow-up for the mother and neonate.

This literature review demonstrates that the relationship between epidural analgesia and breastfeeding remains inconclusive. This is not surprising, considering that the available studies varied in design, outcome definition, sample size, control group, inclusion of many potential confounders, and rigor, making any statistical conclusion difficult. Poor study design is common. Few studies are able to use randomized treatment allocation, most do not use a breastfeeding assessment tool. Some studies have not mentioned the names of medications that were used, at what dose or concentration of the epidural infusion, making it difficult to determine whether any effects are caused by the specific drugs in the epidural infusate or the condition that the epidural analgesia itself has created (Szabo, 2013).

Despite concern regarding adverse effects on breastfeeding, epidural analgesia and other intrapartum interventions are frequently used because of the benefits they confer. Therefore, it is important to find ways of ameliorating any adverse consequences. Hospital practices and providers can lend additional breastfeeding support to women who are at a higher risk of not initiating breastfeeding or for early cessation. Various strategies may be tried, but one promising way to achieve this goal is for hospitals to offer breastfeeding support by promoting unlimited skin-to-skin contact between mother and neonate. Skin-to-skin contact between the neonate and the mother during this sensitive period enhances the long-term interaction between mother and neonate. When this contact occurs, mothers have been shown to be more likely to be breastfeeding at 1 and 4 months after delivery and for a longer duration (Bystrova et al., 2009; Salariya et al., 1978; Wiberg et al., 1989)

Building on the considerations discussed in this chapter, the current study attempts to provide more information on the relationship between epidural analgesia and breastfeeding

success. The next chapter discusses the methods used in this study to answer the research questions.

Chapter 3: Methods

This prospective, observational study investigated whether breastfeeding would be less effective in infants whose mothers received epidural analgesia with hydromorphone compared with those whose mothers received no analgesia, and whether the total amount of drugs given or the presence of multiple stressful events or interventions during labor would be related to the effectiveness of breastfeeding. Chapter 3 presents the specific hypotheses, discusses the study design, and describes the selection of subjects, the setting of the study, the type of epidural analgesia used, the study variables and procedures (including procedures used to ensure rigor of the study and protection of human subjects), the risks and benefits of the study, and the methods used for statistical analysis.

Hypotheses

Based on the research questions posed in Chapter 1, the following hypotheses were formulated:

H1: Compared with healthy term infants whose mothers received no analgesia, healthy term infants of mothers who receive epidural analgesia with hydromorphone will exhibit significantly less effective breastfeeding behaviors at 3, 12, and 24 hours of age.

H2: Duration of infusion/amount of infusate will be significantly negatively related to breastfeeding behaviors at 3, 12, and 24 hours of age in healthy term infants whose mothers receive epidural analgesia with hydromorphone for labor pain.

H3: When multiple stressful events or interventions are present during labor or immediately after birth, healthy term infants will demonstrate significantly less effective breastfeeding behaviors at 3, 12, and 24 hours of age, whether or not labor analgesia was used.

Study Design

To test these hypotheses, a prospective, observational, single-blinded cohort design was used to compare breastfeeding behaviors of infants whose mothers chose to receive epidural analgesia containing hydromorphone with breastfeeding behaviors of infants whose mothers chose to receive no analgesia. An observational cohort design rather than a randomized controlled trial was necessary because it was not ethically possible to randomly assign participants to either receive an epidural or to be in a control group receiving no medication for labor pain. It would be unethical to withhold labor pain medication to someone who requests it or to give pain medication to someone who does not want it and would prefer to try non-pharmacological methods. In an attempt to minimize bias due to differences between the study groups, the eligibility criteria were designed to make the study population as homogeneous as possible. For example, to reduce the likelihood of a prolonged labor, only women who had previously labored and delivered a viable infant were included. In addition, to increase the homogeneity of the sample, only multiparas who had previously breastfed were included.

The time points of 3, 12, and 24 hours were selected because the plasma elimination half-life of hydromorphone in the circulation is approximately 2-3 hours (Felden et al., 2011; Inturrisi, 2002). If epidurally administered medications do affect breastfeeding and neurobehavior, the first assessment should occur before the drugs have been cleared from maternal and neonatal circulation. Therefore, first breastfeeding assessment and neurobehavior tests were to be done within 4 hours after delivery. The 12-hour time point was selected because

8-24 hours is considered the crucial time for the establishment of breastfeeding, and the drugs would be expected to have been metabolized and cleared from mother and neonate. The 24-hour time point was selected to address breastfeeding status at time of discharge.

Subjects

The study population consisted of an unmedicated group (control group) of 51 mother-infant dyads in which the mother did not receive any pain medication or CNS depressants and 51 mother-infant dyads in which the mother elected to receive epidural analgesia for labor pain.

Sample Size

Sample size was determined for comparative analysis using repeated-measures analysis of variance. The minimum difference between groups that would be worth detecting was determined using Cohen's d set at 0.5 (i.e., medium effect) (J. Cohen, 1988; Lakens, 2013). Assuming 80% power and an α value at 0.05, a sample size of 51 cases per group was needed to detect a true difference if it exists. Recruitment continued until the required number of subjects was achieved in each group.

Selection Criteria

Mother-infant dyads were included when the mother met the following criteria: (a) aged 18 years or older; (b) used only epidural analgesia (continuous infusion) or no medication during labor and delivery; (c) had breastfed after previous deliveries; (d) intended to breastfeed again; (e) allowed breastfeeding to be observed at 3, 12, and 24 hours postpartum; (f) was English speaking; (g) had a singleton pregnancy; (h) had an infant ≥ 37 weeks and ≤ 42 weeks gestation; and (i) delivered vaginally. Exclusion criteria comprised (a) any complication of pregnancy such as pregnancy-induced hypertension or insulin-dependent gestational diabetes; (b) any complication of labor; (c) obesity (BMI ≥ 40); (d) alcohol or substance abuse; (e) infant with

congenital anomalies; (f) infant receiving antibiotics or intravenous therapy for hypoglycemia ; (g) infection as evidenced by maternal fever during labor; (h) infant with an Apgar score less than 8 at 5 minutes; (i) infant having resuscitation after delivery; (j) mother has undergone any type of procedure that required anesthesia or analgesia within 24 hours postpartum; (k) abnormal fetal presentation such as occipital posterior or breech.

Setting

The study took place at the Labor and Birth Unit and the Postpartum Unit of YNHH, a 1500-bed teaching facility in New Haven, Connecticut. YNHH has a delivery rate of approximately 5,500 babies per year and is a major obstetrical referral center for physicians throughout the region. YNHH is located in a culturally, economically, and socially diverse neighborhood. Although many of the hospital patients live within the area surrounding the hospital, many come from cities throughout the state of Connecticut.

YNHH is in the process of becoming Baby Friendly and has implemented The Ten Steps to Successful Breastfeeding. To control for delivery room practices known to have an influence on the neonate's ability to suck and establish breastfeeding, the following steps were followed in the same way for all mother-infant dyads in this study. It was expected that all neonates would be placed skin-to-skin immediately after birth, and breastfeeding initiated within the first hour. This is the standard of care at this institution. If the neonate could not be placed immediately skin-to-skin because of a complication with the mother, neonate, or delivery, the mother-infant dyad was excluded from the study. Thus, all babies were placed on the mother's chest in a similar manner. Vitamin K and eye care were provided 24 hours postpartum.

Treatment - Epidural Analgesia

Epidural analgesia was administered according to the standard protocol of Yale New Haven Hospital for healthy parturients who request epidural analgesia for vaginal delivery: The protocol called for 1.5% lidocaine with 1:200,000 epinephrine as a test dose and/or 0.25% bupivacaine with 1:200,000 epinephrine as a bolus, and 100 µg hydromorphone followed by a continuous infusion of 0.05% bupivacaine with 3 µg/mL hydromorphone at a rate of 14 mL/hour.

Study Variables

Demographic and Clinical Characteristics

At the time the participant signed the informed consent form, the study team filled out a patient information sheet related to labor, delivery, and medication received during labor (Appendix A: Patient Information Sheet). Clinical factors such as oxytocin (Pitocin, Syntocinon) use, instrument delivery, maternal temperature, and duration of labor were also recorded.

Epidural Medications

Data were collected regarding the continuous epidural infusion (extent of cervical dilation at the time of epidural placement, dose of the components, infusion rate, and total volume), type, and dose of local anesthetics, and any additional doses for breakthrough pain.

LATCH Breastfeeding Assessment Tool

The LATCH Breastfeeding Assessment Tool (D. Jensen et al., 1994) was used to measure breastfeeding effectiveness. Permission for its use was obtained from the copyright owner (John Wiley & Sons, Inc., Appendix B: Copyright Permission for LATCH Breastfeeding Assessment Tool).

LATCH is a breastfeeding charting system that assesses individual breastfeeding sessions using a systemic model to gather information (D. Jensen et al., 1994). The LATCH score includes all aspects of latching behavior by providing a score of 0, 1, or 2 for each key component of breastfeeding: L = the infant's ability to latch onto the breast, A = the audible sound of swallowing, T = type of nipple the mother has, C = comfort of the mother's breast and nipple, H = holding, which is the amount of assistance the mother needs to hold the neonate. To obtain the score for a particular breastfeeding session, the total of all the scores for the areas of assessment is calculated. A score of 2 on each item meets the criterion for effective breastfeeding. Thus, for this study, effective breastfeeding was defined as a total LATCH score of 10.

The scales are described below:

- *L* indicates how well the neonate latches on to breast during breastfeeding. A score of 2 is given if the neonate's gum line is placed well over the mother's lactiferous sinus, the lips are flanged outward, the infant's tongue is positioned over the areola, and there is rhythmic sucking. If a neonate is too sleepy or reluctant to feed and repeated attempts are needed to meet the criteria, or a staff member must hold the nipple in the infant's mouth, the score will be less than 2. A score of 2 means effective breastfeeding.
- *A* indicates the audible swallowing of the infant during breastfeeding. Swallowing is an indicator of milk intake. A short forceful expiration of air should be heard for a score of 2. During the first 24 hours of life, several bursts of intermittent sucking may be heard before the swallow.

- *T* stands for the mother's nipple type. If the nipple is everted (project outward) after stimulation and rest, a score of 2 is given. An inverted or flat nipple receives a score less than 2. Effective breastfeeding is defined as a score of 2.
- *C* stands for the mother's comfort. Pain in the nipple area and breast will interfere with let-down and the mother's willingness to continue to breastfeed. An assessment score of 2 is given if the nipples have no visible signs of blisters, redness, bruising, cracking, or bleeding, and the breast is soft and tender. A score of 1 is given for moderate discomfort with reddened, small blisters, or bruising. A score of 0 is for severe discomfort and sore breasts. Effective breastfeeding is defined as a score of 2.
- *H* indicates the mother's positioning and holding of the neonate during breastfeeding and the amount of help she requires from staff. A score of 2 is given if the mother cradles the neonate like a football or side laying against the breast, head aligned with the mother's trunk facing the breast, supporting her breast with a cupped hand.

The interrater reliability of the LATCH tool was high among lactation consultants and ranged from 85.7% to 100% (Adams & Hewell, 1997). In a test of the validity of the LATCH tool, significant Spearman correlations were found between nurses' assessment of LATCH scores and mothers' ratings of how well they thought breastfeeding had gone (J. Riordan, Bibb, Miller, & Rawlins, 2001). Findings also showed total LATCH score and mothers' assessment scores positively correlated with duration of breastfeeding. These findings support the construct validity of the LATCH tool.

Because Yale New Haven Hospital uses the LATCH instrument to guide breastfeeding education of mothers, both the PI and the lactation consultant have used the LATCH tool extensively and have spent approximately 1 year in preparation for this study. Both were also

involved in LATCH training of nurses on the Postpartum Unit. Therefore, it was not deemed necessary to conduct an interrater reliability pilot study.

Neurologic and Adaptive Capacity Score (NACS)

The second assessment planned for evaluation of neonates in this study was the NACS. Permission for use was obtained from the copyright holder, Wolters Kluwer Health (Appendix C: Copyright Permission for the Neurologic and Adaptive Capacity Score [NACS]). The NACS was specifically designed to detect central nervous system depression of the neonate from drugs and to differentiate those effects from birth trauma and perinatal asphyxia (Amiel-Tison et al., 1982b). The scale has been widely used by obstetric anesthesia researchers since it was developed in 1982.

The NACS contains portions of the Brazelton Neonatal Behavior Assessment Scale (NBAS), the Amiel-Tison neurologic exam, and the Scanlon ENNS (Amiel-Tison et al., 1982b). The criteria chosen for the NACS were from those used in standard clinical and neurologic behavioral testing. Items chosen for the NACS were those that had been shown to be affected by perinatal asphyxia, birth trauma, or obstetric medications. The test does not specifically assess breastfeeding but uses 20 criteria to assess 5 general areas: adaptive capacity, passive tone, active tone, primary reflexes, and general neurologic status. Each of the 5 general areas is given a score of 0 = absent or grossly abnormal; 1 = mediocre or slightly abnormal; or 2 = normal, with a maximum total of 40. The total score of 35-40 to indicate a vigorous response, scores of 34 or below are low enough to detect neonates with possible problems. The neonatal neurobehavior was evaluated at 3, 12, and 24 hours after birth using the NACS test.

Birth trauma, obstetric medications, neurologic disease, and perinatal asphyxia all demonstrate abnormalities in tone; therefore the NACS uses 8 separate tests for tone. There are 4

tests of passive tone in the upper and lower extremities equally that enable detection of hypotonia, which is indicative of birth trauma or perinatal asphyxia if observed in one side of the body or only seen in the upper body (Amiel-Tison, Sureau, & Shnider, 1988). Drugs and anesthetics frequently show a more general mediocre tone presenting as more general depression. The test does not require any special equipment, it is not noxious to the neonate, and it is simple to perform and score, with an interrater reliability of 92.8% (Amiel-Tison et al., 1982b).

The PI attended the Brazelton Institute at Harvard Medical School and met all the requirements for certification to administer the Brazelton NBAS (Appendix D: Brazelton Institute Certification). The NBAS is a 45 minute thorough neurobehavior exam. The study site would not allow a 45-minute neurobehavior exam. Therefore, the NACS was used, as it contains some of the items from the NBAS but takes only 5 minutes to perform. Prior to data collection, the PI reviewed NBAS training films and completed training exercises for the NACS. The correct method of scoring the infant during an examination was to be observed by a pediatrician at Yale New Haven Hospital who was familiar with the NACS, and the PI was to perform 10 NACS sessions simultaneously with the pediatrician prior to data collection for this study. However, as described in the Results section, because of difficulties in execution, evaluations with the NACS had to be discontinued.

Study Procedures

Procedures Prior to Recruitment

- Approval for the research study was obtained from the Yale University Human Investigations Committee and the Institutional Review Board of the University of

Connecticut (Appendix E: Protocol Approval, IRB Approval, and IRB Authorization Agreement).

- Letters were sent to physicians, midwives, unit managers, and nursing staff in the Labor and Birth Unit and the Postpartum Unit to inform them about the study (Appendix F: Study Information for Physicians, Midwives, etc.).
- An in-service training session was held to educate registered nurses, lactation consultants, nurse anesthetists, anesthesiology residents, and nurse-midwives in these units regarding the study (purpose, inclusion/exclusion criteria, recruitment, and procedures for data collection). The training was conducted by the PI.
- Flyers (Appendix G: Information Flyer for Nurses, Midwives, and Residents) were placed around both the Labor & Birth and Postpartum Units to keep providers aware of the purpose and procedures of the study.

Recruitment Procedures

- Recruitment of subjects was done by the study team of co-investigators, which consisted of two CRNAs who work in labor and delivery and an anesthesiology fellow specializing in obstetric anesthesia. They were trained in depth on study design, inclusion criteria, and recruitment strategies.
- Nurses and midwives alerted a study team member of a possible candidate for the study based on the inclusion criteria and asked the patients if they wanted to speak with a member of the research team who could explain the study and answer any questions they may have (Appendix H: Text for Nurses and Midwives for Speaking With Prospective Subjects)
- The principal investigator was notified of potential subjects.

- After being notified of potential subjects, study team members provided a detailed explanation of the study, answered questions, and obtained written informed consent if the patient agreed to participate (Appendix I: Oral Information for Prospective Participants). The written informed consent form is provided in Appendix J: Written Informed Consent Form.
- Prospective subjects were approached in the labor room after they had made the decision as to whether to have epidural analgesia or within 1 hour after delivery. Women who had decided to have epidural analgesia were approached only after placement of the indwelling catheter. Most laboring women are competent to consent to research and other procedures after the administration of epidural analgesia containing opioid and local anesthesia, because the doses commonly used have little to no sedative effect, and the decrease in pain may make patients more able to consider and discuss options in their care.
- If an unmedicated mother had consented before vaginal delivery but then decided to receive an epidural, she could remain in the study and cross over to the epidural cohort.

LATCH and NACS Data Collection Procedure

The following procedures were to take place at approximately 3, 12, and 24 hours after delivery. The PI was to contact the participant at these times.

If at the time of contact with the participant, the neonate was due to feed, the PI or the lactation consultant was to conduct the NACS and record it on the NACS assessment sheet (Appendix K: Neurologic and Adaptive Capacity Score (NACS). The PI or the lactation consultant then observed a breastfeeding session. Breastfeeding data were recorded on the LATCH Feeding Record (

- Appendix L: LATCH Feeding Record).

- If at the time of contact the neonate was not due to feed, the NACS and breastfeeding observation were to be postponed until the next time that infant was due to feed. The same procedure as above was to be followed.
- If the mother or infant required any help with breastfeeding the PI was to alert the patient's nurse.
- After completion of the three breastfeeding observations and NACS assessment, the PI informed the patients of the completion and thanked them for participation.

Blinded Observation

Observational data collection is susceptible to biases and distortions. Some of the biases may be due to personal interest of the data collector or anticipation of what is to be observed affecting what is actually being observed (Polit & Beck, 2010). Because scoring the LATCH and NACS depends on observational data, it is necessary for the data collector to be blind to the study group. Therefore, the data collectors (the PI and the lactation consultant) did not know whether the participant received analgesia for her labor and delivery.

The consent form and patient information related to labor, delivery, and medication received during labor were placed in a sealed envelope and then coded with the patient's study ID number. These envelopes were kept in a locked office in a locked file cabinet in the office of the Chief Certified Registered Nurse Anesthetist (CRNA). To ensure that the PI did not know which study group a subject was in during the time of data collection, these envelopes were given to the PI only after the study was complete.

The PI also did not have access to the mother's electronic medical record. While performing the study observations, there were to be no discussions about how the labor and delivery was managed. The staff was also instructed not to disclose the information. If at any

time the principal investigator became aware of the patient's status, the participant was to be withdrawn from the study.

Procedures for Ensuring Patient Safety

- As part of the Yale University requirements for researchers, all members of the study team of co-investigators completed training in Human Protection for Research Subjects and HIPAA.
- A HIPAA waiver from the Yale University Human Investigations Committee was granted to allow access to the following information during the recruitment phase of the study: name, medical record number, and whether or not a patient was in labor. The research could not be conducted without the waiver and without access to and use of the protected health information. Once patients entered the study, all data was anonymized/de-identified in the study database.
- Before approaching a patient in the labor room, the PI obtained the permission of the patient's obstetric care provider and also involved the patient's primary nurse in discussions regarding the appropriateness of such an approach.
- If the patient's obstetric care provider and/or primary labor room nurse felt that a particular patient was not in a position to comprehend the research protocol and give informed consent, then that patient was not approached for research participation until the circumstances changed to the satisfaction of the primary care providers.
- Whenever possible, the research investigators discussed the proposed research and obtained informed consent in the presence of one of the patient's independent labor support persons (if such a support person was available and the patient had no objection to that person's involvement).

- All conditions of the epidural were for clinical purposes only and no manipulation occurred for the study. The epidural catheter was placed only upon patient request for pain management.
- The investigators refrained from approaching patients for research participation at certain times during the labor and delivery process when such an approach would have been inappropriate. During the first stage of labor (<4 cm dilation), most women were relatively comfortable and the intervals between contractions allowed for adequate explanation and discussion. Because the second stage of labor may be characterized by considerable pain and exhaustion, women were not approached during this phase.
- Written evidence of informed consent was obtained in all subjects.
- At the time of consent, a detailed explanation of the research was given and questions were answered.
- After delivery, the medication data from the epidural group was collected by the co-investigators: the two CRNAs, and the obstetric anesthesiology fellow.

Risks/Benefits

The study procedures presented no known risks. No experimental conditions were placed on the subjects. The independent variable (epidural analgesia) was the hospital's standard treatment and was self-selected by participants prior to researcher contact. The participants had already decided to breastfeed and were aware of the data collection. Neonates were not awakened for study procedures. The LATCH evaluation tool was not adverse or noxious to the neonate. The PI and the lactation consultant were strictly observers of the breastfeeding. If assistance was needed, the patient's nurse was contacted.

Every measure was taken to ensure patient privacy. To minimize risks to subjects' privacy, patients were invited to participate in their private room. All data collection forms were coded and the master list of names and code numbers was kept in a locked office in a locked file cabinet. Once results were obtained, the patients' medical record numbers were shredded and all that remained were the study ID numbers with no identifiable data. The information was stored on a secure network drive accessed through an encrypted computer belonging to the PI.

No particular benefits accrued to the individual participants. The general benefits of the study were that participants could have the satisfaction of knowing they had contributed to identification of medical interventions that may adversely affect future newborns, helped health care providers anticipate mother-infant dyad's breastfeeding needs, and facilitated women's informed choices during labor and delivery.

Statistical Analysis

The IBM SPSS Statistics Software Package Version 23 (IBM Corp., Armonk, NY) was used for data management and analysis, except for the mixed-effect regression model used to examine the dose relationship between epidural parameters (total amounts of infusate, lidocaine, bupivacaine, and degree of dilation) and LATCH score in the epidural group, which was performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

The data were collected and then coded and examined graphically in box plots and within-group histograms to determine whether the variables in each group were normally distributed and free of outliers and that the spread of data was consistent across the groups. Descriptive analyses of variables relating to demographic characteristics, obstetric history, characteristics of labor and delivery, neonatal characteristics, epidural medications, and breastfeeding behaviors

were performed using means, standard deviations, and ranges for continuous variables and frequencies and proportions for categorical variables.

Group Comparisons

The purpose of this study was to examine the relationship between epidural analgesia used for labor pain relief and effectiveness of breastfeeding in the first 24 hours postpartum. Women who received epidural analgesia during labor and their neonates were compared with those who used no analgesia for labor or delivery and their neonates (control). Hypothesis testing using inferential statistics was carried out to demonstrate any differences between groups regarding demographic and obstetric characteristics, labor variables, and neonatal variables, with independent *t* tests for continuous variables. The Kruskal-Wallis test was used for non-normally distributed data. The Pearson chi-square test or the Fisher exact test was used to test for associations among categorical data, for example when comparing groups regarding the proportion of women with certain characteristics, such as the percentage of women who received oxytocin. For determination of significance of differences between groups, $p < 0.05$ was selected as the level of significance.

Correlational Analyses

To test for bivariate relationships between variables, the Pearson product moment correlation was used. The variables included duration of labor; ruptured membranes; total IV fluids; amount of oxytocin augmentation; induction of labor; LATCH scores at 3, 12, and 24 hours postpartum; meconium suctioning of the neonate; Apgar scores at 1 and 5 minutes; and percentage of weight loss of the neonate.

Multivariate Analyses

Multivariate analysis refers to the modeling of data for related multiple measurements, for example when an outcome is measured for the same individual at multiple time points (repeated measures). If parametric assumptions were met, repeated-measures analyses of variance (RM-ANOVA) were used to assess differences in breastfeeding outcomes on the LATCH total score and subscales over the three time points (3, 12, and 24 hours) and between the infants whose mothers received analgesic medication and whose mothers did not receive medication.

We also examined the effect of epidural on the LATCH score by using a mixed-effect regression model, which included fixed effects of the treatment (epidural versus unmedicated), time post-labor, interaction of treatment and time, covariates that showed significant differences between the two groups at baseline (labor duration, total amount of oxytocin used, induction of labor type, and total fluids), and the random effect of intercept.

Multivariable Analyses

As outlined in the literature review, numerous factors can influence the initiation and success of breastfeeding. Multiple regression and logistic regression can be used to address the effects of potential confounding factors that may introduce bias because of the nonrandomized nature of the study. We therefore performed multiple linear regression analyses to describe the relationship between the LATCH score as the dependent variable and epidural analgesia as a predictor variable, while at the same time adjusting for other predictor variables in the model. Such analyses can predict the probability of outcomes for individuals with a certain set of characteristics (Fields, 2013). Thus, multiple linear regression analysis was performed in the total group to examine whether the following variables may influence total LATCH scores at the specific time points of 3, 12, and 24 hours postpartum:

- Maternal demographic variables, such as age, race, weight, height, BMI, gravidity, parity, and epidural placement
- Neonatal variables such as Apgar scores at 1 and 5 minutes, baby's weight at birth, baby's weight change, meconium stain, sex of the neonate, and whether the baby was suctioned after delivery

To test the hypothesis that infants whose mothers had multiple stressful events or interventions during labor would demonstrate less effective breastfeeding, independent of labor analgesia, labor variables such as duration of labor (2nd and 3rd stage and total), whether labor was induced, rupture of membranes, oxytocin augmentation, epidural placed, group B streptococcus (GBS) status, perineal laceration, and total amount of IV fluids were examined with multiple linear regression analysis.

Regression analysis was also performed in the epidural group alone, with each total latch score at 3, 12 and 24 hours in the model with time of epidural placement to delivery, total 1.5% lidocaine dose, total 0.25% bupivacaine dose, oxytocin for labor augmentation, induction, total volume of epidural infusate, total duration of labor, ruptured membranes, total IV fluids, meconium stain, and baby suctioned.

Summary of Study Methods

This chapter attempted to give the reader a clear understanding of the study design, methodology, and analysis. Breastfeeding behaviors of infants whose mothers chose to receive epidural analgesia containing hydromorphone were compared with those whose mothers chose to receive no analgesia using inferential statistics. Repeated-measures analyses of variance were

used to test differences between groups over time. Multivariable analyses were used to investigate the effects of potential predictor variables on breastfeeding behaviors.

Chapter 4: Results

Chapter 4 presents the findings of the study. The first section of the chapter describes the characteristics of the overall study population and compares the characteristics of the two cohorts. The second section describes the timing and type of medications that were used in the cohort that received epidural analgesia. The third section presents the results for Hypothesis 1—that healthy term infants of mothers who receive epidural analgesia with hydromorphone would demonstrate less effective breastfeeding behaviors at 3, 12, and 24 hours of age when compared with infants whose mothers received no analgesia. The fourth section describes the results of multivariable analyses performed to assess the potentially confounding effects of other factors known to influence breastfeeding. The fifth section presents the results for Hypothesis 2—that healthy term infants of mothers who receive epidural analgesia with hydromorphone would demonstrate less effective breastfeeding behaviors at 3, 12, and 24 hours of age in relation to the duration of infusion and amount of drug given to the mother. The sixth section presents the results for Hypothesis 3—that when multiple stressful events or interventions occur during labor or immediately after birth, the infant would demonstrate less effective breastfeeding, whether or not labor analgesia was used. The last section summarizes the study results.

Study Participants

The study participants were recruited among parturient at the Labor and Birth Unit and the Postpartum Unit of Yale New Haven Hospital from March through April 2015. A total of 106 women were invited to participate in this study. Two women approached to participate declined after the study was explained to them and two women were excluded because they did not meet eligibility criteria (one used formula and the neonate of one was admitted to the neonatal intensive care unit immediately postpartum for shoulder dystocia).

A total of 102 mother-infant dyads met the eligibility criteria and completed the study. No subjects were withdrawn after study entry, and no subjects in the unmedicated group asked to receive epidural analgesia. All mothers were multiparas who had previously breastfed. Of the 102 participants, 51 mothers received epidural analgesia only and 51 mothers received no analgesia for labor or birth. The study flow chart is presented in Figure 1.

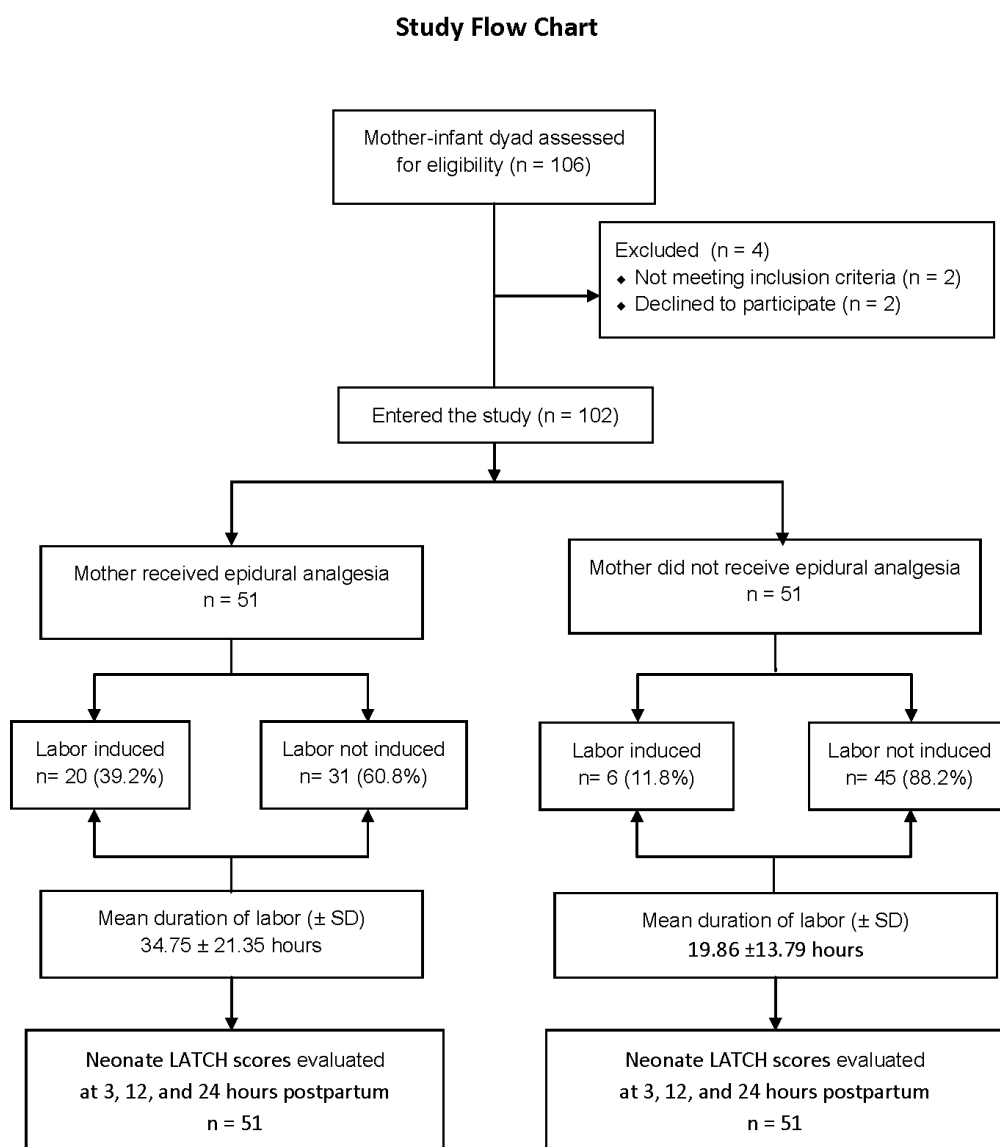


Figure 1. Study Flow Chart

Data from the 102 mother-infant dyads were obtained, recorded, and coded for a total of 306 breastfeeding observation sessions. Visual inspection of normal Q-Q plots and within-group histograms showed that the assumption of normality was satisfied, with the spread of variables fairly consistent between the epidural and unmedicated groups.

Characteristics of the Overall Study Population

Descriptive statistics describing the demographic characteristics and obstetric history of the overall study population are presented in Table 4.

Table 4. Demographic Characteristics and Obstetric History of the Overall Study Population (n = 102)

Variable	Value
Age, years	
Mean \pm SD	29.55 \pm 4.74
Range	21–43
Race, n (%)	
White	66 (64)
Hispanic	24 (23.5)
African American	6 (5.9)
Asian	6 (5.9)
Maternal weight (kg)	
Mean \pm SD	79.5 \pm 14.5
Range	53.6–151.8
Maternal height (cm)	
Mean \pm SD	163.3 \pm 6.6
Range	152.4–182.9
BMI	
Mean \pm SD	29.6 \pm 4.5
Range	19.8–50.8
Number of pregnancies	
Mean \pm SD	2.8 \pm 0.8
Range	2–5
Number of previous live births	
Mean \pm SD	1.4 \pm 0.6
Range	1–3

SD = standard deviation.

Labor and delivery characteristics of the overall study population are presented in Table 5.

Table 5. Labor and Delivery Characteristics in the Overall Study Population (n = 102)

Variable	Value
Duration of labor (min)	
2nd stage	
Mean \pm SD	20.2 \pm 18.4
Range	2–98
3rd stage	
Mean \pm SD	7.1 \pm 5.2
Range	1–39
Total	
Mean \pm SD	27.3 \pm 19.4
Range	6–108
Oxytocin, n (%)	35 (34.3)
Induced, n (%)	26 (25.5)
Spontaneous rupture of membranes, n (%)	47 (46.0)
Episiotomy, n (%)	7 (6.9)
Perineal laceration with vaginal delivery, n (%)	66 (64.7)
GBS+ and received antibiotics, n (%)	33 (32.4)
Total IV fluids (mL)	
Mean \pm SD	1094.6 \pm 892.1
Range	0–3900
Type of delivery	
Forceps	0 (0)
Vacuum	1 (1)

GBS+ = positive for group B streptococcus; IV = intravenous; SD = standard deviation.

Characteristics of the neonates are given for the overall study population in Table 6.

Table 6. Neonatal Characteristics in the Overall Study Population (n = 102)

Variable	Value
Gestational age (weeks)	
Mean \pm SD	39.7 \pm 0.9
Range	37–41
Apgar score	
1 min	
Mean \pm SD	8.83 \pm 0.37
Range	8–9
5 min	
Mean \pm SD	8.98 \pm 0.14
Range	8–9
Meconium stained, n (%)	16 (15.7)
Baby suctioned, n (%)	39 (38)
Sex of neonate, n (%)	
Male	50 (49)
Female	52 (51)
Baby weight at birth (kg)	
Mean \pm SD	3.4 \pm 0.48
Range	2.67–4.80
Baby weight change in 24 hours (%)	
Mean \pm SD	-4.52 \pm 2.28
Range	-9.98 to 2.64

SD = standard deviation.

Comparisons of Participant Characteristics Across Study Groups

The unmedicated control and epidural groups were compared regarding demographic characteristics, obstetric history, labor variables, and neonatal characteristics. No significant differences were observed regarding age, race, weight, height, BMI, gravidity, or parity (Table 7).

Table 7. Demographic Characteristics and Obstetric History by Study Group

	Unmedicated (n=51)	Epidural(n=51)	<i>p</i> ^a
Age, mean \pm SD	32.5 \pm 4.3	32.6 \pm 5.2	0.82
Race, n (%)			
Hispanic/African American/Asian	16 (31.4)	20 (39.2)	0.27
White	35 (68.6)	31 (60.8)	0.27
Maternal weight (kg), mean \pm SD	79.2 \pm 12.6	79.8 \pm 16.3	0.82
Maternal height (cm), mean \pm SD	163.3 \pm 6.4	162.8 \pm 6.4	0.88
BMI, mean \pm SD	29.4 \pm 3.8	29.7 \pm 5.1	0.67
Number of pregnancies, mean \pm SD	2.71 \pm 0.78	2.82 \pm 0.88	0.48
Number of births, mean \pm SD	1.51 \pm 0.70	1.37 \pm 0.60	0.29

BMI = body mass index; SD = standard deviation

^aMeans were compared with a *t* test, and frequencies were compared with a chi-square or Fisher exact test.

As shown in Table 8 below, the duration of the 2nd stage of labor ($p = 0.001$) and duration of the entire labor process (the sum of duration of the 2nd and 3rd stages; $p < 0.001$) were significantly longer in the epidural group than in the unmedicated group. The percentage of women receiving oxytocin ($p = 0.002$), proportion of women with induced labor ($p = 0.003$), and total amount of IV fluids (lactated Ringer's solution) administered ($p < 0.001$) were also significantly greater in the epidural group than in the unmedicated group. No significant differences between the groups were observed regarding duration of the 3rd stage of labor ($p = 0.28$), percentage of mothers with spontaneous rupture of membranes ($p = 0.43$), or degree of laceration ($p = 0.35$).

Four of the 51 women in the epidural group and none of the women in the unmedicated group required corrective action for hypotension. There were no instances of fever, fetal bradycardia, or decreased fetal heart rate variability in either group.

Table 8. Labor Characteristics by Study Group

	Unmedicated (n=51)	Epidural (n=51)	<i>p</i> ^a
Duration of labor (min)			
2nd stage	13.35 ± 12.5	27.12 ± 20.9	0.001
3rd stage	6.51 ± 4.12	7.63 ± 6.05	0.28
Total	19.86 ± 13.79	34.75 ± 21.35	<0.001
Oxytocin, n (%)	11 (22.9)	24 (47.1)	0.002
Induced, n (%)	6 (11.8)	20 (39.2)	0.003
Rupture of membranes, n (%)			0.43
Spontaneous rupture of membranes	26 (51.0)	21 (41.2)	
Artificial rupture of membranes	25 (49.0)	30 (58.8)	
Degree of laceration, n (%)			0.35
0	15 (29.4)	21 (41.2)	
1	17 (33.3)	17 (33.3)	
2 or 3	19 (37.3)	13 (25.5)	
GBS positive, n (%)	18 (35.3)	15 (29.4)	0.67
Total IV fluids (mL), mean ± SD	576 ± 704	1612 ± 750	<0.001

GBS = group B streptococcus. IV = intravenous; SD = standard deviation.

^aMeans were compared with a *t* test, and frequencies were compared with a chi-square or Fisher exact test.

Characteristics of the 51 neonates born to mothers who received epidural analgesia and the 51 neonates born to mothers who had no analgesia are shown in Table 9. The groups were not significantly different regarding birth weight, gestational age, Apgar scores at 1 and 5 minutes, meconium, suction at birth, sex and weight of the baby, or percent weight loss at 48 hours postpartum.

Table 9. Neonatal Characteristics by Study Group

	Unmedicated (n = 51)	Epidural (n = 51)	<i>p</i> ^a
Baby			
Gestational age, mean \pm SD	39.7 \pm 0.8	39.6 \pm 1.0	0.54
Apgar score			
1 min	8.9 \pm 0.35	8.0 \pm 0.40	0.43
5 min	9.0 \pm 0.14	9.0 \pm 0.14	>0.99
Meconium stained, n (%)	8 (15.7)	8 (15.7)	>0.99
Baby suctioned, n (%)	15 (29.4)	24 (47.1)	0.10
Sex of neonate, n (%)			0.55
Male	27 (52.9)	23 (45.1)	
Female	24 (47.1)	28 (54.9)	
Baby weight at birth (kg)	3.44 \pm 0.71	3.33 \pm 0.26	0.065
Baby weight change in 24 hours (%), mean \pm SD	-4.61 \pm 2.14	-4.44 \pm 2.42	0.71

^aMeans were compared with a *t* test, and frequencies were compared with a chi-square or Fisher exact test.

Epidural Medications

Cervical dilation at the time of epidural placement in the epidural group ranged from 3 to 9 cm (Table 10). All women in the epidural group received a continuous infusion of bupivacaine 0.05% with hydromorphone 3 μ g/mL at a rate of 14 mL/h. In addition to the continuous infusion, two types of local anesthetics were administered: bupivacaine 0.25% with epinephrine at a ratio of 1:200,000 (n = 49) and lidocaine 1.5% with epinephrine at a ratio of 1:200,000. Forty-four subjects received both lidocaine and bupivacaine, five subjects received bupivacaine only, and two subjects received lidocaine only. The total volumes are shown in Table 10. Fifteen of the 51 epidural subjects (29.4%) required an additional bolus of bupivacaine 0.25% with epinephrine 1:200,000 during labor for breakthrough pain.

Table 10. Extent of Dilation at the Time of Epidural Placement, Total Amount of Epidural Infusate, and Local Anesthetic Dose (Lidocaine or Bupivacaine)

Name	n	Mean	SD	Range
Extent of dilation at epidural placement	51	5.2	1.34	3–9
Total epidural infusate (bupivacaine/hydromorphone), mL	51	56.38	39.96	0–170
Local lidocaine and/or bupivacaine, mL				
Lidocaine 1.5% ^a	46	3.4	0.92	3–6
Bupivacaine 0.25% ^a	49	7.3	1.78	3–11

SD = standard deviation

^aWith epinephrine at a ratio of 1:200,000.**Hypothesis 1: Effects of Epidural Analgesia on Breastfeeding**

The primary hypothesis was that healthy term infants of mothers who receive epidural analgesia with hydromorphone would exhibit less effective breastfeeding behaviors at 3, 12, and 24 hours of age when compared with infants whose mothers received no analgesia. The likely differences would correspond to the neonates' ability to maintain an active awake state, latch on to the breast, and coordinate the suck-breath-swallow actions necessary to remove milk from the breast.

LATCH Assessment Tool

To test the hypothesis, breastfeeding behaviors were observed at 3, 12, and 24 hours postpartum with the LATCH assessment tool. Repeated-measures ANOVA with independent *t* tests for pairwise comparisons at each time point were performed for unadjusted scores on the total LATCH score and individual LATCH subscales. Unadjusted total LATCH scores did not differ between the unmedicated and epidural groups at any of the time points, $F(1.712, 171.15) = 0.28$, $p = 0.07$ (Table 11). Total scores tended to increase over time in both groups (Figure 2).

Table 11. Total LATCH Scores by Group at 3, 12, and 24 Hours Postpartum

	Unmedicated	Epidural	Epidural vs Unmedicated		
	(n = 51) Mean \pm SD	(n = 51) Mean \pm SD	Mean difference	95% CI	<i>p</i> ^a
First breastfeeding (3 h)	8.35 \pm 1.31	8.47 \pm 1.34	0.12	-0.48 to 0.71	0.65
Second breastfeeding (12 h)	8.94 \pm 1.06	8.90 \pm 1.06	-0.04	-0.52 to 0.44	0.85
Third breastfeeding (24 h)	9.22 \pm 0.86	9.18 \pm 0.84	-0.04	-0.42 to 0.34	0.81

CI = confidence interval.

^aRepeated-measures ANOVA with independent *t* tests for pairwise comparisons.

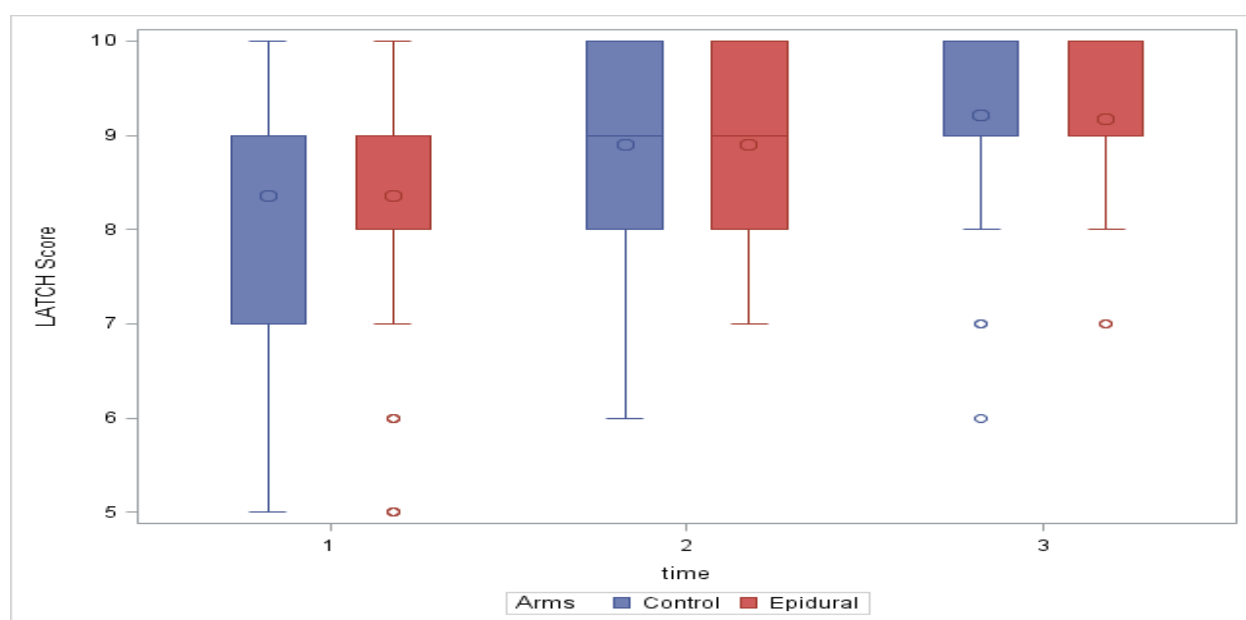


Figure 2. Total LATCH Scores in Unmedicated (Control) and Epidural Groups at Each Time Point (1 = 3 h; 2 = 12 h; 3 = 24 h)

The numbers and percentages of women in each group with total LATCH scores >7 also did not differ between groups at any of the time points (Table 12).

Table 12. Proportion of Women With Total LATCH Scores >7

	Unmedicated (n = 51)		Epidural (n = 51)		<i>p</i> ^a
	n	(%)	n	(%)	
First breastfeeding (3 h)	39	(76.5)	37	(72.5)	0.65
Second breastfeeding (12 h)	42	(82.4)	45	(88.2)	0.40
Third breastfeeding (24 h)	49	(96.1)	48	(94.1)	0.65
^a χ^2 -test					

As shown in Table 13 below, LATCH subscale scores did not differ significantly between groups at any of the time points.

Table 13. LATCH Subscale Scores by Group for Breastfeeding Behaviors at 3, 12, and 24 Hours Postpartum

Breastfeeding session	Unmedicated (n = 51)	Epidural (n = 51)	Epidural vs Unmedicated		
Breastfeeding level	Mean \pm SD	Mean \pm SD	Mean difference	95%CI	<i>p</i> ^a
First breastfeeding (3 h)					
L ¹	1.71 \pm 0.50	1.78 \pm 0.46	0.08	-0.11 to 0.27	0.36
A ¹	1.24 \pm 0.62	1.45 \pm 0.70	0.22	-0.04 to 0.48	0.06
T ¹	2.00 \pm 0.00	1.98 \pm 0.14	-0.02	-0.06 to 0.02	0.32
C ¹	1.92 \pm 0.27	1.90 \pm 0.30	-0.02	-0.13 to 0.09	0.73
H ¹	1.50 \pm 0.61	1.33 \pm 0.59	-0.16	-0.39 to 0.08	0.15
Second breastfeeding (12 h)					
L2	1.88 \pm 0.32	1.86 \pm 0.35	-0.02	-0.15 to 0.11	0.77
A2	1.55 \pm 0.58	1.57 \pm 0.54	0.02	-0.20 to 0.24	0.94
T2	2.00 \pm 0.00	1.98 \pm 0.14	-0.02	-0.06 to 0.20	0.32
C2	1.96 \pm 0.20	1.86 \pm 0.35	-0.10	-0.21 to 0.01	0.08
H2	1.55 \pm 0.58	1.63 \pm 0.50	0.08	-0.13 to 0.30	0.58
Third breastfeeding (24 h)					
L3	1.94 \pm 0.24	1.96 \pm 0.20	0.02	-0.07 to 0.10	0.65
A3	1.78 \pm 0.41	1.73 \pm 0.53	-0.06	-0.25 to 0.13	0.74
T3	2.00 \pm 0.00	2.00 \pm 0.00			>0.99
C3	1.82 \pm 0.38	1.84 \pm 0.367	0.02	-0.13 to 0.17	0.80
H3	1.67 \pm 0.48	1.67 \pm 0.47	0.00	-0.19 to 0.19	>0.99

L = infant's ability to latch onto the breast; A = audible sound of swallowing; T = maternal nipple type; C = comfort of the mother's breast and nipple; H = holding, i.e., amount of assistance the mother needs to hold the neonate.

^a Kruskal-Wallis test (all measures skewed).

The linear regression model was used to adjust the effects of epidural on the total LATCH score for the effects of labor duration, total amount of oxytocin used, total IV fluids (lactated Ringer's solution), and labor type (induction). After adjusting for these variables, we still did not find statistically significant differences in LATCH scores between the two groups at any time point (Table 14).

Table 14. Differences Between Neonates of Mothers With vs Those Without Epidural Analgesia in Total LATCH Scores Adjusted for Duration of Labor, Oxytocin Administration, Total IV Fluids, and Labor Type

Time	Epidural vs. Unmedicated		
	Difference	95% CI	<i>p</i> ^a
3 h	0.19	-0.37 to 0.74	0.51
12 h	0.19	-0.27 to 0.64	0.42
24 h	0.15	-0.22 to 0.52	0.43

CI = confidence interval.

^aMixed-effect model.

Thus, the data from the LATCH evaluation did not support the primary hypothesis that infants of mothers who receive epidural analgesia with hydromorphone would demonstrate less effective breastfeeding behaviors than infants of unmedicated mothers.

NACS Assessment

The study was originally designed to conduct the NACS and the LATCH together at 3, 12, and 24 hours after delivery. The exact times depended on the baby's hunger and willingness to feed. According to the developers of the NACS, the test can be performed on the neonate in any sleep state (Amiel-Tison et al., 1982b). However, the babies performed best when the test was performed 30 minutes before they were due to breastfeed. Thus, neonates would be observed for signs of waking approximately 2 hours before the assessments needed to be done. This was to

ensure the neonate could be tested when they were awake and not distressed. This became increasingly difficult to time and babies were being tested at different states of arousal, which altered specific items on the tool. If the babies were examined when they were crying, they would have low active and adaptive tone scores. If the babies were sleeping, their adaptive and active tone scores were also lower. The NACS was designed to be sensitive to the effects of narcotics on the neonate. Therefore, those specific categories were especially important (Amiel-Tison et al., 1982b). If the babies were distressed, they were permitted to feed, and the NACS would have to be done before the next feed. If the baby was sleeping, the parents became upset because they could not comfort the child or because the baby was awakened. If the LATCH was performed before the NAC, the infant would still be skin-to-skin with the mother after feeding, and the mothers did not want their babies tested at that time. To get the best results, it is recommended to wait at least 1 hour after feeding before conducting a neurobehavior exam on a neonate (Brazelton & Nugent, 2011). As part of the BFHI, it was also hospital policy to keep babies skin-to-skin with the mother as frequently and as long as possible. The NACS was therefore performed in only three patients (data not shown) and was then discontinued. Thus, only data from the LATCH breastfeeding observations are available for hypothesis testing.

Effects of Confounding Variables on Breastfeeding

Multivariable analyses were performed to assess the potentially confounding effects of other factors known to influence breastfeeding.

Maternal Demographic and Obstetric variables

Maternal demographic and obstetric variables, including maternal age, race, BMI, height, weight, gravidity, parity, and epidural placement were examined with total LATCH scores at 3, 12, and 24 hours using multiple linear regression to test whether any of these variables could

predict total LATCH score at the three time points (Table 15). Neither epidural placement nor maternal demographic/obstetric history variables showed an independent effect. Table 16 shows the R^2 , F, and p values as variables are added to the regression analysis. Statistical significance was achieved for the overall model tested at 12 and 24 hours. Together, these maternal demographic and obstetric variables contributed 20% of the variability in total LATCH scores in the model at 3 hours postpartum, 30% at 12 hours, and 30% at 24 hours. The total LATCH score at the first feeding (3 hours postpartum) was the only variable that significantly contributed to the total LATCH score at the second feeding (12 hours postpartum) ($p = <0.001$), and the total LATCH score at the second feeding was the only variable that significantly contributed to the total LATCH score at the third feeding (24 hours postpartum) ($p = <0.001$). This indicates that the same infant improved their LATCH score between birth and 24 hours regardless of maternal demographic/obstetric factors and exposure to epidural analgesia medications.

Table 15. Summary of Multiple Linear Regression Analysis of the Effects of Maternal Demographic and Obstetric Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Total Sample (n = 102)

Variable	Total LATCH 3 h			Total LATCH 12 h			Total LATCH 24 h		
	B (SE)	<i>p</i>	β (95%CI)	B (SE)	<i>p</i>	β (95%CI)	B (SE)	<i>p</i>	β (95%CI)
Age	0.002 (0.028)	0.943	.007 (.053-.057)	0.019 (0.022)	0.403	.056 (-.026-.063)	-0.001 (0.018)	0.977	-.003 (-.036-.035)
Race	0.000 (0.003)	0.900	-.013 (-.007-.006)	0.000 (0.003)	0.870	-.017 (-.006-.005)	-0.002 (0.002)	0.292	-.107 (-.006-.002)
Maternal weight	-0.004 (0.004)	0.290	-.109 (-.013-.004)	-0.001 (0.003)	0.774	-.030 (-.008-.006)	-0.002 (0.003)	0.456	-.076 (-.007-.003)
Maternal height	0.097 (0.060)	0.106	.191 (-.021-.215)	0.039 (0.049)	0.427	.094 (-.058-.135)	-0.001 (0.039)	0.978	-.003 (-.078-.076)
BMI	-0.083 (0.126)	0.511	-.285 (-.333-.167)	-0.004 (0.103)	0.969	-.017 (-.208-.200)	-0.009 (0.082)	0.912	-.048 (-.172-.154)
Gravidity	0.158 (0.162)	0.333	.100 (-.164-.480)	0.035 (0.133)	0.794	.028 (-.229-.299)	-0.078 (0.106)	0.460	.007 (-.288-.131)
Parity	-0.059 (0.253)	0.816	-.029 (-.562-.444)	0.208 (0.207)	0.318	.128 (-.203-.619)	0.091 (0.165)	0.071	.071 (-.236-.419)
Epidural placed	-0.022 (0.268)	0.935	-.009 (-.554-.511)	-0.004 (0.219)	0.987	-.002 (-.439-.431)	-0.085 (0.174)	0.626	-.052 (-.432-.261)
Total LATCH 3h	Constant			0.251 (0.070)	< 0.001	.312 (.112-.390)	0.161 (0.066)	0.016	.250 (.030-.291)
Total LATCH 12 h	0.515 (0.116)	<0.001	.415 (.285-.745)	Constant			0.425 (0.070)	<0.001	.533 (.285-.564)
Total LATCH 24 h	0.381 (0.155)	0.016	.244 (.071-.688)	0.670 (0.111)	<0.001	.534 (.450-.890)	Constant		

Table 16. R², F, and Probability for Regression Analysis of Maternal Demographic and Obstetric Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Total Sample (n = 102)

	Total LATCH 3 h			Total LATCH 12 h			Total LATCH 24 h		
	R ²	F	<i>p</i>	R ²	F	<i>p</i>	R ²	F	<i>p</i>
Age	0.000	0.005	0.943	0.007	0.704	0.403	0.000	0.001	0.977
Race	0.000	0.011	0.990	0.007	0.362	0.697	0.011	0.562	0.572
Maternal weight	0.012	0.385	0.764	0.008	0.267	0.849	0.017	0.560	0.643
Maternal height	0.038	0.960	0.433	0.015	0.358	0.838	0.017	0.416	0.797
BMI	0.042	0.851	0.517	0.015	0.284	0.921	0.017	0.332	0.893
Gravity	0.052	0.866	0.523	0.015	0.246	0.960	0.023	0.367	0.898
Parity	0.052	0.743	0.636	0.026	0.355	0.926	0.026	0.356	0.925
Epidural placed	0.052	0.644	0.739	0.026	0.307	0.962	0.028	0.339	0.949
Total LATCH 3h	Constant			0.389	5.800	< 0.001	0.088	0.982	0.460
Total LATCH 12h	0.220	2.881	0.005	Constant			0.305	4.479	<0.001
Total LATCH 24h	0.110	1.268	0.460	0.303	4.441	<0.001	Constant		
Model			0.265			<0.001			<0.001

Neonatal Variables

Multiple linear regression analysis was also performed to assess neonatal variables shown in the literature to be predictive of breastfeeding behaviors, including Apgar scores at 1 and 5 minutes, baby weight at birth, weight change during the first 24 hours, sex of neonate, meconium stain, and whether the baby was suctioned after delivery (Table 17). None of the neonatal factors had a significant effect on total LATCH scores at 3, 12, or 24 hours. Altogether, these variables accounted for less than 10% of the variability in LATCH scores in the model at 3, 12, and 24 hours (Table 18).

Table 17. Summary of Multiple Linear Regression Analysis for Neonatal Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Total Sample (n = 102)

Variable	Total LATCH 3 h			Total LATCH 12 h			Total LATCH 24 h		
	B (SE)	<i>p</i>	β (95%CI)	B (SE)	<i>p</i>	β (95%CI)	B (SE)	<i>p</i>	β (95%CI)
Apgar score 1 min	-0.303 (0.375)	0.422	.375 (-1.048-.443)	0.418 (0.310)	0.181	.148 (-.198-1.033)	0.084 (0.243)	0.729	-.037 (-.567-.399)
Apgar score 5 min	1.135 (1.009)	0.263	.121 (-.868-3.139)	0.599 (0.834)	0.474	.079 (-1.056-2.255)	1.282 (0.654)	0.053	.212 (-.016-2.581)
Baby weight at birth	-0.118 (0.134)	0.381	-.090 (-.384-.148)	0.027 (0.111)	0.807	.026 (-.193-.247)	-0.056 (0.087)	0.522	-.066 (-.228-.117)
% of baby weight change in 24 hours,	0.062 (0.059)	0.293	.108 (-.054-.178)	0.010 (0.048)	0.830	.023 (-.086-.107)	0.025 (0.038)	0.505	.069 (-.050-.101)
Meconium stained	0.561 (0.290)	0.138	.157 (-.184-1.306)	-0.227 (0.310)	0.466	-.079 (-.843-.389)	0.015 (0.243)	0.952	.006 (-.468-.497)
Sex of neonate	0.108 (0.269)	0.690	.041 (-.427-.642)	0.027 (0.223)	0.905	.013 (-.416--.469)	-0.083 (0.174)	0.635	-.049 (-.429-.263)
Baby suctioned	0.251 (0.290)	0.390	.093 (-.325-.827)	0.024 (0.240)	0.922	.011 (-.453-.500)	-0.090 (0.188)	0.633	-.052 (-.463-.283)

Table 18. R², F, and Probability for Regression Analysis of Neonatal Variables as Predictors of Total LATCH Scores at 3, 12, and 24 hours Postpartum: Total Sample (n = 102)

	Total LATCH 3 h			Total LATCH 12 h			Total LATCH 24 h		
	R ²	F	<i>p</i>	R ²	F	<i>p</i>	R ²	F	<i>p</i>
Apgar score 1 min	0.000	0.040	0.422	0.028	2.846	0.181	0.000	0.011	0.729
Apgar score 5 min	0.028	1.450	0.263	0.033	1.704	0.474	0.044	2.258	0.053
Baby weight at birth	0.031	1.044	0.381	0.033	1.124	0.807	0.050	1.731	0.522
% of baby weight change in 24 hours	0.044	1.120	0.293	0.034	0.843	0.830	0.055	1.416	0.505
Meconium stained	0.074	1.525	0.138	0.038	0.765	0.466	0.055	1.123	0.952
Sex of neonate	0.074	1.269	0.690	0.039	0.640	0.905	0.058	0.969	0.635
Baby suctioned	0.079	1.158	0.390	0.040	0.555	0.922	0.058	0.832	0.633
Model			0.334			0.790			0.563

Hypothesis 2: Effects of Extent of Epidural Drug Exposure on Breastfeeding Behaviors

The second hypothesis was that healthy term infants of mothers who receive epidural analgesia with hydromorphone would demonstrate less effective breastfeeding behaviors at 3, 12, and 24 hours of age in relation to the duration of infusion and amount of drug given to the mother. This hypothesis was based on the assumption that if exposure to the drug affects the neonate's muscle tone and reflexes, then breastfeeding behaviors such as the necessary facial tone to maintain latch-on would be worse with longer epidural infusions and greater amounts of infusate.

Examination of the dose relationship between epidural medication and LATCH score in the epidural group using the mixed-effect regression model did not show a significant effect for total amount of epidural infusate, total dose of lidocaine, or total dose of bupivacaine (Table 19). The degree of dilation at the time of placement of the epidural also did not significantly affect the LATCH score (Table 19). Thus, study findings did not support the hypothesis that healthy term infants born to mothers who received epidural analgesia would demonstrate less effective breastfeeding behaviors with greater exposure to epidural medications.

Table 19. Mixed-effect Regression Analysis of Effects of Total Epidural Infusate, Dose, and Extent of Dilation on Total LATCH Score (n = 51)

Name	Coefficient	95% CI	<i>p</i>
Total amount of epidural infusate	-0.039	-0.363 to -0.389	0.937
Total dose of lidocaine	0.116	-0.157 to 0.388	0.396
Total dose of bupivacaine	-0.026	-0.154 to 0.102	0.686
Degree of dilation at epidural placement	-0.033	-0.200 to 0.134	0.690

Furthermore, multiple linear regression analysis in a model comprising multiple interventions during labor also did not find significant relationships of these variables with total LATCH scores within the epidural group (see Table 24 under Hypothesis 3: Effects of Multiple Stressful Events or Interventions, below).

Hypothesis 3: Effects of Multiple Stressful Events or Interventions During Labor

The third hypothesis predicted that when multiple stressful events or interventions are present during labor or immediately after birth, healthy term infants would demonstrate less effective breastfeeding, whether or not labor analgesia was used. Such factors might include maternal factors, e.g., long duration of labor (2nd stage, 3rd stage, or total stage 2/3), large total amount of IV fluids administered, oxytocin administration, induction of labor, epidural placement, group B streptococcus positive status, and perineal laceration, or neonatal factors, e.g., meconium staining, baby suctioned, low Apgar score at 1 and/or 5 minutes, and neonatal weight loss. Multiple linear regression analyses of these explanatory variables were therefore performed with total LATCH score at 3, 12, and 24 hours as dependent variables tested individually in the model. These analyses were performed both for the entire patient collective (n = 102) and for the epidural group alone (n = 51).

Total Sample

Prior to the multiple regression analyses, Pearson's correlation coefficients were calculated to examine possible linear relationships between variables. The results of the correlation matrix for the entire patient collective are presented in Table 20.

Table 20. Correlation Matrix for Labor and Neonatal Variables and LATCH Scores in the Total Sample (n = 102)

	Duration Stage 2	Rupture membranes	Total IV fluids	Oxytoci n	Induction	Epidural placed	Total stage 2&3	Baby suctioned	Meconium	Apgar 1 min	Apgar 5 min	Weight loss (%)	3 h LATCH	12 h LATCH	24 h LATCH
Duration Stage 2															
Rupture of membranes	-0.027														
Total IV fluids	0.172	0.133													
Oxytocin	0.023	-0.254*	-0.401**												
Induction	-0.023	-0.315**	-0.301**	0.620**											
Epidural placed	-0.374**	-0.098	-0.584**	0.268**	0.315**										
Total Stage 2 & 3	0.964**	-0.012	0.199*	-0.009	0.061	-0.386**									
Baby suctioned	-0.074	-0.039	-0.116	0.069	0.003	0.182	-0.049								
Meconium	-0.048	-0.016	-0.103	-0.080	-0.131	-0.004	-0.059	0.269**							
Apgar 1 min	-0.041	0.009	-0.130	-0.046	0.040	0.079	-0.053	0.189	0.167						
Apgar 5 min	-0.110	0.011	-0.065	-0.102	-0.083	0.000	-0.144	0.180	0.133	0.316**					
Weight loss (%)	0.040	0.087	0.061	0.107	0.049	-0.037	0.043	0.075	0.017	-0.109	0.066				
3 h LATCH	-0.110	-0.055	-0.172	-0.041	-0.005	-0.045	-0.114	0.124	0.183	-0.020	0.153	0.137			
12 h LATCH	-0.086	-0.125	-0.042	0.025	-0.001	-0.019	-0.053	0.056	-0.037	0.166	0.124	0.007	0.421**		
24 h LATCH	-0.155	-0.135	-0.031	0.095	0.083	0.023	-0.169	-0.008	0.005	0.010	0.201*	0.096	0.239*	0.526**	

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

The results of multiple linear regression analysis of multiple events or interventions during labor are presented in Table 21 for the entire study population. The only significant effect was a negative effect at the first breastfeeding (3 hours postpartum) when the mother received high volumes of IV fluids (lactated Ringer's solution) ($p = 0.021$). Other labor and neonatal variables were not useful in predicting LATCH scores at 3, 12, or 24 hours postpartum. Table 22 shows the R^2 values as variables are added to the model. The largest R^2 value (0.083) was achieved at 24 hours (Table 22), indicating that the variability of LATCH scores accounted for by the labor and neonatal variables altogether was not more than approximately 8% at any of the three time points. Thus, study findings did not support the hypothesis that healthy term infants born to mothers with multiple stressful labor interventions or events demonstrate less effective breastfeeding, whether or not labor analgesia was used.

Table 21. Multiple Linear Regression Analysis of Labor Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Total Sample (n = 102)

Variable	Total LATCH 1 (3 h)			Total LATCH 2 (12 h)			Total LATCH 3 (24 h)		
	B (SE)	<i>p</i>	β (95% CI)	B (SE)	<i>p</i>	β (95% CI)	B (SE)	<i>p</i>	β (95% CI)
Duration of 2nd stage of labor	-0.008 (0.007)	0.272	-.110 (-.022-.006)	-0.005 (0.006)	0.387	-.086 (-.016-.006)	-0.007 (0.005)	0.051	-.155 (-.016-.002)
Duration of 3rd stage of labor	-0.008 (0.25)	0.759	-.031 (-.058-.043)	0.023 (0.020)	0.254	.114 (-.017-.064)	-0.012 (0.016)	0.454	-.075 (-.044-.020)
Duration of total labor	-0.008 (0.007)	0.279	-.008 (-.002-.006)	-0.005 (0.006)	0.365	-.095 (-.017-.006)	-0.007 (0.005)	0.127	-.160 (-.016-.002)
Induction	-0.037 (0.305)	0.904	-.012 (-.641-.568)	0.034 (0.244)	0.891	.014 (-.451-.519)	0.135 (0.194)	0.487	.070 (-.249-.519)
Rupture of membranes	-0.175 (0.279)	0.532	-.067 (-.728-.378)	-0.302 (0.222)	0.176	-.143 (-.743-.138)	-0.214 (0.176)	0.228	-.127 (-.563-.136)
Oxytocin	-0.173 (0.357)	0.629	-.063 (-.881-.535)	0.084 (0.284)	0.768	.038 (-.480-.648)	0.117 (0.225)	0.605	.066 (-.330-.564)
Epidural placed	-0.124 (0.290)	0.671	-.048 (-.700-.453)	-0.004 (0.232)	0.988	-.002 (-.463-.456)	-0.190 (0.183)	0.301	-.116 (-.552-.173)
GBS positive	-0.033 (0.289)	0.910	-.012 (-.608-.542)	-0.254 (0.229)	0.271	-.113 (-.710-.202)	-0.221 (0.181)	0.224	-.123 (-.580-.137)
Perineal laceration	0.022 (0.171)	0.896	.014 (-.318-.363)	-0.044 (0.136)	0.744	-.034 (-.314-.225)	0.084 (0.107)	0.433	.081 (-.128-.295)
Total IV fluids infused	0.000 (0.000)	0.021	-.304 (-.001-.000)	-5.891 (0.00)	0.706	-.051 (.000-.000)	-8.377 (0.000)	0.945	-.009 (.000-.000)

Table 22. R², F, and Probability for Regression Analysis of Labor Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Total Sample (n = 102)

Variable	Total LATCH 3 h			Total LATCH 12 h			Total LATCH 24 h		
	R ²	F	<i>p</i>	R ²	F	<i>p</i>	R ²	F	<i>p</i>
Duration of 2nd stage labor	0.012	1.222	0.272	0.007	0.753	0.387	0.024	2.456	0.120
Duration of 3rd stage labor	0.013	0.653	0.759	0.021	1.037	0.254	0.030	1.510	0.454
Duration of total labor	0.013	0.653	0.279	0.021	1.037	0.365	0.030	1.510	0.127
Induced	0.013	0.436	0.904	0.021	0.691	0.9891	0.034	1.164	0.487
Rupture of membranes	0.017	0.423	0.532	0.039	0.987	0.176	0.049	1.246	0.228
Oxytocin	0.020	0.383	0.629	0.040	0.800	0.768	0.052	1.043	0.605
Epidural placed	0.021	0.347	0.671	0.040	0.660	0.988	0.062	1.050	0.301
GBS positive	0.022	0.296	0.910	0.052	0.742	0.271	0.077	1.119	0.224
Perineal laceration	0.022	0.258	0.896	0.053	0.656	0.744	0.083	1.052	0.433
Total IV fluids infused	0.077	0.857	0.021	0.055	0.594	0.706	0.083	0.926	0.945
Model			0.566			0.799			0.507

Within the Epidural Group

Women who receive epidural analgesia may be even more likely than women without epidural analgesia to have multiple stressful interventions and events during labor or immediately postpartum (e.g., oxytocin administration, induction of labor, ruptured membranes, total IV fluids administered, longer long duration of labor, meconium staining, and need for baby suctioning), which might affect the neonates' breastfeeding behaviors. Therefore, a second multiple linear regression analysis of the effects of labor and neonatal variables was performed in the epidural group alone.

To examine possible linear relationships among labor and neonatal variables, Pearson correlation coefficients among variables were examined. The correlation matrix is presented in Table 23.

Table 23. Correlation Matrix for Labor Variables and LATCH Scores in the Epidural Group (n = 51)

	Duration S2	Rupture memb	Total IV	Oxytocin	Induction	Dilation	Total S2&3	1.5% lido	0.25% bupiv	Total epidural	Baby suction	Meconium	Apgar 1 min	Apgar 5 min	Wt loss (%)	3 h LATCH	12 h LATCH	24 h LATCH
Duration S2																		
Rupture memb	-0.082																	
Total IV	-0.097	0.097																
Oxytocin	0.182	-0.150	-0.182															
Induction	0.038	-0.263	0.104	0.530**														
Dilation	-0.228	-0.239	0.110	-0.040	-0.092													
Total S2&3	0.959**	-0.061	-0.074	0.154	0.051	-0.260												
1.5% lidocaine	0.130	-0.042	0.039	0.137	0.094	-0.026	0.086											
0.25% bupiv	-0.255	-0.047	0.051	-0.312*	-0.219	0.225	-0.189	-0.175										
Total epidural	0.165	0.091	0.150	-0.250	-0.346*	-0.290*	0.155	0.193	-0.220									
Baby suction	0.710	0.009	-0.116	0.056	0.018	-0.129	0.013	-0.025	-0.080	0.320*								
Meconium	-0.083	-0.032	-0.116	-0.083	-0.207	-0.209	-0.056	-0.005	0.134	-0.002	0.088							
Apgar 1 min	0.184	-0.012	-0.012	-0.070	0.089	-0.136	0.235	0.111	0.140	0.235	0.371	0.059						
Apgar 5 min	-0.067	0.169	-0.169	-0.133	-0.139	-0.296*	-0.115	-0.270	0.351*	0.038	0.263	0.328*	0.286*					
Wt loss (%)	0.064	0.115	0.047	0.233	0.152	0.018	0.086	0.568	0.017	0.258	-0.163	0.099	-0.099	-0.003				
3 h LATCH	-0.125	-0.033	-0.289*	-0.050	0.170	-0.096	-0.114	0.224	0.099	-0.091	0.038	0.193	-0.011	0.156	0.075			
12 h LATCH	-0.117	-0.078	-0.258	0.099	0.095	-0.110	-0.072	0.205	0.051	-0.183	-0.050	0.062	0.142	-0.148	-0.054	0.620**		
24 h LATCH	-0.253	0.082	-0.037	0.105	0.208	-0.020	-0.275	0.026	-0.111	-0.277	-0.129	0.091	-0.014	0.030	0.165	0.331*	0.467**	

Bupiv = bupivacaine; rupture memb = ruptured membrane; S2 = 2nd stage of labor; S2&3 = 2nd and 3rd stages of labor; total epidural = total epidural infusate; wt loss = neonatal weight loss.

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed)

The regression analysis for the epidural group is presented in Table 24. As in the total sample, only total IV fluids (lactated Ringer's solution) contributed significantly to model for the first LATCH session at 3 hours postpartum ($p = 0.012$). Thus, high volumes of IV fluids may lower the total LATCH score at 3 hours postpartum. No variable showed an independent significant effect on LATCH scores during the second or third breastfeeding session. Table 25 shows the R^2 values as variables are added to the model. Altogether, in women undergoing epidural analgesia, these variables contributed 30% of the variability in LATCH scores in the model at 3 hours and 15% at 12 hours, and 30 % at 24 hours. However, no statistical significance was achieved for the model.

Table 24. Multiple Linear Regression Analysis for Labor and Neonatal Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Epidural Group (n = 51)

Variable	Total LATCH 3 h			Total LATCH 12 h			Total LATCH 24 h		
	B (SE)	<i>p</i>	β (95%CI)	B (SE)	<i>p</i>	β (95%CI)	B (SE)	<i>p</i>	β (95%CI)
Oxytocin	-0.134 (0.381)	0.726	-.050 (-.900-.632)	0.208 (0.300)	0.490	-.011 (-.394-.811)	0.176 (0.237)	0.742	.105 (-.301-.653)
Induction	0.611 (0.413)	0.145	-.229 (-.219-1.440)	0.138 (0.331)	0.679	.065 (-.528-.804)	0.330 (0.258)	0.208	.198 (-.189-.849)
Total epidural infusate	-0.001 (0.005)	0.811	-.036 (-.011-.009)	-0.003 (0.004)	0.513	-.1099 (-.011-.005)	-0.005 (0.003)	0.118	-.230 (-.011-.001)
Rupture of membranes	0.014 (0.405)	0.972	.005 (-.800-.829)	-0.116 (0.323)	0.722	-.054 (-.766-.535)	0.248 (0.244)	0.314	.147 (-.243-.740)
Total IV fluids	-0.001 (0.000)	0.012	-.373 (-.001-.000)	0.000 (0.000)	0.091	-.260 (-.001-.000)	-5.351 (0.000)	0.748	-.048 (.000-.000)
Extent of dilation	-0.056 (0.157)	0.722	-.056 (-.372-.259)	-0.092 (0.129)	0.482	-.115 (-.352-.169)	-0.088 (0.100)	0.385	-.140 (-.291-.114)
Total stage 2 & 3	-0.009 (0.009)	0.327	-.144 (-.028-.009)	-0.006 (0.008)	0.451	-.116 (-.021-.010)	-0.011 (0.006)	0.054	-.287 (-.023-.000)
Meconium	0.735 (0.534)	0.176	.200 (-.343-1.812)	0.053 (0.453)	0.907	.018 (-.860-.967)	0.193 (0.337)	0.569	.084 (-.487-.873)
Baby suctioned	-0.225 (0.421)	0.597	-.084 (-1.075--.626)	-0.195 (0.357)	0.587	-.093 (-.916-.526)	-0.232 (0.264)	0.384	-.139 (-.766-.301)
1.5% lidocaine	0.421 (0.226)	0.072	.290 (-.040-.881)	0.295 (0.196)	0.142	.258 (-.104-.694)	0.089 (0.157)	0.572	.092 (-.229-.408)
0.25% bupivacaine	0.137 (0.150)	0.370	.181 (-.170-.444)	0.065 (0.134)	0.632	.106 (-.208-.338)	-0.135 (0.102)	0.196	-.264 (-.345-.074)

Table 25. R², F, and Probability for Regression analysis of Labor and Neonatal Variables as Predictors of Total LATCH Scores at 3, 12, and 24 Hours Postpartum: Epidural Group (n = 51)

Variable	Total LATCH 1 (3 h)			Total LATCH 2 (12 h)			Total LATCH 3 (24 h)		
	R ²	F	<i>p</i>	R ²	F	<i>p</i>	R ²	F	<i>p</i>
Oxytocin	0.003	0.124	0.726	0.010	0.483	0.490	0.011	0.550	0.462
Induction	0.046	1.159	0.145	0.013	0.324	0.679	0.044	1.094	0.208
Total epidural infusate	0.047	0.777	0.811	0.022	0.358	0.513	0.093	1.597	0.118
Rupture of membranes	0.047	0.571	0.972	0.025	0.296	0.722	0.113	1.458	0.314
Total IV fluids	0.172	1.873	0.012	0.086	0.845	0.091	0.115	1.165	0.748
Extent of dilation	0.175	1.552	0.722	0.096	0.780	0.482	0.130	1.094	0.385
Total stage 2 & 3	0.193	1.470	0.327	0.108	0.745	0.451	0.206	1.592	0.054
Meconium	0.228	1.550	0.176	0.108	0.638	0.907	0.212	1.412	0.569
Baby suctioned	0.233	1.386	0.597	0.115	0.591	0.587	0.227	1.334	0.384
1.5% lidocaine	0.305	1.448	0.072	0.157	0.616	0.142	0.260	1.157	0.572
0.25% bupivacaine	0.305	1.195	0.370	0.146	0.465	0.632	0.297	1.152	0.196
Model			0.332			0.910			0.359

Summary of the Study Results

Breastfeeding behaviors measured with the LATCH Breastfeeding Assessment Tool did not differ significantly between the groups at any of the three time points studied (3, 12, and 24 hours after birth) and were not related to total amount of drugs administered. The presence of multiple stressful events and interventions during labor, e.g., duration of labor, large amount of IV fluids, oxytocin administration, induction of labor, and meconium staining/suctioning of the baby, did not significantly affect breastfeeding behavior in the overall study population ($n = 102$), altogether contributing not more than 8% of the variability of LATCH scores in the regression model. Within the group receiving epidural analgesia ($n = 51$), which had significantly longer duration of labor, higher rates of oxytocin administration and induction of labor, and larger amounts of IV fluid administration, the combination of these factors contributed about 30% of the variability of LATCH scores in the regression model at 3 and 24 hours. However, the model was not significant in this group. These results are discussed in Chapter 5.

Chapter 5: Discussion

This chapter discusses the results of the study in relation to the theoretical framework of neonatal breastfeeding behaviors, and the findings are compared to similar research studies in the scientific literature. The strengths and limitations of the study and implications for clinical practice are described, and recommendations for continued research are given.

The current study assessed breastfeeding behaviors in the first 24 hours postpartum in neonates whose mothers used epidural analgesia with hydromorphone for labor and delivery compared with neonates whose mothers used no analgesia. The primary hypothesis of the study was that healthy term infants of mothers who receive epidural analgesia with hydromorphone would demonstrate less effective breastfeeding behaviors at 3, 12, and 24 hours of age when compared with infants whose mothers received no analgesia. The findings did not support this hypothesis. Assessment of breastfeeding behaviors with the LATCH Breastfeeding Assessment Tool (D. Jensen et al., 1994) showed no significant differences at any time point in breastfeeding behaviors between neonates born to mothers who used epidural analgesia containing hydromorphone and neonates whose mothers used no analgesia for labor. With a total sample size of 102, the study had the power to detect a medium effect size if a true effect existed.

The second hypothesis—that effectiveness of breastfeeding would be related to the duration of infusion/amount of drug given—was also not supported. Regression analyses showed no significant effects of total amount of epidural infusate, total dose of lidocaine, total dose of bupivacaine, or degree of dilation at the time of placement of the epidural.

The third hypothesis—that the presence of multiple stressful events or interventions during labor or immediately after birth (e.g., duration of labor, large amount of IV fluids, oxytocin administration, induction of labor, and meconium staining/suctioning of the baby) would be related to less effective breastfeeding, whether or not labor analgesia was used—was also not supported. The only significant variable was administration of a large amount of IV fluids (lactated Ringer’s solution). Taken together, these variables accounted for no more than approximately 8% of the variability in LATCH scores in the overall study population ($n = 102$), and the model was not significant. This sample size was large enough to have an 80% chance of detecting a true difference if it had existed.

Mothers who chose to receive epidural analgesia ($n = 51$) had significantly longer duration of labor, higher rates of oxytocin administration, induction of labor, and larger amounts of IV fluid administration compared to those who did not choose to have analgesia. Within the epidural group, the combination of stressful factors contributed about 30% of the variability of LATCH scores in the regression model at 3 and 24 hours, suggesting that having an epidural and then also needing multiple labor interventions may indeed have a negative effect on breastfeeding. However, this effect was not significant, and the sample size of 51 was too small to have the power to detect a true effect of this size if it did exist. Therefore, no conclusion can be drawn.

These data indicate that, by itself, epidural analgesia with hydromorphone has no effect on breastfeeding behaviors as measured during the first 24 hours after birth by the LATCH assessment tool, at least in this population of healthy term neonates born in a hospital environment strongly supportive of breastfeeding.

Comparison with Results Reported in the Literature

As discussed in Chapter 2, review of published reports of empirical studies specific to labor epidural analgesia and breastfeeding (French et al., in press) found conflicting results: 11 studies found that epidural analgesia was not implicated in adverse breastfeeding outcomes (10 found no effect and 1 found a positive effect), and 12 studies showed negative associations between epidural analgesia and breastfeeding success. Comparison of the current study with these published studies is difficult because of methodological differences, including differences in study design. Only three were randomized, some were prospective cohort studies, as was the current study, and some were retrospective surveys. The type and dosage of epidural drug used also varied. No study used hydromorphone as the epidural opioid. Most used fentanyl or did not give information on the opiate used. The studies also varied widely in timing and techniques for measuring breastfeeding success. Only a few studies reported using any kind of standardized breastfeeding instrument (Baumgardner, Muehl, Fischer, & Pribbenow, 2003a; Beilin et al., 2005; Chang & Heaman, 2005; Radzysinski, 2003; J. Riordan et al., 2000), and only three of these used the LATCH tool to assess breastfeeding behaviors. Two found negative effects of the epidural analgesia on LATCH scores (Baumgardner et al., 2003b; J. Riordan et al., 2000), and one found no effect (Chang & Heaman, 2005). All three of these studies performed at least one assessment during the first 24 hours after birth, and all three were prospective cohort studies.

Potential Influences on the Study Results

Furthermore, the following factors need to be considered:

- It is possible that the LATCH assessment tool was not sensitive enough to detect subtle differences in breastfeeding behavior due to epidural analgesia.

- The type of epidural medications used in this study (ultralow-dose bupivacaine and hydromorphone) may have provided such a low amount of drug exposure to the neonate that any effects of the medication may have been too small to detect.
- The study was not randomized, and factors that may play a role in determining breastfeeding behaviors were different in each group.
- The breastfeeding support provided by the hospital's BFHI environment may have helped to overcome potential negative effects of the epidural medications.

Usefulness of Breastfeeding Assessment Tools in Detecting Effects of Epidural

Analgesia

LATCH Breastfeeding Assessment

The LATCH breastfeeding tool was chosen because it reflects aspects of the individual neonate's feeding activities as well as maternal variables that are used to predict breastfeeding problems. High interrater reliability (85.7-100%) was found among lactation consultants using the tool (Adams & Hewell, 1997). Significant correlation between mother's ratings of how well she thought breastfeeding went (0 = not at all well to 3 = very well) and the evaluators' LATCH scores ($n = 132$, $r = 0.56$, $p = 0.001$) supported the construct validity of the tool (J. Riordan et al., 2001). In two studies (S. P. Kumar, Mooney, Wieser, & Havstad, 2006; J. Riordan et al., 2001), LATCH scores were predictive of breastfeeding duration up to 6 weeks. Both studies found higher LATCH scores for those who were still breastfeeding at 6 weeks compared with those who weaned before 6 weeks.

The LATCH scoring system was a relatively easy data collection tool to use for this study, and easy to score, with clear criteria for each category of breastfeeding. It was observational and well tolerated by the mothers. Many of the women liked being in the study because they got

instant feedback on how well the neonate was feeding. Also, many liked the extra attention they were getting from the data collectors. This brought into question whether the presence of the data collector had any effect on the breastfeeding session. The system gave the caregiver key components of maternal and neonatal variables of effective breastfeeding behaviors and defined areas where intervention may be needed. The tool was defined to pick up abnormalities. When the observer in the room provided positive feedback, the mothers felt they were successful. Even neonates that breastfed poorly were able perform key components of an effective breastfeeding session, which were interpreted as positive feedback by the mother. This was part of the purpose of developing the instrument (D. Jensen et al., 1994).

The LATCH score is based on observations by the data collectors and is subject to their interpretation. The score is dependent on the ability of the researcher to use the instrument. Subjectivity and bias can occur with instruments that rely on observation methods (Polit & Beck, 2012). Observer bias was minimized by keeping the data collectors (or the PI and the lactation consultant) blinded to the participants' use or non-use of epidural analgesia. Both the PI and the lactation consultant had extensive training in using the LATCH tool.

There were some factors the LATCH tool did not assess that would have been helpful during the breastfeeding sessions. Attitudes and opinions of the mother related to frequency of feeding and who initiated or ended the feed—mother, baby, or possibly staff. All the mothers had breastfed previously and had predetermined from their experience the patterned frequency of feeding. When neonates were feeding well at the breast, many mothers would stop the feed, determining they had had enough milk or stop and ask for formula because they thought the baby wasn't getting enough milk. Information was given to mothers about infant feeding cues and baby-led feeding was optimal for the development of a mother/neonate feeding dyad. Because

the amount of milk being consumed by the infant can't be seen or measured, extra reassurance should be provided to these mothers. The attitudes of the mother and her perception of the breastfeeding experience contribute to the success of breastfeeding. A simple addition to the LATCH such as to how often the baby is fed or who initiates the feeding would add to the body of knowledge.

It is important to note that during the first 24 hours of life a considerable number of neonates do not have a good latch or audible swallow, with several bursts of sucking preceding the swallow. The LATCH tool was designed to detect these differences in a neonate <24 hours old and therefore provided a mechanism to analyze the coordination of the suck-swallow cycle, which is so important when assessing breastfeeding behaviors. Items also included whether the infant was not able to latch, needed help with latch, or latched, or whether there were no audible swallows, a few audible swallows with stimulation, or spontaneous and intermittent swallows. The criteria for scoring were clear. The scores defined the breastfeeding behaviors and were useful in data interpretation. Although the LATCH lacked some measures that may have been helpful, and although it depended on the researcher's ability to observe and use the instrument correctly, it was sensitive enough to detect differences between neonates. Thus, it proved to be a useful way to measure which neonates were able to exhibit successful breastfeeding behaviors in this study.

As described in Chapter 4, the original study plan was to conduct the NACS and the LATCH together at the 3, 12 and 24 hours after delivery, but the test was discontinued because of difficulties in finding appropriate times when the neonates would be in equivalent states of arousal and when it could be performed without disturbing the neonate's sleep or distressing the mother. There were also occasional difficulties in scheduling the LATCH test. During the first 24

hours of life, many neonates may be slow to feed and may have a long period of sleep after they are born (Holmes, 2013). All of the infants in this study were healthy and breastfed vigorously within 40 minutes of delivery. They would then sleep for hours, making it very difficult to get the first LATCH score at the 3-hour time point. Nevertheless, we were able to perform three LATCH breastfeeding assessments of all neonates in a 24 hour period.

Assessment of Neonatal Neurobehavior

It is well known that term infants are born with the reflexes such as rooting, sucking, and swallowing which are necessary for feeding. In order for the neonate to feed the behavioral states are also important in facilitating the reciprocal communication and relation with the mother during feeding. For assessment purposes there are predictable patterns of behavior in neonatal cranial nerve function and maturation as well as reflexes (Als, 1991). Cranial nerve function and maturation are required for the neonate to breastfeed, especially the cranial nerves V, VII, IX, X, XI, and XII. It therefore would seem logical that if some factor such as analgesia depresses the functioning of one of these cranial nerves, it would result in an altered corresponding feeding behavior associated with that nerve. Effective and efficient feeding requires the neonate to be in an awake state (the psychomotor ability to cue they are ready to feed) must have enough oropharyngeal muscle strength (tone) to latch onto the breast and maintain the breast in the mouth, create enough oral pressure to form a maternal teat and maintain the muscle tone to elevate the tongue to massage the alveolar ducts and rhythmically coordination of breathing with sucking and swallowing which involves the functional interaction of lips, jaw, palate, tongue, larynx, pharynx and esophagus (Bu'Lock et al., 1990). To accomplish this, the neonate has to have intact function of their cerebral and brainstem structures and 6 of the 12 cranial nerves (V,

VII, IX, X, XI, and XII). These nerves are involved in the muscle tone of the face, structures of the mouth, swallowing and breathing.

For the infant to latch onto the breast the infant must be able to respond to the environment in an organized alert state. The more an infant that can regulate and manage their state the more alert the neonate is. Awake and alert infants are able to latch onto the breast and maintain their latch; thus, the better they will feed. Cranial nerve V, the trigeminal nerve, and cranial nerve VII, the facial nerve, are necessary for the neonate to open its mouth, move its lips to the breast, and create suction with the tongue and soft palate involved in rooting, latching, and sucking responses. Cranial XI, the gloss pharyngeal nerve controls the gag reflex. Suctioning a neonate may cause hyper responsive gagging which in turn can inhibit deep latch at the breast. Cranial nerve X, the Vagus nerve allows for flexion and extension of the head, neck, and extremities. It also controls breathing and heart function, therefore disruption of this nerve could interfere with the suck-swallow-breath coordination. If the neonate cannot flexion their neck they will not be able to latch on. Cranial nerve XI, the spinal accessory nerve controls muscles involved in head position, torticollis, and airway patency. An active tone of these muscles allows the neonate to move their head and maintain spatial relation to the body and other objects (Amiel-Tison, 1976). Absence of active tone would mean the neonate could not lift their head or move their head toward the breast. Once the neonate is attached to the breast, Active tone allows the neonate to maintain the attachment without their head falling forward breaking the suction.

Cranial nerve XII, the hypoglossal nerve controls tongue movements that produce sequential, smooth contractions of the voluntary and involuntary muscles of the tongue. Disruption of this nerve manifests as nonsequential, erratic, and weak tongue movements which interfere with normal sucking and swallowing and milk intake.

The information provided by the LATCH Breastfeeding Assessment Tool in relation to neurobehaviors involved in breastfeeding was clinically useful for the purposes of this study. The breastfeeding behaviors involved in the infants ability to breastfeed correlate with tests of passive tone, adaptive responses and primary reflexes on the NACS neurobehavior test. For example the NACS has 5 tests for adaptive response which is the ability of the neonate to respond to their environment. When observing the breastfeeding session, the infant's ability to manage sensory stimuli and observations of consolability when the neonate is agitated would manifest as a good latch and the ability of the infant to feed well. There are three tests for reflexes on the NACS which are related to the function of cranial IX, X, XI, and XII. There are 4 tests for passive tone on the NACS related to the function of cranial nerve V and VII.

Severe neonatal injury or depression is easy to detect and readily apparent by standard neurologic exams that are performed on the neonate shortly after birth and again at 24 hours postpartum. However mild injury or depression is not as readily observable in the neonate. Infants that have subtle neurologic signs of drug depression display mild hypotonia, mediocre primary reflexes, and poor habituation to outside stimuli. Therefore many of the neurobehavior the NACS evaluates can be evaluated through breastfeeding observations using a valid tool such as the LATCH. If a normal healthy infant can't latch and maintain breastfeeding immediately after birth something is wrong. It was not necessary to put the baby through a neurologic exam when the information could be gleaned from the breastfeeding session.

Ultralow-dose Epidural Analgesia Medications

Most drugs, including those used for analgesia and anesthesia, readily cross the placenta by passive diffusion. Diffusion is dependent on a concentration gradient across the placenta with drugs, including opioids and local anesthetics passively moving from areas of high concentration

to low. Maternal blood concentration of local anesthetics and opioids is determined by the physiochemical characteristics of the drug, the amount of drug given, the site of administration, metabolism, and excretion and effects of adjuvants (Santos, Karpel, & Noble, 1999; Santos & Pedersen, 1994). In order for epidurally administered bupivacaine and hydromorphone to affect the fetus they must be absorbed into maternal circulation before fetal transfer, and the maternal blood concentration determines fetal drug exposure (Griffiths & Campbell, 2014).

Hydromorphone is a mu receptor agonist with pharmacokinetic properties intermediate between highly hydrophilic morphine and highly lipophilic opioids such as fentanyl and sufentanil (Reisine & Pasternak, 1996). After epidural administration, the amount of drug that penetrates dura and pia-arachnoid to enter the CSF and spinal compartments is inversely proportional to its lipid solubility and polarity (Chrubasik et al., 1993; Herz & Teschemacher, 1971; Plummer et al., 1990; Sinatra et al., 2000; Yaksh et al., 1988). For example, high lipid solubility increases systemic absorption and reduces availability of the drug in the dorsal horn of the spinal cord. Therefore, more drug is continually needed to extend the limited duration of action (Bernards, 2004; Sinatra et al., 2000). Hydrophilic opioids have more difficulty traversing neural and vascular membranes, staying in the spinal compartment, increasing the availability of drug on the dorsal horn of the spinal cord, ensuring that a lower concentration of drug is needed for continued receptor site activity (Sinatra et al., 2000). Because placental transfer of hydrophilic opioids is impeded, they diffuse across slowly and are unlikely to attain effective concentration in the fetus (Reynolds, 2011; Syme et al., 2004).

This gain in opioid-mediated analgesic effect provides a local anesthetic “dose-sparing” effect, allowing the use of bupivacaine as an adjunct rather than primary analgesic where infusions are 2 to 2.5 times as dilute as those traditionally seen in continuous labor epidural

infusions (Sinatra et al., 2000). Very little data exists on neonatal exposure to epidurally administered hydromorphone in the mother. However, these theoretical considerations are supported by the unpublished study conducted by the author of this dissertation and colleagues at Yale New Haven Hospital (Shah, French, Dai, & Snegovskikh, unpublished data, 2012) described in the section on epidural medications in Chapter 2. In that study, 10 healthy parturients with uncomplicated pregnancies received an initial 100 µg hydromorphone and a 9 mL 0.25% bupivacaine bolus, followed by continuous infusion of 0.05% bupivacaine and 3 µg/mL hydromorphone. Whereas the average maternal venous concentration of bupivacaine was 0.23 ± 0.18 µg/mL, only two of the 10 umbilical venous samples had detectable levels of bupivacaine, with an umbilical/maternal ratio approaching 0, much lower than in a comparable study of bupivacaine with fentanyl (Bader et al., 1995). The only umbilical vein samples with detectable bupivacaine levels were from patients who required more than one additional bolus. The average hydromorphone concentration was 0.26 ± 0.09 ng/mL in the maternal vein samples and 0.23 ± 0.09 ng/mL in the umbilical vein samples, with a calculated umbilical/maternal ratio of 0.88 ± 0.18 , comparable to the fentanyl levels found in the Bader et al. (1995) study, despite the higher concentration of hydromorphone in the infusate. Neither our study nor the Bader et al (1995) study found evidence of drug accumulation with increasing length of infusion time, and results suggested rapid placental transfer and equilibration of both fentanyl and hydromorphone between maternal and neonatal blood.

Thus, the lower overall concentration of bupivacaine in the infusate in the current study and the greater hydrophilicity of hydromorphone as compared to fentanyl may have contributed to the lack of detectable effects in the neonate. This conclusion is also consistent with our finding

that duration of epidural hydromorphone infusion (total amount of hydromorphone) had no effect on breastfeeding behaviors.

Differences in the Patients' Labor Experience

As it was not ethically possible to perform a randomized controlled trial of epidural analgesia vs no epidural during labor, the study population was selected to be as homogeneous as possible to limit external influences on the results. To keep factors such as experience with labor, familiarity and confidence with the maternal role, and the mother's comfort level in caring for her newborn as similar as possible, both groups consisted of multiparous women who had previously breastfed. Furthermore, the labor experience was similar for both groups regarding the care they received from caregivers, all participants had support persons, and high-risk pregnancies were excluded so that no complications were expected during labor or delivery. Nevertheless, there were differences between the group with epidural analgesia and the unmedicated group.

Longer Duration of Labor

Previous studies showed epidural analgesia is associated with a longer duration of stage 2 labor (Anim-Somuah et al., 2011). Similarly, the women in the epidural group in the current study had a longer duration of labor measured from stage 2 through stage 3 compared with the unmedicated group ($p = <0.0001$). Longer duration of stage 2 labor can lead to very tired mothers and stressed babies, making breastfeeding difficult. However, when analyzed as an independent variable in the regression analyses in this study, duration of labor was not significantly related to breastfeeding effectiveness scores.

Instrumented Delivery

Moreover, labor epidural analgesia and longer stage 2 labors have been associated with higher rates of instrumented vaginal delivery (forceps and vacuum) in some previous studies (Anim-Somuah et al., 2011; Nyuyen et al., 2010). One meta-analysis of randomized control trials found the use of epidural analgesia was associated with a 2-fold increase in instrumental vaginal deliveries (Halpern et al., 1999). However, others have found mixed results (Leighton & Halpern, 2002). In the present study, one woman in the epidural group had a vacuum-assisted delivery, but this did not produce any significant findings related to her infant's breastfeeding behavior scores. Our study results suggest that, although the women in the epidural group had longer stage 2 labors, the low-dose epidural infusate was not potent enough to impair the strength of pushing and create a need for instrument delivery.

Oxytocin Administration

The women in the epidural group in our study were given oxytocin to induce or augment labor significantly more often than women who remained unmedicated during labor (47.1% vs. 22.9%; $p = 0.002$). These data support the results of others showing that women who receive epidural analgesia for labor pain have higher rates of oxytocin augmentation than unmedicated parturients (Anim-Somuah et al., 2011; Chang & Heaman, 2005; Wiklund et al., 2009). Some studies suggest exogenous oxytocin augmentation along with epidural analgesia may reduce the normal rise in endogenous serum oxytocin levels in response to sucking (Jonas et al., 2009) and may shorten breastfeeding duration (Beilin et al., 2005). Other studies have found negative effects of synthetic oxytocin on feeding behaviors. In our study, multiple linear regression analyses showed that oxytocin did not have an independent effect on breastfeeding behavior.

Induction of Labor

The epidural group also had significantly more women in whom labor was induced compared to the unmedicated group (39.2% vs. 22.9%; $p = 0.0027$). Women may have been more likely to request an epidural when they undergo labor induction because the intensity of labor tends to be greater after induction than with spontaneous labor. This is in agreement with other studies that also found significantly higher rates of epidural analgesia for relief of pain in induced labor (Alexander et al., 2001; Duff & Sinclair, 2000; Prysak & Castronova, 1998).

While examining the effects of labor induction on obstetric outcomes in a study of 410 women, Bodner-Adler and colleagues also found that the use of epidural ($p = 0.001$) and oxytocin ($p = 0.006$) was significantly increased in the induction group compared with the control group (Bodner-Adler et al., 2005). Furthermore, the need to augment labor with oxytocin was increased in women who were induced (Prysak & Castronova, 1998). Although the combination of these factors might be expected to negatively influence breastfeeding, we found no independent effects of labor induction on breastfeeding scores.

Intravenous Fluids

In addition, the epidural group received a greater amount of IV fluids compared to the unmedicated group ($p = <0.001$). This may be the result of factors related to the differences in the labor experience between women who received epidural analgesia and those who were unmedicated. Women who request an epidural must have an IV catheter in place, and before the epidural is placed they must receive a fluid bolus of 500-1000 mL of lactated Ringer's solution. Most of the women in the unmedicated group were patients of a midwife group and often would come to the hospital only after they had been in an active labor pattern for some time and had had significant cervical dilation. If the women were not group B streptococcus positive and did

not require antibiotics, they could choose not to have an IV catheter placed. Twenty-six (51%) of the women in the nonmedicated group did not have an IV. Thus, the significant difference between groups in the amount of IV fluids received was not unexpected. Multiple linear regression analysis only of data from the epidural analgesia group showed that high volumes of IV fluids had a significant independent effect on the first breastfeeding session ($p = 0.01$). Given the difference in amount of IV fluids received, this result led to an expectation of a difference in breastfeeding behaviors between the groups, which was not the case.

Multiple linear regression analysis also showed a significant independent effect of higher volumes of IV fluids on the 3-hour LATCH score in the entire study population ($p = 0.02$). As 49% of the unmedicated group did receive IV administration of Ringer's solution, it is also possible that factors related to the volume of IV fluids may have been at work in both groups. When mothers receive IV fluids, neonates also may have hyponatremia and lose more weight compared with neonates whose mothers received fluids only by mouth (Dahlenburg, Burnell, & Braybrook, 1980; Noel-Weiss, Woodend, Peterson, Gibb, & Groll, 2011). The neonates in both groups in our study were feeding well, with weight losses of less than 7% in all neonates. We found no significant difference between the groups in the percentage of neonatal weight loss during the first 48 hours postpartum. However, early postpartum maternal breast, nipple, and areola edema has been described in association with IV fluid hydration of the mother during labor (Kujawa-Myles, Noel-Weiss, Dunn, Peterson, & Cotterman, 2015; V. Miller & Riordan, 2004). Edema may cause latching problems, nipple pain, low milk transfer, or poor breast milk volumes, which may in turn have a negative effect on neonatal breastfeeding behaviors.

Nevertheless, it is not clear whether the findings regarding IV fluid administration represent a true effect. We did not use a correction factor to compensate for the relatively large number of significance tests in this study. Thus, it may have been a chance result.

Influence of the Baby-Friendly Hospital Environment

We had expected that epidural analgesia and the various stressors it involves, particularly the combination of longer duration of labor, greater use of instruments during delivery, oxytocin administration, and more frequent induction of labor, would result in significantly reduced scores for breastfeeding effectiveness on the LATCH assessment scale in the epidural group. However, this hypothesis was not confirmed. One explanation for the lack of difference between groups may be that any negative effects of epidural analgesia might have been overcome by factors operating to promote breastfeeding success in both groups. High success rates in both groups may have precluded detection of any detrimental effects.

As noted in Chapter 2, breastfeeding can be considered successful if the total LATCH score is greater than 7 at two feeds in 24 hours (Baumgarder et al., 2003b; Bramson et al., 2010). This criterion was reached by a high proportion of both groups in this study. Total LATCH scores above 7 were achieved in more than 70% of both groups at the 3-hour breastfeeding session, more than 80% at 12-hour session, and approximately 95% at the 24-hour session (see Table 12). The mean LATCH score was greater than 8 at all three feeds, and greater than 9 at 24 hours in both groups.

The study hospital was following the Baby-Friendly Hospital Initiative by implementing the 10 Steps for Successful Breastfeeding program and working toward achieving accreditation from Baby-Friendly USA as a Baby-Friendly Hospital (World Health Organization, 1998). All neonates in this study were placed skin-to-skin after delivery and all breastfed within the first 40

minutes. The infants “roomed in,” breastfed on demand, and the mothers had access to lactation consultants around the clock. All the postpartum nurses were trained in using the LATCH tool as an intervention and teaching instrument, and a LATCH score is documented in the electronic medical record every 8 hours as a matter of routine. LATCH assessments for the study were independent of these scores. None of the study neonates received a pacifier or formula. In addition, the vitamin K shot and eye ointment were not administered until 24 hours postpartum. These practices are the standard of care and a similar environment was provided for all the patients. This breastfeeding-friendly environment may have limited the effects of other variables on breastfeeding and may have ameliorated any negative influences of the epidural analgesia in this study.

Breastfeeding is both a nutritional method and a process of connection between the mother and infant. John Bowlby first introduced the idea of attachment as a biological response between mother and infant that organized neurobehavior (Bowlby, 1982). Studies of mother-infant interaction have highlighted the role of the infant’s perceptual, communicative, and interactive competency (Brazelton et al., 1983). The bi-directionality of the mother-infant interaction is characterized by synchrony and reciprocity (Bowlby, 1982; Tronick & Cohn, 1989). The early postpartum period is an important time for mother and infant to develop this synchrony and reciprocity and is known as the “sensitive” period (Kennell et al., 1974). The neonate placed skin-to-skin with the mother during this sensitive period enhances the long-term interaction between mother and neonate and mothers were more likely to be breastfeeding at 1 and 4 months after delivery and for a longer duration (Bystrova et al., 2009; E. R. Moore et al., 2012; Salariya et al., 1978; Wiberg et al., 1989). If this interaction is interrupted for any reason, and the baby is less alert, less able to orient, and less able to show organized movement, this may interfere with

the mother-infant relationship (A.D. Murray et al., 1981; Sepkoski et al., 1992) and subsequently impact breastfeeding.

Skin-to-skin contact in the immediate postpartum allows the neonates innate behaviors to occur. The neonate next to the mother's skin helps regulate their temperature, crying, respirations and nursing behaviors. It assists the neonate in the transition to extrauterine life by decreasing the stress of birth through the mother's warmth, touch, and odor, guiding the neonate to her nipple and release of maternal oxytocin. Spontaneous vaginal delivery with immediate maternal-infant skin-to-skin contact increases the likelihood of successful baby-led breastfeeding (Righard & Alade, 1990; Widstrom et al., 2011). The timing of the first breastfeed is associated with duration of breastfeeding. Bramson and colleagues analyzed data from a prospective cohort on 21,842 mother-infant pairs and determined the longer the mother and infant experienced skin-to-skin in the first 3 hours after delivery the more likely she was to be exclusively breastfeeding during her hospital stay (Bramson et al., 2010). The earlier the initiation of the first breastfeed and/ or the mother-neonate contact the longer the duration of breastfeeding (Berra et al., 2003; Buxton et al., 1991; Salariya et al., 1978). The unstructured interactions and responses between mother and neonate allow hormonal levels in both to change in response to one another.

Limitations and Strengths of the Study

The study was limited by its nonrandomized nature, which rules out definitive conclusions regarding cause and effect (Polit & Beck, 2012). However, attempts at randomizing women to an epidural or unmedicated group have resulted in high crossover rates (Dickinson, Paech, McDonald, & Evans, 2002; Nikkola et al., 1997). Self-selection to epidural vs unmedicated groups would likely be associated with various confounding variables that would influence results, such as the general opinion of the mother regarding interventions for childbirth. Because

the decision to have epidural analgesia was voluntary, certain characteristics leading to the decision may also have influenced results. Two women declined to participate after the study was described to them. Demographic information on those who decline participation would have been valuable in determining the direction and nature of bias (Polit & Hungler, 1999).

The study was limited regarding the selection of the convenience sample. Minorities were underrepresented, making the study less generalizable. However, white and minority women were equally represented in the two groups. In addition, the research findings apply only to healthy multiparous women and infants with no complications of pregnancy and delivery. The findings of this study are therefore generalizable only to healthy term infants born in a Baby-Friendly environment where immediate skin-to-skin, rooming-in, and breastfeeding on demand are the standard of care. Also, the findings of this study also only apply to the first 3, 12, and 24 hours of life.

A further limitation was that only a certain number of potential predictor variables could be analyzed, and the study did not address the mothers' attitudes, feelings, or opinions toward breastfeeding.

There were several factors that strengthen the quality of this research. Many previous studies did not have any type of comparative group. Although this study was not randomized, it was able to compare women with epidural analgesia with unmedicated women in a similar environment. Equal numbers of women were included in each group, and efforts were made to achieve a relatively homogeneous study population. Also all the medicated women received the same medication at the same dose. Many studies have wide variations in the type and concentrations of epidural medications used or include systemic opioids which influence the findings.

The LATCH assessment method was noninvasive. Patients did not mind having an observer, and the assessment did not hinder the breastfeeding sessions or other interaction between the mother and infant.

Implications for Nursing Practice

The benefits of breastfeeding are important enough that healthcare providers should encourage and support breastfeeding. However, because their own beliefs and opinions may influence their patients, healthcare providers should remain cautious when providing information about possible risks and barriers to breastfeeding. Systemic opioids used in labor have been clearly associated with attenuating the neonate's ability to breastfeed in the early postpartum, leading to concern on the part of both caregivers and mothers about pain medications during labor. The literature so far has provided inconsistent data on the effects of epidural analgesics on breastfeeding outcomes. Currently, most women in the US choose to have epidural analgesia, but they are often frightened about the effect labor analgesic medications might have on the fetus or neonate, and therefore they may decline to breastfeed if they need pain relief. Women in labor place a high priority on pain relief—so high that they may be willing to sacrifice breastfeeding for pain relief in the immediate moment. If the mother feels she did not make a good decision during labor, it can lead to anxiety during the feeding and anxiety about breastfeeding.

Although no conclusions can be drawn from these data as to the comparative effects of different epidural medications, the current study shows that epidural analgesia with a low dose of hydromorphone is not likely to have an effect on breastfeeding behaviors. Women in this study breastfed equally well whether they had epidural analgesia or no analgesia. All of the babies in this study fed vigorously the first hour after birth. The neonates were alert, rooting, and searching for the breast. Based on these data, if a mother has decided to have epidural analgesia during

labor, nurses can recommend and facilitate breastfeeding without worrying that the epidural would harm the infant by decreasing breastfeeding success, at least if hydromorphone is used as the epidural opioid. We therefore conclude that in this population, it is unwarranted to counsel women to not receive epidural medication for labor pain relief because it may negatively affect breastfeeding. If the correct amount of medication is administered it, is now possible for women go through labor pain free and still breastfeed.

Although not significant, the finding that the presence of multiple stressful events or interventions contributed about 30% of the variability of LATCH scores in the regression model at 3 and 24 hours suggests that mothers who have a long duration of labor, receive oxytocin administration or large amounts of IV fluid, or in whom labor is induced, may need more intensive help from the nurse or lactation consultant to achieve success in breastfeeding.

This study highlighted the importance of objective assessments in enabling nurses to analyze and help the mother correct feeding problems. There are many reasons that some babies do not breastfeed well, and it is important to identify factors that may impede breastfeeding in the immediate postpartum. The identification of such factors can improve breastfeeding outcomes. The mothers in this study were interested in how we were measuring breastfeeding behaviors during the breastfeeding observation sessions, and the LATCH tool helped nurses to teach them how to recognize feeding cues, the infant's ability to latch correctly, rhythmic sucking, audible swallows, mother's comfort, and positioning. The LATCH scoring system is used at the study hospital for frequent breastfeeding evaluations from delivery room to discharge home. In addition to allowing objective assessments, this use of the LATCH tool provides mothers with nursing attendance throughout a breastfeeding session.

Assessment of LATCH scores can serve as a basis for nurses to give breastfeeding assistance and anticipatory guidance. Lactation consultants and nurses can prioritize assistance, focusing on mothers and infants with low LATCH scores that indicate a need for prompt intervention and support. Breastfeeding is strongly encouraged in the current healthcare environment but so is early discharge home. Use of the LATCH tool can help postnatal caregivers to identify mothers at risk for weaning and who need postdischarge follow-up. The most frequent causes of breastfeeding difficulties in hospital and at home are sore nipples, problems with the infant latching on or sucking, and “not enough milk.” Many women may stop breastfeeding before they want to as a result of these problems. Nurses in the hospital play a significant role in providing the support needed by women in breastfeeding establishment. To prevent the common breastfeeding problems, early assessment, support, and education are imperative. All breastfeeding issues should be attended to during the hospital stay with a follow-up plan in place for unresolved issues.

Clinicians should provide anticipatory guidance about common breastfeeding issues likely to occur in the coming weeks, such as management of sore nipples, correct latching and unlatching techniques, and alternating feeding positions to reduce friction exerted by the infant’s mouth during feeding. Without guidance, many women stop breastfeeding prematurely as a result of these problems. With continued support in the community, many of these problems are preventable. The early discontinuation of breastfeeding can cause distress and disappointment to the mothers and health problems for her and her infant. This is where public health nurses can continue the work and care of hospital nurses in providing breastfeeding support and education to the mother-infant dyad. Breastfeeding support can consist of praise, reassurance, instruction, and time to answer the mothers’ questions.

Support by both professionals and lay supporters has a positive impact on breastfeeding outcomes (Renfrew, McCormick, Wade, Quinn, & Dowswell, 2012). However, lay support and combinations of lay and professional support were more effective for exclusive breastfeeding continuation than professional support alone (Renfrew et al., 2012). The authors indicated that as a strategy to improve breastfeeding behaviors, face-to-face support was associated with greater success than telephone support. When support was offered only if women sought help, it was unlikely to be effective. This suggests women should be offered regular scheduled ongoing visits.

Prenatal nurses are in an excellent position to educate mothers about the benefits of breastfeeding. Decisions about how a woman is going to feed her baby are made before the pregnancy or in the prenatal course (Earle, 2002; Ertem et al., 2001; Scott, Binns, & Aroni, 1997; Scott et al., 2001). Up-to-date information on the benefits of breastfeeding and positive messages about breastfeeding by prenatal clinicians during the pregnancy help mothers make informed choices. Prolonged breastfeeding is associated with high maternal self-efficacy (Dennis, 2002; Meedya et al., 2010). A woman's exposure to breastfeeding and her personal experience with breastfeeding have a positive effect on her confidence in her breastfeeding ability (Blyth et al., 2002; Dennis, 2002). Maternal attitudes toward breastfeeding also affect duration of breastfeeding. Women who perceived breastfeeding to be easier, more convenient, and healthier than bottle feeding breastfed longer than those who regarded breastfeeding as inconvenient, uncomfortable, or more difficult (Dennis, 2002). Similarly, intended duration of breastfeeding was associated with actual duration of breastfeeding (Dennis, 2002; Meedya et al., 2010). This is important to prenatal nurses, because it has been suggested that simply asking women who

intend to breastfeed how long they plan to do so is an efficient method of identifying prenatally those who are at risk for short breastfeeding duration (O'Campo, Faden, Gielen, & Wang, 1992).

Providing effective breastfeeding support requires highly skilled and knowledgeable nurses or lactation consultants who can be available to provide the necessary guidance needed by the mother and infant in their early breastfeeding experience. Nurse managers and hospital administrators must evaluate the resources available to meet the needs of mothers and infants to extend the breastfeeding success from birth, through discharge, and into the home environment. Communication between hospital and community nurses is vital to the continuity of breastfeeding supportive care. The community setting would benefit from an objective breastfeeding assessment tool, such as the LATCH scale, in order to help public health nurses to reinforce and continually reassess breastfeeding skills and knowledge, while providing the eye of the skilled observer and the experience of a trained clinician.

Implications for Future Research

To be useful clinically, the results of this study need to be generalizable to other populations and other types of epidural medications. Thus, future studies should include primiparas and women of different ethnic backgrounds and birth experiences. As the results of this study apply only to epidural analgesia with ultralow-dose bupivacaine and hydromorphone, comparative studies should be conducted with different concentrations of bupivacaine and fentanyl doses compared with the hydromorphone to determine whether the type of drug, dose, or drug interaction affects breastfeeding behavior. When it is not ethically possible or feasible to randomly assign patients to receive different treatments, carefully planned prospective comparative cohort studies should be performed to provide at least some means of comparing interventions.

Studies should measure breastfeeding success using an objective breastfeeding scoring system, such as the LATCH system, and record the specific time point after delivery when the first breastfeeding attempt occurred. A breastfeeding analysis should be completed in the first 3 hours after delivery and then at 24 hours postpartum. Evidence-based recommendations can then be made to change practice in order to improve labor outcomes and provide additional breastfeeding support to the women who need it most postpartum.

This study has highlighted the complexity of the potential influences on breastfeeding. Epidural analgesia is just one of the intrapartum interventions that can affect the course of labor and breastfeeding. The relationship of epidural analgesia with breastfeeding involves complex interactions among the various intrapartum interventions. One intervention may lead to another in a cascade that may either directly or indirectly affect breastfeeding. Future studies on labor epidural analgesia and breastfeeding need to view labor, birth, and interventions as a whole—in an integrated process that must be evaluated for potential adverse effects on the course of labor, neonatal and maternal behavior, and breastfeeding.

Conclusion

Labor epidural analgesia provides women with excellent pain relief. Although the study was limited by its nonrandomized nature, these data indicate that, by itself, epidural analgesia with low-dose hydromorphone does not decrease the effectiveness of breastfeeding behaviors as measured during the first 24 hours after birth by the LATCH assessment tool. However, women who receive epidural analgesia have an increased risk of experiencing multiple stressful events or interventions during labor, which may contribute to breastfeeding difficulties. Women in this situation may need more intensive help from the nurse or lactation consultant to achieve success in breastfeeding.

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Appendices

Appendix A: Patient Information Sheet



The research group of the Department of Anesthesiology of Yale University, School of Medicine.

Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life

A. PATIENTSTUDY ID NUMBER _____	B. Maternal INFORMATION 1. ASA: I II III IV Height: _____ Weight: _____ LMP _____ 2. _____ PMH: _____ _____ _____ _____
C. DELIVERY INFORMATION 1. Time of Delivery _____ 2. Time of Placenta _____ 3. Apgars 1 minute _____ 5 minutes _____ 4. Baby Weight at Birth _____ 5. Weight at 24 hours _____ 5. Duration of Labor _____ First stage _____ Second stage _____ Third Stage _____	3. _____ PSH: _____ _____ 4. Allergy: _____ 5. MEDICATIONS: _____ _____ GESTATIONAL INFORMATION 1. Gestational Age _____ 2. G ____ P ____

<p>D. EPIDURAL-RELATED COMPLICATIONS</p> <p>1. Maternal Hypotension_____</p> <p>Corrective Action_____</p> <p>Duration_____</p> <p>2. Fetal Bradycardia_____</p> <p>Corrective Action_____</p> <p>Duration_____</p> <p>3. Maternal Temp_____</p> <p>Corrective Action_____</p> <p>Duration_____</p> <p>4. Pitocin During Labor Yes____No____</p> <p>Total ML of Infusion_____</p> <p>5. AROM SROM</p> <p>6. Total Fluids</p>	<p>E. EPIDURAL INFORMATION</p> <p>1. TIME EPIDURAL PLACED_____</p> <p>2. TOTAL DOSE AND TYPE LOCAL ANESTHETIC 1.5% LIDO_____TIME_____</p> <p>_____</p> <p>.25% BUPIE_____TIME_____</p> <p>_____</p> <p>3. TOTAL DOSE DILAUDID AT INSERTION_____</p> <p>TIME_____</p> <p>4. INFUSION RATE_____</p> <p>5. TIME EPIDURAL REMOVED_____</p> <p>6. NUMBER OF BOLUSES AND TIMES OF BOLUS_____</p> <p>_____</p> <p>BOLUS_____</p> <p>_____</p> <p>BOLUS_____</p> <p>_____</p> <p>7. DILATION AT TIME OF EPIDURAL PLACEMENT_____</p> <p>_____</p> <p>F. INSTRUMENT DELIVERY</p> <p>Yes_____ (Circle Vacuum or Forceps) No_____</p> <p>G.</p> <p>Episiotomy_____ Tear_____</p> <p>_____</p> <p>Use of Local Anesthetic Yes No (Circle)</p> <p>If yes type and amount_____</p> <p>Time_____</p> <p>_____</p>
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T. Berry Brazelton, MD Professor Emeritus		Yvette Blanchard, ScD, PT Faculty	
		<i>January 20, 2014</i>	
J. Kevin Nugent, PhD Director		Date Certified	

Appendix E: Protocol Approval, IRB Approval, and IRB Authorization Agreement

Protocol Approval



PEDIATRIC PROTOCOL REVIEW COMMITTEE
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PPRC Review and Administrative Approval

August 1, 2014

Principal Investigator: Denis Snegovskikh, MD

Protocol Title: Maternal and Neonatal Hydromorphone and Bupivacaine Concentrations After Epidural Analgesia During Labor and its Effect on Neonatal Neurobehavior and Breastfeeding

HIC: TBD

Dear Dr. Snegovskikh,

Your HIC protocol application entitled *Maternal and Neonatal Hydromorphone and Bupivacaine Concentrations After Epidural Analgesia During Labor and its Effect on Neonatal Neurobehavior and Breastfeeding*, was administratively reviewed, and approved in its revised format by the Pediatric Protocol Review Committee on August 1, 2014. The procedures of this protocol present minimal risk to the pediatric subjects. This protocol may proceed to HIC.

Please note that the PPRC review focuses primarily on scientific issues, bio-medical risks and benefits to minors as well as study assent forms (as applicable) that are developmentally appropriate for children/adolescents. PPRC review may additionally suggest recommendations helpful for HIC review; however, PPRC review compliments review by HIC who has the final approval authority.

Please include this signed form with your submission to the HIC including the revised protocol and consents (version II).

Sincerely,

Allison Gavaletz, BS, CCRP
 Administrative Reviewer
 Pediatric Protocol Review Committee

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To: Keun Chung, M.D.
From: The Human Investigation Committee
Date: 03/23/2015
HIC Protocol #: 1407014373
Study Title: Effect of Labor Epidural Analgesia with Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life
Committee Action: Expedited Approval
HIC Action Date: 03/23/2015
Expiration Date: 09/30/2015
Submission Type: Amendment

This protocol was amended following an expedited review by the Human Investigation Committee. This review meets approval criteria set forth in 45 CFR 46.111. Please be advised that the protocol is due to be reapproved by the expiration date noted above.


Review Comments:

- The amendment to change the PI from Denis Snegovskikh to Keun Sam Chung has been approved.
- Enclosed: Approved HIC protocol application, compound authorization and consent. Review and acknowledged: Change of PI form.

It is the investigator's responsibility to apply for reapproval prior to the Expiration Date noted above. Please allow two months for reapproval.

If you have not already done so, please prepare a current, comprehensive protocol inclusive of all previously approved amendments by the time of this protocol's renewal. This means that the changes must be incorporated into the body of the document.

Yale University Human Investigation Committee Applications

 <div style="display: inline-block; vertical-align: middle; text-align: center;"> <p>333</p> <p>YALE UNIVERSITY</p> <p>HUMAN INVESTIGATION COMMITTEE</p> <p>Application to Involve Human Subjects in Biomedical Research</p> <p>100 FRI (2013-1)</p> </div>
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Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	HIC OFFICE USE ONLY

SECTION I: ADMINISTRATIVE INFORMATION			
Title of Research Project: Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life			
Principal Investigator: Dr Kuen Sam Chung		Yale Academic Appointment: Assistant Professor of Anesthesiology	
Department: Obstetric Anesthesiology			
Campus Address: Yale University School of Medicine, 333 Cedar Street, TMP 3, P.O. Box 208051, New Haven, CT, 06520-8051			
Campus Phone: 203-737-1818	Fax: 203-785-6897	Pager: 3595	E-mail: Keun.chung@yale.edu
Protocol Correspondent Name & Address (if different than PI): Cynthia French 6 Koury Ct West Haven, CT 06516			
Campus Phone: 688-2751	Fax:	E-mail: cyntfre@aol.com	
Yale Cancer Center CTO Protocol Correspondent Name & Address (if applicable):			
Campus Phone:	Fax:	E-mail:	
Business Manager:			
Campus Phone :	Fax :	E-mail	
Faculty Advisor: (required if PI is a student, resident, fellow or other trainee) <input type="checkbox"/> NA		Yale Academic Appointment:	
Campus Address:			
Campus Phone:	Fax:	Pager:	E-mail:

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research

<http://www.yale.edu/hrpp/policies/index.html#COI>

☐ Yes ☒ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☒ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: <http://www.yale.edu/coi/>

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION
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1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- | | |
|--|---|
| <input type="checkbox"/> Magnetic Resonance Research Center (MR-TAC) | <input type="checkbox"/> Yale University PET Center |
| <input type="checkbox"/> Yale Cancer Center/Clinical Trials Office (CTO) | <input type="checkbox"/> YCCI/Church Street Research Unit (CSRU) |
| <input type="checkbox"/> Yale Cancer Center/Smilow | <input type="checkbox"/> YCCI/Hospital Research Unit (HRU) |
| <input checked="" type="checkbox"/> Yale-New Haven Hospital | <input type="checkbox"/> YCCI/Keck Laboratories |
| <input type="checkbox"/> Cancer Data Repository/Tumor Registry | <input type="checkbox"/> Yale-New Haven Hospital—Saint Raphael Campus |
| <input type="checkbox"/> Specify Other Yale Location: | |

b. External Location[s]:

- | | |
|---|--|
| <input type="checkbox"/> APT Foundation, Inc. | <input type="checkbox"/> Haskins Laboratories |
| <input type="checkbox"/> Connecticut Mental Health Center | <input type="checkbox"/> John B. Pierce Laboratory, Inc. |
| <input type="checkbox"/> Clinical Neuroscience Research Unit (CNRU) | <input type="checkbox"/> Veterans Affairs Hospital, West Haven |
| <input type="checkbox"/> Other Locations, Specify: | <input type="checkbox"/> International Research Site |
- (Specify location(s)):

c. Additional Required Documents (check all that apply):

- | | |
|---|------------------------------|
| <input type="checkbox"/> *YCCI-Scientific and Safety Committee (YCCI-SSC) | <input type="checkbox"/> N/A |
| <input checked="" type="checkbox"/> *Pediatric Protocol Review Committee (PPRC) | Approval Date: |
| <input type="checkbox"/> *YCC Protocol Review Committee (YRC-PRC) | Approval Date: |
| <input type="checkbox"/> *Dept. of Veterans Affairs, West Haven VA HSS | Approval Date: |
| <input type="checkbox"/> *Radioactive Drug Research Committee (RDRC) | Approval Date: |
| <input type="checkbox"/> YNH-H Radiation Safety Committee (YNHH-RSC) | Approval Date: |
| <input type="checkbox"/> Magnetic Resonance Research Center PRC (MRRC-PRC) | Approval Date: |
| <input type="checkbox"/> YSM/YNHH Cancer Data Repository (CaDR) | Approval Date: |
| <input checked="" type="checkbox"/> Dept. of Lab Medicine request for services or specimens form | |
| <input type="checkbox"/> Imaging on YNH-H Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx | |

**Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.*

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 1-1½ years

3. Research Type/Phase: (Check all that apply)**a. Study Type**

- ☒ Single Center Study
☐ Multi-Center Study

Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐

- ☐ Coordinating Center/Data Management
☐ Other:

b. Study Phase

- ☐ N/A
☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV

☐ Other (*Specify*)

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

<input checked="" type="checkbox"/> Clinical Research: Patient-Oriented	<input type="checkbox"/> Clinical Research: Outcomes and Health Services
<input type="checkbox"/> Clinical Research: Epidemiologic and Behavioral	<input type="checkbox"/> Interdisciplinary Research
<input type="checkbox"/> Translational Research #1 ("Bench-to-Bedside")	<input type="checkbox"/> Community-Based Research
<input type="checkbox"/> Translational Research #2 ("Bedside-to-Community")	

5. Is this study a clinical trial? Yes ☐ No ☒

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☐

Other (*Specify*)

Registration of clinical trials at their initiation is required by the FDA, NIH and by the ICMJE.

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, <http://ycci.yale.edu/researchers/ors/registerstudy.aspx> or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No ☒

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☒ No ☐

If you answered "yes", this study will need to be set up in OnCore Support
<http://medicine.yale.edu/ymg/systems/ppm/index.aspx>

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes X No *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? No

c. Will a novel approach using existing equipment be applied?

No

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Kuen Sam Chung MD		Anesthesia Departmental Funding	<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
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IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. **Note: the PI's home department will be billed if this information is not provided.**

Send IRB Review Fee Invoice To:

Name:
 Company:
 Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training.

	Name	Affiliation: Yale/Other Institution (Identify)	NetID
Principal Investigator	Kuen Sam Chung MD	Yale University School of Medicine	Keunsam
Role: Co-Investigator	Cynthia French CRNA	YNHH	CF356
Role: Co-Investigator	Rachel Rachler CRNA	YNHH	RR382
Role: Co-Investigator	Denis Snegovskikh MD	Yale School of Medicine	DS567
Role: Co-Investigator	Angelique Garay CRNA	YNHH	amg68
Role:			
Role:			

A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR
AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibility MD

Kuen Sam Chung MD

PI Name (PRINT) and Signature

Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

- ☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☒ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

- ☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☒ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

 Chair Name (PRINT) and Signature

 Date

 Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.

- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

YNHH HSPA Name (PRINT) and Signature _____

_____ Date

For HIC Use Only

March 23, 2015
Date Approved

M. Antisdelo
Human Investigation Committee Signature

This protocol is valid through Sept. 30, 2015

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The objective's of this study are: (1) Determine if there is a difference in observable breastfeeding behaviors and neonatal neurobehavior status between neonates whose mother's received epidural hydromorphone and bupivacaine for labor pain and a control group of neonates whose mother's received no analgesia for labor pain. (2) Determine whether neurobehavior responses in the newborn are predictive of the neonates ability to exhibit breastfeeding behaviors in the first 24 hours of life.

(1) We hypothesize because of our solution utilizing significantly less bupivacaine than standard solutions and the greater hydrophilicity of hydromorphone, dilute solutions of 0.05% bupivacaine plus 3mcg/cc hydromorphone there will be no measurable differences in breastfeeding behaviors and neonatal neurobehavior scores of neonates born to mothers who received epidural analgesia for labor compared to neonates whose mothers were unmedicated.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

It has been estimated that 78% of infants born in the United States are exposed to epidural analgesia during labor and birth (24). Continuous epidural infusions are often maintained for many hours. Epidural infusions for labor pain can be a source of undesired neonatal exposure to analgesics. Since the 1990's the standard solution used at our institution is

0.05% bupivacaine with 3mcg/mL **hydromorphone**, which has shown equal analgesic efficacy to the commonly used and well studied 0.125% bupivacaine with 2 mcg/mL **fentanyl** solution. Numerous in vivo and in vitro studies have examined the uptake and accumulation of epidurally administered bupivacaine and fentanyl into maternal and neonatal circulation(25,49,69,79).

The type and amount of drug given epidurally determine how it is absorbed by the blood (speed of which is determined by lipid solubility), distributed throughout the body (crosses the placenta), metabolized by the liver (the fetus has immature liver), and excreted by the kidney (clearance has to do with the half-life of the drug; that is the time the concentration of the drug in the blood has decreased by half). The lipid solubility of the opioid is very important because it determines how the drug is absorbed.

Fentanyl is highly lipophilic, which means it diffuses freely from the epidural space into the maternal blood and across the placenta. The side effects of fentanyl, such as sedation, vomiting, pruritus, and although rare, neonatal respiratory depression, are well known (18,51,52,40,41).

Hydromorphone is hydrophilic, which means it is not absorbed quickly into the vascular system, and stays at the site on the spinal cord that blocks the pain pathway (dorsal horn). Because hydrophilic opioids stay at the site of action longer, placental transfer is slower and less likely to attain a high concentration in the fetus.

Numerous studies on fentanyl solution's has shown to impair effective breastfeeding in the early post-partum. Breastfeeding has been shown to have significant benefits to the newborn, including protection from infectious disease, improved cognitive development and benefits to maternal health (26). The most important concern regarding epidurals and breastfeeding is epidurally administered local anesthetic's and especially opioids readily cross the placenta and fetal blood brain barrier decreasing neonatal neurobehavior which may depress necessary neonatal reflexes needed for rooting, swallowing or sucking.(19,38,50,63,64). Because of the health benefits of breastfeeding to the mother and neonate, factors that have a negative impact on breastfeeding success need to be identified. **There have been no studies that examined whether epidural hydromorphone analgesia during labor has an impact on breastfeeding or neonatal neurobehavior.**

If there is a dose response relationship between epidural opioids with negative breastfeeding and neurobehavior outcomes, and these drugs act directly on brain tissue of the neonate thereby impeding the behaviors necessary for breastfeeding initiation, then research needs to focus on the transfer of drugs from the maternal epidural space, maternal circulation, across the placenta and across the neonatal blood brain barrier. The investigators completed a pilot study with 10 patients in 2012 that examined maternal and neonatal exposure to our hydromorphone/bupivacaine infusate. The study title: "Maternal and Neonatal Hydromorphone and Bupivacaine Concentration After Epidural Infusion During Labor" HIC# 1202009680. We compared our hydromorphone results with a similar study that evaluated MV and UV concentrations of fentanyl and bupivacaine after continuous labor epidural. Bader et al. (1995) examined the accumulation of epidurally administered 0.125% bupivacaine and 2 mcg/mL fentanyl at 14ml/hr in both maternal and fetal blood in 21 parturients. Their results did not find a statistically significant relationship between accumulation of either drug and length of infusion time but did suggest rapid placental transfer and equilibration of fentanyl between maternal and neonatal

blood and a maternal-neonatal gradient for bupivacaine concentration, attributed to placental deposition and protein binding (7).

The results of our study were consistent with our hypotheses. We found with our solution of 0.05% bupivacaine plus 3 mcg/mL hydromorphone, MV and UV concentrations were also independent of infusion length and the UV and MV concentrations of bupivacaine and hydromorphone were lower. This is because of the lower overall concentration of bupivacaine in the infusate and the greater hydrophilicity of hydromorphone as compared to fentanyl. All three measures (UV concentration, MV concentration, and UV/MV ratio) were lower for bupivacaine in our study with only 2/10 UV samples having detectable levels. All 21 UV samples in the Bader et al. (1996) study had detectable levels of bupivacaine.

In contrast, these three measures are almost equal for our 42 mcg/hr infusion of hydromorphone versus 28 mcg/hr infusion of fentanyl. Despite the 50% higher concentration of hydromorphone in our solution (3mcg/cc of hydromorphone versus 2mcg/cc of fentanyl in Bader's solution), the overall UV concentration of hydromorphone is similar to that of fentanyl. This is significant because other studies have found incidences of neonatal respiratory depression with fentanyl UV concentrations that were found in the Bader (1996) study(19,51,52,40,41). Given that the potency of hydromorphone is only 1/10 to 1/12 that of fentanyl, the fetus is exposed to a lower equipotent opioid dose (65). The use of our solution could be more favorable with respect to limiting neonatal exposure to foreign substances, given the equal analgesic efficacy of our solution to that of the combination of 0.125% bupivacaine and 2mcg/ml fentanyl.

Pharmacodynamics/ Pharmacodynamics of Epidural Analgesia Medications

The most common drugs used for epidural analgesia contain combinations of local anesthetics with an opioid and are set on a continuous infusion, often for many hours. Bupivacaine is the mainstay local anesthetic used and is commonly combined with fentanyl. The dosage frequently used in this setting for continuous labor epidural infusions is 0.125% bupivacaine with 2 mcg/cc fentanyl. While solutions of fentanyl and 0.125% bupivacaine provide safe and effective analgesia, they are also associated with hypotension, lower extremity weakness and numbness leading to longer stage 2 labor, increased instrument deliveries and urinary retention (67).

At YNHH, there is a standard protocol for otherwise healthy parturients who request epidural analgesia for vaginal delivery, a continuous infusion of 0.05% bupivacaine with 3 mcg/mL hydromorphone at 14 mL/hr. The basis for this protocol is based on a prospective observational study of 1830 patients by Sinatra et al, who found similar analgesic efficacy and quality as compared to solutions of 0.125% bupivacaine and 2 mcg/cc fentanyl. (65). Hydromorphone has not been widely accepted in the management of pain in the obstetric setting despite evidence of safety and efficacy of pain management (Sinatra). At YNHH we utilize hydromorphone in our continuous labor epidurals and believe it exhibits the necessary pharmacodynamics that promotes analgesia without the unintended side-effects seen with traditional opioid infusions.

Lipid solubility of an opioid is one of the most important factors in determining its individual property (74). Lipid solubility determines how the drug is absorbed into local tissue, traverse the dura and gain access to the cerebral spinal fluid (CSF), or be absorbed systemically (16). Once the drug is administered in the epidural space, the pharmacology and pharmacodynamics of the drug allocate its unique profile of analgesia and side effects.

Pharmacokinetic studies have shown that highly lipophilic opioids such as fentanyl and sufentanil diffuses freely from the epidural space into the maternal blood and across the placenta (25,49). The side effects of fentanyl such as sedation, vomiting, pruritus, and, although rare, neonatal respiratory depression, are known (18,51,52,40,41). Most studies have focused on neonatal outcomes in the delivery room ignoring the possibility of late occurring side effects that can arise up to several hours after exposure due to the longer terminal half life of fentanyl in neonates and from secondary peaks in plasma drug concentration since it is bound principally to albumin, and becomes unbound during the first day of life increasing the free concentration of fentanyl (60,42,43,39,37,47). A 2014 case control study showed a positive association between exposure to traditional fentanyl bupivacaine infusate in maternal epidural analgesia and respiratory distress in neonates ≥ 34 weeks gestation, within 24 hours of life, requiring supplemental oxygen ≥ 2 hours and/or positive pressure in the neonatal intensive care unit (40). There are no published studies of respiratory depression of the neonate after continuous labor epidural solutions containing hydromorphone.

Hydromorphone is a mu receptor agonist with pharmacokinetic properties intermediate between morphine and highly lipophilic opioids such as fentanyl and sufentanil (59). After epidural administration, the amount of drug that penetrates dura and pia-arachnoid to enter the CSF and spinal compartments is inversely proportional to its lipid solubility and polarity.(66,81,54,21,33). Highly lipid solubility increases systemic absorption and reduces availability of the drug in the dorsal horn of the spinal cord thereby continually needing more drug to extend their limited duration of action(11,66). Hydrophilic opioids have more difficulty traversing neural and vascular membranes ensuring lower concentration of drug needed to ensure continued receptor site activity Sinatra et al. (2000). Placental transfer of hydrophilic opioids are impeded and therefore diffuse across slowly and are unlikely to attain effective concentration in the fetus (60,68).

This gain in opioid mediated analgesic effect provides a local anesthetic 'dose sparing' effect allowing us to employ bupivacaine as an adjunct rather than primary analgesic as our infusions are 2-2.5 times as dilute as those traditionally seen in continuous labor epidural infusions Sinatra et al. (2000). A 2013 meta analysis that included 15 articles involving 1,997 patients, compared the effect of low concentration (defined as $\leq 0.1\%$ epidural bupivacaine or $\leq 0.17\%$ ropivacaine) versus high concentration of local anesthetics on obstetric and anesthetic outcomes (67). They concluded low concentrations of labor epidural solutions improve obstetric outcomes (decreased AVD, shorter duration of second stage of labor) and reduced maternal side effects (less motor blockade, better ambulation and decreased urinary retention) without compromising analgesia Sultan et al. (2013). One minute Apgar scores <7 favored the high concentration group. They recommended the use of low concentrations of local anesthetics for epidural analgesia to optimize obstetric outcome Sultan et al. (2013).

Quality of pain relief for continuous epidural infusion containing 0.05% bupivacaine plus 3 mcg/cc hydromorphone was evaluated in 1830 parturients requesting analgesia during labor and delivery (65). The infusion provided rapid and effective analgesia and minimal adverse events for patients whom differed in parity and at varying stages of labor. Pain relief was maintained in most patients without need for epidural reinforcement, Sinatra et al. (2002). Clinically significant adverse events including excessive maternal sedation, profound hypotension, respiratory depression, clinically significant motor blockade and severe fetal bradycardia were

not observed Sinatra et al. (2002). The fact that patients report highly effective pain control with epidural doses comparable to fentanyl is significant considering intravenous doses of fentanyl are 10-12 times more potent than hydromorphone Sinatra et al. (2000).

If there is a dose response relationship between epidural opioids with negative breastfeeding and neurobehavior outcomes, and these drugs act directly on brain tissue of the neonate thereby impeding the behaviors necessary for breastfeeding initiation, then research needs to focus on the transfer of drugs from the maternal epidural space, maternal circulation, across the placenta and across the neonatal blood brain barrier. Numerous in vivo and in vitro studies have examined the uptake and accumulation of epidurally administered bupivacaine and fentanyl into maternal and neonatal circulation(69,49,71,25)

To determine neonatal and maternal exposure to the agents of the epidural solution, a pilot study has been done by the author in 2013 at YNHH (French, 2012). In this prospective observational study, 10 healthy parturients with uncomplicated pregnancies received an initial 100 mcg hydromorphone and 9 ml 0.25% bupivacaine bolus, followed by continuous infusion of 0.05% bupivacaine and 3 mcg/ml at 14 ml/hr. (Standard protocol at YNHH). If necessary, additional boluses of 0.25% bupivacaine were given to maintain analgesia. Umbilical vein (UV) and Maternal vein (MV) blood samples were obtained within 15 minutes of delivery to determine hydromorphone and bupivacaine concentrations and the UV/MV ratio was calculated for each sample.

We compared our hydromorphone results with a similar study that evaluated MV and UV concentrations of fentanyl and bupivacaine after continuous labor epidural. Bader et al. (1995) examined the accumulation of epidurally administered 0.125% bupivacaine and 2 mcg/mL fentanyl at 14ml/hr in both maternal and fetal blood in 21 parturients. Their results did not find a statistically significant relationship between accumulation of either drug and length of infusion time but did suggest rapid placental transfer and equilibration of fentanyl between maternal and neonatal blood and a maternal-neonatal gradient for bupivacaine concentration, attributed to placental deposition and protein binding (7).

The results of our study were consistent with our hypotheses. We found with our solution, MV and UV concentrations were also independent of infusion length and the UV and MV concentrations of bupivacaine and hydromorphone were lower. This is because of the lower overall concentration of bupivacaine in the infusate and the greater hydrophilicity of hydromorphone as compared to fentanyl. All three measures (UV concentration, MV concentration, and UV/MV ratio) were lower for bupivacaine in our study with only 2/10 UV samples having detectable levels. All 21 UV samples in the Bader et al. (1996) study had detectable levels of bupivacaine.

In contrast, these three measures are almost equal for our 42 mcg/hr infusion of hydromorphone versus 28 mcg/hr infusion of fentanyl. Despite the 50% higher concentration of hydromorphone in our solution (3mcg/cc of hydromorphone versus 2mcg/cc of fentanyl in Bader's solution), the overall UV concentration of hydromorphone is similar to that of fentanyl. This is significant because other studies have found incidences of neonatal respiratory depression with fentanyl UV concentrations that were found in the Bader (1996) study(18,51,52,40,41). Given that the

potency of hydromorphone is only 1/10 to 1/12 that of fentanyl, the fetus is exposed to a lower equipotent opioid dose (Sinatra et al., 2002). The use of our solution could be more favorable with respect to limiting neonatal exposure to foreign substances, given the equal analgesic efficacy of our solution to that of the combination of 0.125% bupivacaine and 2mcg/ml fentanyl.

Labor Epidural Analgesia and Breastfeeding/ Neurobehavior

Breast milk provides all the necessary nutrients an infant needs and is the preferred choice of feeding according to the American Academy of Pediatrics (1). Breastfeeding has been reported to decrease the incidence of gastroenteritis, asthma, sudden infant death syndrome, otitis media, type 1 and 2 diabetes, lower the risk of obesity, improved performance on tests of cognitive function and certain types of childhood cancers (34). Benefits of lactation for the mother include decreased incidence of type 2 diabetes, breast, and ovarian cancer (34). Considering all the benefits that breastfeeding provides mother and infant it is imperative that factors that impact successful breastfeeding are identified to improve outcomes.

Continuous labor epidurals contain a combination of a local anesthetic and opioid are a popular technique for the treatment of labor pain with vaginal delivery. Epidural analgesia has been identified as a barrier to breastfeeding success (78,9,8,72,73,58,32,79). One mechanism is epidurally administered local anesthetic and opioid drug combination's readily crosses the placenta and fetal blood brain barrier and may depress necessary neonatal reflexes needed for rooting, swallowing or sucking (19,64,38,50,63). Evidence indicates neonates exposed to opioids have a less organized suck even when neurobehavior scores are similar to non-medicated neonates (53,61). Riorden et al. compared unmedicated and epidural exposed infants who scored similarly on neurobehavior scales but differed when breastfeeding behaviors were specifically examined, with opioid exposed neonates in the first 24 hours exhibiting increased sleepiness and a disorganized suck (61). If the neonates tone is depressed from epidural opiates it will impede the neonates ability to latch on to the breast. These factors may prevent good feeding behaviors in the first 24 hours of life which may prompt the mother to quit breastfeeding too soon. Most of the studies that assessed neurobehavior after epidural did not measure the complex behaviors of feeding that occur or the mothers contribution to the process. There have been very few studies that have focused specifically on breastfeeding behaviors (19,22,46), and only 2 studies that incorporated a breastfeeding assessment tool and a neonatal neurobehavior test.

A current review of the epidural analgesia and breastfeeding literature finds 3 studies where epidural analgesia was not implicated in adverse breastfeeding outcomes (19,57,80) while 3 retrospective studies (73,79,8) reported a significant negative association between breastfeeding outcomes and epidural analgesia. Those infants were less likely of suckling at the breast within the first 4 hours of life, their mothers reported not having enough milk, they were more likely to be partial breastfeeding or formula feeding at discharge and 12 weeks, and were less likely to have 2 successful breastfeeding encounters within the first 24 hours of life as assessed by the LATCH breastfeeding assessment tool (69) Appendix A

Prospective cohort studies also found epidural analgesia increased likelihood of breastfeeding difficulties after epidural with increased use of formula the first week postpartum (14) decreased

sucking in the first 2 hours after birth (58,10) and decreased breastfeeding rates at 2 and 6 months (14,16) compared to a control group of women who did not receive medication. Although there have been numerous studies that have addressed the relationship between epidural analgesia and breastfeeding there have been conflicting findings due to study design flaws and the use of different medications and doses (57,58,69). This has prevented the current literature from producing statistically significant findings of a link between breastfeeding success and the administration of epidural opioids (69). **None of these published studies that have addressed if there is a relationship between epidural hydromorphone and successful breastfeeding.**

Many studies do not assess breastfeeding outcomes in the immediate post-partum (73,32) instead mailing questionnaires to the mothers months after delivery which does not provide reliable data. After a woman is discharged there are a number of factors which may confound breastfeeding success. Returning to work (14,36) lack of social support,(14) race, level of education, (20) socioeconomic status (20) parity(44), marital status,(14) biological, physiological(44), psychological, smoking and elevated BMI(44), and socioeconomic status all impact early cessation of breastfeeding. Long-term successful breastfeeding, while clinically important, short term breastfeeding outcomes should be assessed, to determine exactly what is causing the decreased breastfeeding rate. If epidural hydromorphone (or any opioid) has the possibility of causing a physiological effect on breastfeeding, and the 1/2 life of epidural hydromorphone in maternal circulation is 2.5-3 hours then breastfeeding should be studied within the first few hours after delivery before the drugs have been metabolized and cleared in neonatal and maternal circulation (69). Many studies do not perform breastfeeding analysis until 24 hours or more after delivery, by which time the drugs have been completely metabolized by the neonate. For these reasons, this study will specifically measure short-term breastfeeding outcomes in epidural hydromorphone mother-infant dyads compared to nonmedicated mother- infant dyads.

Early contact between the newborn and mother is essential for the establishment of breastfeeding and should occur within the first hour postpartum (23). Placed skin-to-skin between the mother's breasts the newborn exhibits the instinctual behavior by rooting, finding the breast and sucking at approximately 1 hour of age (77). A prospective study in 19 hospitals with 21,842 mothers determined there was a positive correlation between the number of minutes a baby was skin-skin in the first 3 hours of life with the likelihood of exclusive breastfeeding even after controlling for intent to breastfeed (13). As part of our institutions Baby Friendly Initiative, skin-skin contact between the mother and baby occurs immediately after birth unless there is a contraindication. The first hour after birth is a very sensitive period for mother-infant interaction with early skin-to-skin contact shown to increase maternal oxytocin levels. Oxytocin stimulates milk ejection and production (31). Previous studies of epidural analgesia and breastfeeding (73,9,78) did not record the exact time the first breastfeed was initiated. One study (28) found if the first breastfeed occurred over 1 hour after delivery cessation of breastfeeding at 6 weeks postpartum was more likely. Because skin-to-skin contact in the immediate postpartum has been shown to have long term positive effects on over all breastfeeding duration the first breastfeeding measurement will occur at 1 hour.

Breastfeeding Assessment

Very few studies that examined epidural analgesia and breastfeeding have used an objective breastfeeding assessment scoring tool (80,73,79,32). There is no standardized method to assess

the breastfeeding encounter but several tools have been developed for breastfeeding assessment. These include the LATCH scoring system, Infant Breastfeeding Assessment Tool (IBAT), and the Mother Baby Assessment Tool (IBFAT). The LATCH (Jensen, Wallace) scoring system is used extensively by nurses at birthing centers and hospitals and is the breastfeeding assessment tool used at YNNH. It has been used by researchers (Baumgardner et al. and Cheng et al.) in their assessment of the effects of labor analgesia on breastfeeding and will be used for this study. LATCH is a breastfeeding charting system that assess individual breastfeeding sessions using a systemic model to gather information (35). The LATCH score includes all aspects of latching behavior by providing a score of 0, 1, 2 to key components of breastfeeding. L= is the infants ability to latch onto the breast, A= is the audible sound of swallowing, T=Type of nipple the mother has, C= Comfort of the mothers breast and nipple, H=Holding which is the amount of assistance the mother needs to hold the neonate (35). (Appendix A) To obtain the score all the areas of assessment are added to get a total for that breastfeeding session. For example a mother with previous breastfeeding experience, everted nipple, and an alert and vigorous infant could get a score of 9 or 10 (35). Successful breastfeeding defined by LATCH is a score >7 for 2 feeds in 24 hours (13,8).

The interrater reliability of the LATCH tool was high and ranged from 85.7%-100% and strong construct validity (2,62). Riorden et al. found a significant correlation between nurses and mothers assessment scores and both assessment scores positively correlated with duration of breastfeeding. These findings support previous research that assessed the validity of LATCH tool (2) and Matthews who found interrater reliability between raters' scores and mothers' scores 91%. A more recent study (3) found positive and significant correlations between researchers' scores for 46 observations using the IBFAT, MBA and LATCH. They reported all 3 assessment tools were compatible in the assessment of breastfeeding performance.

To obtain the effect of epidural analgesia on the neonates ability to breastfeed in the first 2-4 hours after delivery, 12 hour and 24 hours the LATCH assessment tool will be used. The 2-4 hour window coincides with the 1/2 life of hydromorphone. If hydromorphone does in fact potentially interfere with effective breastfeeding through a physiological mechanism breastfeeding will be assessed before the drug has been metabolized and cleared from maternal and neonatal circulation. The window also allows the researcher flexibility to accommodate the mother and infants feeding schedule.

Evaluating Neurobehavior of the Neonate

Assessment of the neonate after delivery is evaluated by Apgar scores at 1 and 5 minutes. While the Apgar score evaluates depression of vital function, it is not sensitive to the subtle differences or delayed onset of medications that may depress the neonate. The Neurologic and Adaptive Capacity Score (NACS) was specifically designed to detect central nervous system depression of the neonate from drugs and to differentiate those effects from birth trauma and perinatal asphyxia (4). The NACS has been the most widely used by obstetric anesthesia researchers since it was developed in 1982.

The NACS was developed by Amiel-Tison, Barrier and Shnider and contains portions of the Brazelton Neonatal Behavior Assessment Scale (NBAS) the Amiel-Tison neurological exam, and the Scanlon Early Neonatal Neurobehavior Scale (ENNS)(5). The criteria chosen for the NACS was from those used in standard clinical and neurologic behavioral testing. Items chosen for the NACS were those that have been shown to be affected by perinatal asphyxia, birth trauma

or obstetric medications. . It does not specifically assess breastfeeding but uses 20 criteria to assess 5 general areas: adaptive capacity, passive tone, active tone, primary reflexes and general neurologic status (4). The 5 general areas are given a score of 0=absent or grossly abnormal; 1= mediocre or slightly abnormal; or 2= normal with the maximum total of 40.(Appendix B). Because reflexes and passive muscle tone depend on the age of the neonate it was designed to be used by infants greater than 37 weeks.

Birth trauma, obstetric medications, neurologic disease and perinatal asphyxia all demonstrate abnormalities in tone, therefore the NACS uses 8 separate tests for tone. There are 4 tests of passive tone in the upper and lower extremities equally, that allows for detection of hypotonia, which if is in one side of the body or only seen in the upper body is indicative of birth trauma or perinatal asphyxia (4). The tests of active tone allows detection of abnormally high tone in the neck extensors which occurs in intracranial hypertension (6,63). Drugs and anesthetics frequently show a more general mediocre tone presenting as more general depression (6,63). This portion of the test takes 60-90 seconds.

4 primary reflexes were chosen in the general assessment. Motor activity, alertness/ state of consciousness and quality of cry is observed throughout the exam. The adaptive capacity portion of the tests assessed decrement response to light and sound which both are affected with drugs (12,48,15). This portion of the tests takes a bit more time than the reflex portion and requires close observation in testing and assessment to decrement responses.

The NACS test gives a total score that evolves from a sum of the scores on each individual test made possible by the fact poor performance and optimal performance are scored progressively like the APGAR (4). The score 35-40 was chosen to represent a neurological robust neonate and scores of 34 and below may identify neonates with potential problems. The scores should be closely examined, and low scores within a certain group of items such as tone or adaptive capacity may be of greater importance than the total score. For example the neonate may have a high score of 35, but all 5 points may have been lost in one category such as tone or adaptive capacity (4). The grouping of the tests allows the observer to distinguish the various response patterns, and in subsequent testing the examiner can focus on the score that was not optimal (4). Although the 20 items can be performed in any order, they are listed on the score sheet in the most logical and easiest to follow the examiner may change the order dependent on the neonates state of consciousness. (Appendix B). The examiner determines the neonates best performance, therefore if a neonate scores a 0 or 1 on an item, the item should be retested later in the exam to confirm the low number (5).

The test does not require any special equipment, it is not noxious to the neonate, it is simple to perform and score with an interrater reliability of 92.8%. The test takes about 5 minutes to perform and will take place with the mother present. The NACS test will be administered at the same time points of the LATCH assessment: 3, 12 and 24 hour.

There have been studies that have addressed the association between Neonatal Adaptive Capacity Scores (NACS) and epidural opioids (45,9,55). Beilin (9) reported NACS scores when mothers epidural infusions contained greater than 150 Mcg of fentanyl were significantly lower

compared to bupivacaine without fentanyl. The high dose fentanyl group of women were also less likely to be breastfeeding at 6 weeks postpartum when compared to the other group. Loftus et al. randomized women into 3 groups, to either receive fentanyl and bupivacaine, bupivacaine and sufentanil or bupivacaine alone in their continuous labor epidural infusions. The fentanyl bupivacaine group had the lowest scores compared to the other 2 groups at 24 hours post-partum, but no differences at 2 hours after birth. The fentanyl bupivacaine group did not show an improvement in NACS at 24 hours postpartum that is normally seen. The authors postulated due to the immature liver enzymes of the neonate the clearance of the fentanyl was low. Radzysinski (2004) evaluated 56 breastfeeding mother infant dyads 28 unmedicated and 28 delivered with epidural analgesia. Breastfeeding behaviors were evaluated using the Preterm Infant Breastfeeding Behavior Scale (PIBBS) and the infants neurobehavior with the NACS. Results indicated the higher the infant score on the NACS the higher the infant scored on breastfeeding behaviors. When determining what is important for the infant to physiological latch and feed, and intact central nervous system may be an essential component (58). Cheng et al. found a positive correlation between effective breastfeeding and NACS scores. The authors concluded the NACS score may prove beneficial in identifying neonates which may be at a high risk of breastfeeding problems.

There have been no studies that examined whether epidural hydromorphone impacts breastfeeding or neonatal neurobehavior. Use of the LATCH and NACS for assessment of epidural analgesia and breastfeeding will allow for individual components of breastfeeding behavior in the neonate as well as general neurologic effects the epidural analgesia may produce in the neonate.

Because breastfeeding has so many positive health benefits, in 2010 the United National Children's Fund and World Health Organization launched a program to promote exclusive breastfeeding for the first 6 weeks of life called the Baby Friendly Hospital Initiative. YNHH is in the process of becoming Baby Friendly, a designation that states as its goal of increasing the initiation and duration of exclusive breastfeeding. Epidural hydromorphone is commonly used on our labor and delivery unit and it should be determined whether epidural hydromorphone has an observable effect on neonatal breastfeeding neuro behaviors. It's important that we provide up to date and accurate information to the mother so she can make an informed decision about labor pain management.

The purpose of our study is to determine neonatal (and maternal) exposure to the agents of our epidural solution and determine if there is a difference in observable breastfeeding behaviors and neonatal neurobehavior status between neonates whose mother's received epidural hydromorphone and bupivacaine for labor pain and neonates whose mother's received no analgesia for labor pain.

1. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

* Indicates Research Procedures

Study Design: This is a prospective observational and comparative study

Setting: The study will take place on the Labor and Birth and Postpartum unit's of Yale New Haven Hospital.

Sample: An unmedicated control group of 51 mother-infant dyads who did not receive any pain medication or central nervous system (CNS) depressants and 51 mother-infant dyads who have elected epidural analgesia for labor pain and were exposed to our standard epidural analgesia infusate.

Procedure: Before initiation of this study, an in-service will be provided to the Labor and Birth, and Post-Partum RN's as well as the nurse-midwives by Cynthia French Co-Investigator, concerning the aims of the research project. The educational in-service will provide a review of the current literature on the effects of epidural analgesia on breastfeeding and neurobehavior. An explanation of the meaning of the various drugs and doses used in epidural analgesia in relation to nursing practice and the problem the research is addressing. Emphasis will be placed on our current practice of hydromorphone in our epidural analgesia and the lack of literature on epidural hydromorphone and its effects on breastfeeding, neurobehavior and placental transfer. Cynthia French CRNA will be blinded and sole data collector of breastfeeding using the LATCH breastfeeding assessment tool and neurobehavior using the NACS test. She was trained to use the LATCH tool by Marie Pulito and Heather Henry, lactation consultant's at YNHH. Cynthia French attended the Brazelton Institute at Harvard Medical School and is certified to administer the Neonatal Behavior Assessment Scale (NBAS). (Appendix C). After all evidence of the epidural has been removed, she will stay with the mother-infant dyad during data collection sessions and record and time of observations at 3, 12 and 24 hours.

The study group will consist of 51 mother- infant dyads whose mothers request epidural for pain relief during labor and desire to breastfeed. After the epidural is placed she will be given a 9 cc bolus of 0.25% bupivacaine with 1:200,000 epinephrine, 100 mcg hydromorphone followed by a continuous infusion of 0.05% bupivacaine with 3 mcg. hydromorphone at 14 mL/hr. This is the standard of care used for labor epidurals at our institution and was developed by our obstetric anesthesia department. If the patient fits the criteria for inclusion in the study she can be consented by any of the co-investigators excluding Cynthia French CRNA. Only healthy women will be included with no complications of pregnancy, no fetal anomalies and they must vaginally deliver.

All conditions of the epidural are for clinical purposes only and no manipulation will occur for study. The epidural will be placed only upon patient request for pain management. After the patient has received her epidural and is in a pain free state, she will be asked if she would like to be included in this study. Risks and benefits will be discussed with the patient and consent obtained. It will be made clear to the patient her care will not change if she decides to participate in the study and she can withdraw at any time.

The control group will consist of 51 mother-infant dyads who were unmedicated during labor, vaginally deliver and desire to breastfeed. The unmedicated will be recruited by the OB nurses and nurse-midwives. They will alert a study team member of a possible candidate for the study

based on the criteria of being unmedicated, healthy mother, uncomplicated pregnancy, healthy term infant and received no analgesic medications during labor. She will be consented for the study before she vaginally delivers. If she crosses over to an epidural she can remain in the study in the epidural cohort.

Methods for Both Epidural and Non-Medicated Mother-Infant Dyads

The first breastfeed data collection (LATCH) and NACS* will take place within 3-4 hours after delivery. The 3-4 hour time frame was chosen to avoid the adverse and/or stimulating effects of birth and routine neonatal care on neonatal breastfeeding and neurobehavior. The OB nurses use the LATCH tool to guide patient teaching, this is the standard of care at YNHH. The NACS is research, takes about 5 minutes to administer and will be performed in the presence of the mother with an explanation of the assessment. LATCH and neurobehavior(NACS)* will occur again at 12 hours after birth. The standard of care at our institution is for the nurses to document LATCH scores every shift and enter the scores into the computerized charting system. The 3 hour time frame was used to be within the crucial time of establishing breastfeeding (19) and to coincide with the 1/2 life of the epidural hydromorphone (19). The NACS is research. LATCH scores will also be collected at 24 hours after delivery as standard of care. The 24 hour time point is long after the expected time the neonate would complete metabolism of the epidural opioids.(69) A final NACS score will be assessed at 24 hours postpartum.* Cynthia French will remain blinded to study group despite access to EMR. After delivery and the epidural is removed the epidural record is closed. When accessing the patients EMR after closure of the epidural record, the history of epidural analgesia does not come up automatically but requires specific steps to access that information. Ms French will only open the LATCH assessment section.

The information we will record from the mother will be age, weight, parity, height, allergies, weeks of gestation, time of epidural test dose and time of delivery of neonate and delivery of placenta. The mother will be asked to fill out a demographic form after consent has been obtained (Appendix D). The information collected from the demographic form will help to control for confounding variables which are known to affect breastfeeding success.

The information gathered about the neonate will be, sex, weight at birth and 24 hours, Apgars, LATCH and NACS scores.

2. Genetic Testing N/A ☒

A. Describe

- i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
- ii. the plan for the collection of material or the conditions under which material will be received
- iii. the types of information about the donor/individual contributors that will be entered into a database
- iv. the methods to uphold confidentiality

- B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
- C. Is widespread sharing of materials planned?
- D. When and under what conditions will materials be stripped of all identifiers?
- E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
 - i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?
- F. Describe the provisions for protection of participant privacy
- G. Describe the methods for the security of storage and sharing of materials

3. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

This study will include mother-infant dyads who are aged 18 or older, uncomplicated pregnancy, labor, and vaginal delivery; use of either epidural analgesia only or no analgesic medications during labor and delivery; delivery of a healthy term infant; maternal desire to breastfeed.

4. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

- | | | |
|--|--|---|
| <input checked="" type="checkbox"/> Children | <input type="checkbox"/> Healthy | <input type="checkbox"/> Fetal material, placenta, or dead fetus |
| <input type="checkbox"/> Non-English Speaking | <input type="checkbox"/> Prisoners | <input type="checkbox"/> Economically disadvantaged persons |
| <input type="checkbox"/> Decisionally Impaired | <input type="checkbox"/> Employees | <input checked="" type="checkbox"/> Pregnant women and/or fetuses |
| <input type="checkbox"/> Yale Students | <input type="checkbox"/> Females of childbearing potential | |

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

5. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

All parturients in labor who request an epidural who have received Hydromorphone bolus in the epidural space and continuous infusion of Bupivacaine and Hydromorphone in the epidural space.

Inclusion criteria:

Healthy multigravida patients in an active labor, receiving obstetrical and anesthesia care (neuraxial labor analgesia) on the Labor and Delivery unit at Yale New Haven Hospital

Healthy multigravida patients who received no analgesia for labor and delivery
 Healthy neonates
 Uncomplicated Pregnancy's
 Between 38- 41 weeks gestation
 English speaking patients.
 Previously breastfed and desire to breastfeed again
 Head down fetal position

Exclusion criteria:

Any women with any complication of pregnancy (preeclampsia etc)
 Any women with preexisting medical conditions
 Any woman with a history of a chronic back pain or back surgery, or congenital abnormalities of vertebral column(scoliosis, hemivertebra) or spinal cord(syrinx), or spinal cord layers (dural ectasia).
 Any fetal abnormality.
 Malposition of fetus

Relations with the subjects:

Only the patients under active anesthesia care with established neuraxial labor analgesia will be approached. No charts will be reviewed prior to establishment of neuraxial labor analgesia.

6. How will eligibility be determined, and by whom?

The standard practice of our obstetric anesthesia department is to be aware of all the women on the labor floor at any given time whether they have an epidural or not. This ensures the safety of all patients if an unanticipated event occurs that would jeopardize the life of a mother or her unborn child that require an emergency intervention such as a cesarean section. It also informs the anesthesia team of patients with complications of pregnancy that have anesthetic implications and determine her care. Because the anesthesia providers know the health status of all the women on the floor including women who are unmedicated, the study investigators can determine eligibility when they review the medical record.

7. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The study procedures present no known risks. No experimental conditions are placed on the subjects. The independent variable (epidural analgesia) will be the hospital's standard treatment and will be self-selected by participants prior to researcher contact. The participants will have already decided to breastfeed. Participants will be aware of the data collection. Neonates will not be awakened for study procedures. The LATCH and NACS are not adverse or noxious to the neonate. The principal investigator will be strictly an observer of the breastfeeding, and if assistance is identified, the patient's nurse will be contacted.

The NACS test takes 5 minutes to perform and will be done in the presence of the mother with an explanation of the findings as the test proceeds and any changes that may or may not be noted over the 24 hour time frame. Every consideration will be made to time the test so it

remains convenient for the mother as well as fall into an appropriate window for data to remain relevant to the study.

The LATCH test is the standard of care for mother-infant dyads every 12 hours postpartum. The first LATCH assessment in the first 3 hours after delivery is research. Again every consideration will be made to be convenient for the mother as well as remain in an appropriate window to maintain integrity of the study.

If for any reason the mother decides she no longer wants to be a part of the study she will be withdrawn and clearly stated it will not affect the care she receives.

8. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

Consent for anesthesia will be obtained before the epidural catheter is placed is done at the request of the laboring women. It is always the patient's choice to receive or not to receive an epidural for labor.

The LATCH test and NACS test will be performed by an experienced APRN who has been trained and certified (Appendix C) to assure no risk to the infant. The assessments will be performed in the presence of the mother, with an explanation of the test as it moves along. If for any reason she wants the test to stop and withdraw from the study she may with no affect on the care she receives.

To minimize risks to subjects privacy, patients will be invited to participate in their private room. All data collection forms will be coded and the master list of names and code numbers will be locked in a locked office in a locked file cabinet.

9. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

- a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal Risk
- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? Minimal Risk
- c. Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from <http://www.yale.edu/hrpp/forms-templates/biomedical.html> for
 - i. Minimal risk
 - ii. Greater than minimal/moderate risk
 - iii. High risk

The principal investigator is responsible for monitoring the data, assuring protocol

compliance, and conducting the safety reviews at the specified frequency This will be done monthly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment.

Either the principal investigator or the Human Investigation Committee (HIC) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. In the unlikely event that such events occur, serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the HIC or HSC (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project There will be weekly meeting and discussions between Dr Chung and the co- investigators. If modifications need to be made they will be adjusted accordingly, and the HIC board will be notified. All measures will be taken to ensure patient safety and confidentiality

10. Statistical Considerations: Describe the statistical analyses that support the study design.

Breastfeeding and Neurobehavior

A power analysis was used to estimate the sample size needed to test for differences between means of 2 groups (80% power; 1-sided α of .05, for medium effect size of .50), which indicated the need for 51 participants in each of the study groups.

The data will be collected by Cynthia French who will be blinded to whether they received an epidural or not. The data will then be coded and examined graphically in box plots and within group histograms to determine whether the variables were distributed symmetrically and free of outliers and that the spread of data is consistent across the groups. Measure of central tendency will be calculated and multiple regression will determine the degree of relationship between the NACS and breastfeeding behaviors on the LATCH. Pearson correlations between the variables will be reviewed to examine the possibility of a linear relationship between the variables.

<p align="center">SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES</p>
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If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS N/A

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

- a. targeted for enrollment at Yale for this protocol_102 Mother/Infant Dyads__
- b. If this is a multi-site study, give the total number of subjects targeted across all sites__N/A__

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

- | | | |
|---|--|---|
| <input type="checkbox"/> Flyers
<input type="checkbox"/> Posters
<input type="checkbox"/> Letter
<input checked="" type="checkbox"/> Medical Record Review
<input type="checkbox"/> Departmental/Center Newsletters
<input type="checkbox"/> YCCI Recruitment database
<input type="checkbox"/> Other (describe): | <input type="checkbox"/> Internet/Web Postings
<input type="checkbox"/> Mass E-mail Solicitation
<input type="checkbox"/> Departmental/Center Website
<input type="checkbox"/> Departmental/Center Research Boards
<input type="checkbox"/> Web-Based Clinical Trial Registries
<input type="checkbox"/> Clinicaltrials.gov Registry (do not send materials to HIC) | <input type="checkbox"/> Radio
<input type="checkbox"/> Telephone
<input type="checkbox"/> Television
<input type="checkbox"/> Newspaper |
|---|--|---|

Recruitment Procedures:

- a. Describe how potential subjects will be identified.
Patients will be identified through medical chart review.
- b. Describe how potential subjects are contacted.
Upon request by a women in labor for an epidural for pain management, the epidural will be placed under the anesthesia departments standard of care for epidural placement. After placement, routine pain medication will be administered and a continuous epidural infusion started; all standard of care. After the patient achieves a state of comfort and inclusion criteria has been met, either Dr Chung or a co-investigator will approach the patient, explain the aims of the study and ask if she would like to be included. If she would like to be included inconveniences, risks and benefits of the study will be discussed and consent signed.

Unmedicated mothers will be contacted by the study team (excluding Cynthia French). The standard practice of our obstetric anesthesia department is to be aware of all the women on the labor floor at any given time whether they have an epidural or not. This ensures the safety of all patients if an unanticipated event occurs that would jeopardize the life of a mother or her unborn child that require an emergency intervention such as a cesarean section. It also informs the anesthesia team of patients with complications of pregnancy that have anesthetic implications and determine her care. Cynthia French will not be working on the labor and delivery unit when patients are recruited.

- c. Who is recruiting potential subjects?
Recruitment will be by all study personnel excluding Cynthia French.

Screening Procedures

- d. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No
- e. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

- ☐ Names
- ☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
- ☐ Telephone numbers
- ☐ Fax numbers
- ☐ E-mail addresses
- ☐ Social Security numbers
- ☐ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
- ☐ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers, including license plate numbers
- ☐ Device identifiers and serial numbers
- ☐ Web Universal Resource Locators (URLs)
- ☐ Internet Protocol (IP) address numbers
- ☐ Biometric identifiers, including finger and voice prints
- ☐ Full face photographic images and any comparable images
- ☐ Any other unique identifying numbers, characteristics, or codes

3. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

- ☐ Yes, all subjects
- ☒ Yes, some of the subjects
- ☐ No

If yes, describe the nature of this relationship.

Members of the research team may have direct patient contact with potential subjects. The obstetric anesthesia team, including co-investigators, responds promptly to women who request epidural analgesia for pain relief during labor. There are many members of the anesthesia team who are not co-investigators who will introduce us to patients who are potential subjects. Nurses, nurse mid-wives and OB-GYN physicians who are part of the women's care team also may introduce the researchers to potential subjects.

4. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one: For entire study: _____ For recruitment purposes only: X _____

- i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
A large number of potential subjects are seen in the department every day. It would be impracticable to obtain authorization and screening from each patient. Authorization will be obtained for the study, after potential subjects are identified.
- ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

5. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

- ☒ Compound Consent and Authorization form
☐ HIPAA Research Authorization Form

6. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

The PI and co- investigators will obtain consent from subjects except Cynthia French CRNA

7. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Consent for inclusion in the study will be discussed with the parturient after she has received her epidural and is in a comfortable state. Non-medicated mothers will be consented for inclusion in the study 1-2 hours after delivery. All discussions will take place in the patients private room with family members that are present. This will allow for ample time for the mother's as well as other family members to ask questions and consider if they want to take part in the study. The mothers will give permission for their infants to be in the study.

8. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

If the patient has capacity to consent to medical care and treatment during labor she can consent for inclusion in the study. Because labor pain may cause women to temporarily not have the ability to think thoroughly and make decisions a plan is in place to assure the women are comprehending the study and know what they are consenting to. The epidural mother's will be approached after their epidural is placed and they are in a state of comfort. Non-medicated mother's will be approached 1-2 hours after delivery when she is no longer in labor pain.

9. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.
Consent form is included.

10. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

Only English speaking parturients for initial study

11. **Consent Waiver:** In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

- ☐ Not Requesting a consent waiver
☐ Requesting a waiver of signed consent
☐ Requesting a full waiver of consent

A. Waiver of signed consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6)**

- ☐ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

- a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☐ No

- b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☐ No

OR

- c. Does the research activity pose greater than minimal risk?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note:

Recruitment/screening is generally a minimal risk research activity

☐ No

AND

- d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the Entire Study** (Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes *If you answered yes, stop. A waiver cannot be granted.* ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. Full waiver of consent: (No consent from subjects will be obtained for the activity.)

☒ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?

☐ Yes *If you answered yes, stop. A waiver cannot be granted.* Please note: Recruitment/screening is generally a minimal risk research activity

☒ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☒ No

c. Why would the research be impracticable to conduct without the waiver? A large number of potential subjects are seen in the department every day. It would be impracticable to obtain authorization for screening from each patient. Authorization will be obtained for the study, after potential subjects are identified.

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

There is no pertinent information for the subjects.

☐ **Requesting a full waiver of consent for the Entire Study** (Note: If PHI is collected, information here must match Section VII, question 6.)

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?

☐ Yes *If you answered yes, stop. A waiver cannot be granted.*

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS
--

Confidentiality & Security of Data:

- a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

The patients age, weight, height, allergy information, medication information, time of epidural placement, total time of epidural infusion, time of infant delivery, time of placenta delivery, LATCH scores, NACS scores and MRN number.

The newborns weight at delivery and 24 hours, Apgars will be recorded.

- b. How will the research data be collected, recorded and stored?

Initially data will be collected on paper forms and kept in study files that will be stored in a locked file cabinet in the anesthesia office. De-identified data will be entered into an electronic data base and stored on the PI's network drive. After 6 months, the paper copies will be shredded immediately and data inputted into the computer with an ID number with no identifiable data.

- c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☐ Desktop Computer ☐ Other
- d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? All data will be stored on encrypted software.

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see <http://hipaa.yale.edu/guidance/policy.html>

- e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Paper files will be entered into excel spread sheet in network server password protected that only key members will have access to. After 6 months the paper files will be destroyed and all that will remain are the study ID numbers with no identifiable data. Cynthia French will be in charge of destroying the paper copies.

- f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

Dr Chung and the co- investigators will have access to the PHI. Cynthia French will only have access to the de-identified data during the study. When the study is completed, Cynthia French will have access to all the information.

- g. If appropriate, has a Certificate of Confidentiality been obtained? N/A

- h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -

incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported. None

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)


The potential benefit to our laboring women and neonates is significant. Our goal is to provide our mothers excellent labor pain relief while minimizing adverse affects epidural analgesics may have on the neonate which may impede neonatal neurobehavior and breastfeeding.

Subjects in this study will benefit from participation because we are performing breastfeeding assessment and neurobehavior test 3 times in a 24 hour time period. Because of the study procedures we may find some of our subjects may be having problems breastfeeding or the baby's may have depressed neurobehavior that is impeding breastfeeding that might have gone undetected under normal circumstances. If we detect problems we can alert the postpartum nurses or lactation consultants to assist the subjects which has the potential to improve breastfeeding outcomes.

There is no data on hydromorphone drug accumulation in the MV/UV after epidural infusion. This study will contribute to the literature and may prove to have a better neonatal safety profile.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research? The alternative is to not participate in the study and to receive assessments such as LATCH as part of routine care.
2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
No payment.
3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
No cost to subjects
4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
This is a minimal risk study, therefore N/A.
 - a. Will medical treatment be available if research-related injury occurs?
 - b. Where and from whom may treatment be obtained?
 - c. Are there any limits to the treatment being provided?
 - d. Who will pay for this treatment?
 - e. How will the medical treatment be accessed by subjects?

 <p style="text-align: center;"> Yale University Human Investigation Committee Request for Approval of Amendment to Add or Remove Co-Investigator(s) and Study Personnel 100 FR 11 (2014-1) </p>		
<p>Instructions: This form should be used only to submit to the HIC requests to <i>add or remove</i> co-investigators or other study personnel* from active protocols. The updated HIC application and any other study documents incorporating requested changes should be submitted as usual to the HIC at time of reapproval <i>unless</i> the personnel are individually named on the consent form (e.g., consenting personnel; medical back-up; etc.) If so, the updated consent form must be submitted with this request.</p> <p>* A separate form is available and must be used for a change in principal investigator.</p>		
<p>HIC Protocol Number: _1407014373_ Date: 3/28/15</p> <p>Title of Research Project: _ :Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life</p>		
<p>Name of Principal Investigator: _Keun Sam Chung MD</p> <p>PI Signature: _____</p>		
<p>PI Campus Address: Yale University School of Medicine, 333 Cedar Street, TMP 3, P.O. Box 208051, New Haven, CT, 06520-8051</p>		
<p>Email: keun.chung@yale.edu</p>	<p>Phone Number: 203-737-1818</p>	
<p>Correspondent Name: Cynthia French</p>	<p>E-mail: cyntfre@aol.com</p>	
<p>Yale Cancer Center CTO Correspondent (If applicable) Name:</p>	<p>E-mail:</p>	

Please complete a new line for each addition or removal of study personnel (to extend the grid, press TAB from the last cell in the last row of the grid, and a new row will automatically be created):

- **Name** – Enter the full name **and** degree of the person to be added to or removed from the study.
- **Add or Remove** – Enter ‘Add’ or ‘Remove’ as appropriate for each person being added or removed from the protocol.
- **Role of Personnel** – Please identify the study role of the added or removed personnel: **Co-Investigator, Study Personnel, Correspondent or Consultant** (see definitions in the HIC Application Instructions, p. 10, at <http://www.yale.edu/hrpp/forms-templates/biomedical.html>)
- **HSPT Training** – Has this person completed required Human Subjects Protection Training? If not completed through Yale University, please submit copies of any certificate of completion.
- **HIPAA Training** – Has this person completed the required HIPAA Training? If not completed through Yale University, please submit copies of any certificate of completion.
- **Yale Affiliation** – Please identify whether this person is a faculty member, an employee, trainee or student of Yale University. If Yale-affiliated, please identify their position with Yale. If **non-Yale-affiliated**, please identify the organization with which they are affiliated.
- **NetID** – Please indicate the Yale researcher’s NetID. This will provide accurate information for training completion information.

Investigator Interests:

Do any new research personnel who are responsible for the design, conduct or reporting of this project, or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research

<http://www.yale.edu/hrpp/policies/index.html#COI>

☐ Yes ☒ No

Does a newly added member on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☒ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form:

<http://www.yale.edu/coi/>


NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

Name	Add or Remove	Ability to consent (check box if Yes)	Co-Investigator, Study Personnel, Correspondent or Consultant?	HSPT & HIPAA Training ? Y/N/ N/A	Yale Affiliation/non-Yale Affiliation (identify institution)	NetID
Katrina Pinkerton-Lloyd	Add	<input type="checkbox"/>	Co-Investigator	Yes	Yale University Student	Kp389
		<input type="checkbox"/>				
		<input type="checkbox"/>				

Does this amendment add any new study locations? ☐ Yes

☒ No

If yes, list location:

 <p>Yale University Human Investigation Committee Request for Approval of Amendment to Add or Remove Co-Investigator(s) and Study Personnel 100 FR 11 (2014-1)</p>						
<p>Instructions: This form should be used only to submit to the HIC requests to <i>add or remove</i> co-investigators or other study personnel* from active protocols. The updated HIC application and any other study documents incorporating requested changes should be submitted as usual to the HIC at time of reapproval <i>unless</i> the personnel are individually named on the consent form (e.g., consenting personnel; medical back-up; etc.) If so, the updated consent form must be submitted with this request.</p> <p>* A separate form is available and must be used for a change in principal investigator.</p>						
<p>HIC Protocol Number: <u>1407014373</u> Date: Jan 27, 2015</p> <p style="text-align: center;">Title of Research Project: <u>Old Title Maternal and Neonatal Hydromorphone and Bupivacaine Concentrations After Epidural Analgesia During Labor and its Effect on Neonatal Neurobehavior and Breastfeeding</u> New Title: Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life</p>						
<p>Name of Principal Investigator: <u>Denis Snegovskikh MD</u></p> <p>PI Signature: _____</p>						
<p>PI Campus Address: Yale University School of Medicine 333 Cedar St, TMP 3, P.O. Box 208051, New Haven, Ct 06520-8051</p>						
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Email: <u>denis.snegovskikh@yale.edu</u></td> <td style="width: 50%;">Phone Number: <u>203-737-1818</u></td> </tr> <tr> <td>Correspondent Name: <u>Cynthia French CRNA</u></td> <td>E-mail: <u>cyntfre@aol.com</u></td> </tr> <tr> <td>Yale Cancer Center CTO Correspondent (If applicable) Name:</td> <td>E-mail:</td> </tr> </table>	Email: <u>denis.snegovskikh@yale.edu</u>	Phone Number: <u>203-737-1818</u>	Correspondent Name: <u>Cynthia French CRNA</u>	E-mail: <u>cyntfre@aol.com</u>	Yale Cancer Center CTO Correspondent (If applicable) Name:	E-mail:
Email: <u>denis.snegovskikh@yale.edu</u>	Phone Number: <u>203-737-1818</u>					
Correspondent Name: <u>Cynthia French CRNA</u>	E-mail: <u>cyntfre@aol.com</u>					
Yale Cancer Center CTO Correspondent (If applicable) Name:	E-mail:					

Please complete a new line for each addition or removal of study personnel (to extend the grid, press TAB from the last cell in the last row of the grid, and a new row will automatically be created):

- **Name** – Enter the full name **and** degree of the person to be added to or removed from the study.
- **Add or Remove** – Enter ‘Add’ or ‘Remove’ as appropriate for each person being added or removed from the protocol.
- **Role of Personnel** – Please identify the study role of the added or removed personnel: **Co-Investigator, Study Personnel, Correspondent or Consultant** (see definitions in the HIC Application Instructions, p. 10, at <http://www.yale.edu/hrpp/forms-templates/biomedical.html>)
- **HSPT Training** – Has this person completed required Human Subjects Protection Training? If not completed through Yale University, please submit copies of any certificate of completion.
- **HIPAA Training** – Has this person completed the required HIPAA Training? If not completed

through Yale University, please submit copies of any certificate of completion.

- **Yale Affiliation** – Please identify whether this person is a faculty member, an employee, trainee or student of Yale University. If Yale-affiliated, please identify their position with Yale. If **non-Yale-affiliated**, please identify the organization with which they are affiliated.
- **NetID** – Please indicate the Yale researcher's NetID. This will provide accurate information for training completion information.

Investigator Interests:

Do any new research personnel who are responsible for the design, conduct or reporting of this project, or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research

<http://www.yale.edu/hrpp/policies/index.html#COI>

☐ Yes ☒ No

Does a newly added member on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☒ No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form:

<http://www.yale.edu/coi/>

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

Name	Add or Remove	Ability to consent (check box if Yes)	Co-Investigator, Study Personnel, Correspondent or Consultant?	HSPT & HIPAA Training? Y/N/ N/A	Yale Affiliation/non-Yale Affiliation (identify institution)	NetID
Zachary Walton MD	Add	<input checked="" type="checkbox"/>	Co-Investigator	Y	Yale Anesthesiology Fellow	Zdw4
		<input type="checkbox"/>				
		<input type="checkbox"/>				

Does this amendment add any new study locations? ☐ Yes

☒ No

If yes, list location:

Yale University and University of Connecticut IRB Authorization Agreement

Yale University IRB Authorization Agreement

Institution A —Name of Institution or Organization Providing IRB Review: Yale University Federalwide Assurance (FWA) #: 00002571

Institution B —Name of Institution Relying on the Designated IRB: University of Connecticut Federalwide Assurance (FWA) #: 00007125
--

The Officials signing below agree that Institution B may rely on the designated IRB for review and continuing oversight of its human subject research described below (*check one*)

☒ This agreement is limited to the following:

Study Title: Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life

IRB# 1407014373

Funding Source: Departmental Funding

The review performed by the designated IRB (Institution A) will meet the human subjects protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA and with all applicable laws, rules and regulations. Institution B will also ensure that all tests and procedures involving human subjects will be conducted at properly licensed facilities staffed by qualified personnel. This Agreement shall remain in effect until completion and closure of the study, unless terminated by either party upon thirty (30) days' advance written notice. This document must be kept on file at both institutions and provided to OHRP upon request.

Roles of Institution A:

1. Conduct review of research according to all applicable regulations and laws, including initial review, continuing review, and review of modification to previously approved research.
2. Suspend or terminate IRB approval.
3. Review unanticipated problems involving risks to participants or others.
4. Review incidents of serious or continuing non-compliance.
5. Notify the researchers and organizations in writing of its decisions.
6. When appropriate, conduct on-site or remote post-approval monitoring or audits, unless delegated to Institution B.
7. Specify the contact person and provide contact information for Institution A.
8. Institution A is responsible for reporting to organizational officials, regulatory agencies and sponsors any determinations of serious or continuing non-compliance, unanticipated problems involving risks to participants or others, or any suspensions or terminations of IRB approval.

17. Institution B will specify the contact person and provide contact information for Institution B.

Signatures:

Authorized Official of (A):


(signature)

2/2/15
(date)

Name: Andrew Rudczynski, Ph.D.

Title: Associate Vice President, Research Administration

Mailing Address: Office of Research Administration

Yale University

47 College Street, Suite 216Y

New Haven, CT 06510 - 3209

Phone: (203) 785-3012

Fax: (203) 785-3510

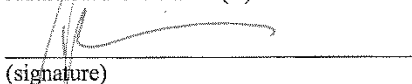
Email: andrew.rudczynski@yale.edu

Administrative Contact:

Monika Lau, HRPP, 55 College St., New Haven, CT 06510

Phone: (203) 737-4434; Fax (203) 785-4688; email: monika.lau@yale.edu

Authorized Official of (B):


(signature)

4/15/15
(date)

Name: Jeffrey R. Seemann, Ph.D.

Title: Vice President for Research

Phone: 860-486-3619

Email: Jeffrey.seemann@uconn.edu

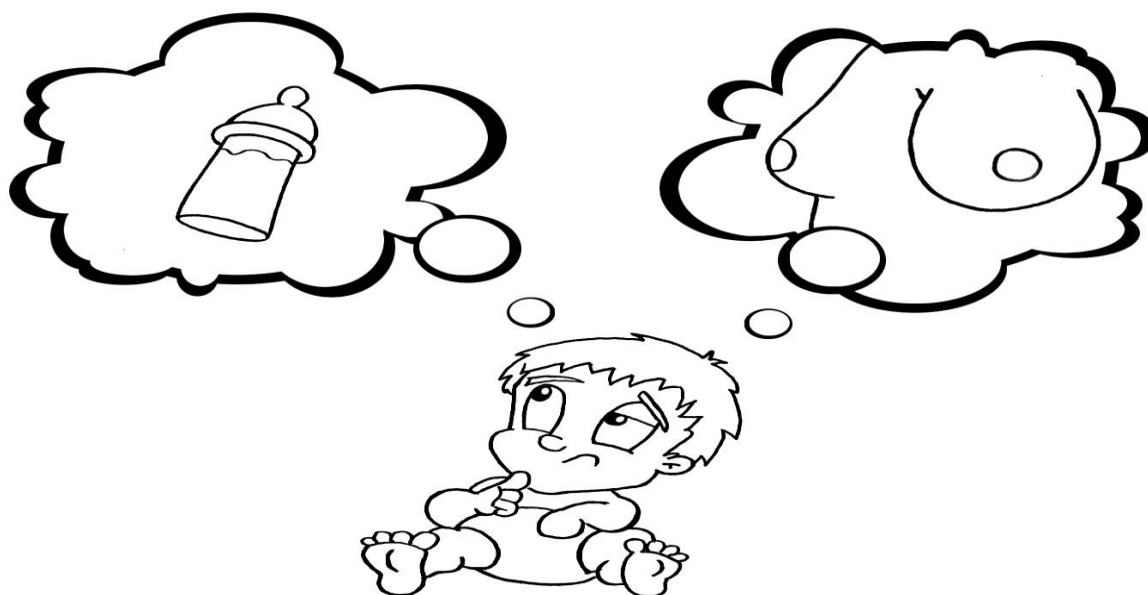
Appendix F: Study Information for Physicians, Midwives, etc.**Effect of Labor Epidural Analgesia with Hydromorphone on Breastfeeding and Neonatal Neurobehavioral Outcomes in the First 24 Hours of Life**

Given the benefits of breastfeeding and widespread recommendations for its promotion, it is important to identify factors that impact early breastfeeding success. Epidural analgesia is the most effective method of pain relief currently available for women during labor, and the majority of infants born in the United States are exposed to maternal analgesia, however, effects of specific types of epidural analgesia on breastfeeding and neonatal neurobehavioral outcomes are still unknown. The use of hydromorphone as the narcotic in the epidural infusion appears to represent a promising alternative to fentanyl and may deliver acceptable analgesia without the unintended side effects seen with traditional opioid infusions. If so, neonates whose mothers receive labor epidural analgesia with hydromorphone and those whose mothers do not receive labor analgesia may show similar breastfeeding and neurobehavioral outcomes, however, results of previous research are inconclusive and further studies are needed.

The primary purpose of this study is to assess breastfeeding and neonatal neurobehavior in neonates whose mothers have received a continuous epidural infusion of bupivacaine (local anesthetic) and hydromorphone (narcotic) for labor pain in comparison with neonates whose mothers have not received epidural analgesia. A secondary purpose of the study is to determine whether there is a relationship between the duration of continuous epidural infusion and breastfeeding or neurobehavioral outcomes.

A prospective observational cohort study will be conducted at Yale New Haven Hospital. Eligible subjects will be mothers who intend to breastfeed and who will self-select to undergo labor with epidural analgesia containing hydromorphone as the narcotic or labor without pain medication. A total of 102 mother-infant dyads will be recruited, with 51 dyads in each group. Infant breastfeeding behaviors will be measured using the LATCH breastfeeding assessment tool, and neurobehavioral responses (central nervous system function) will be measured with the Neurologic and Adaptive and Capacity Scoring System (NACS). Assessments will take place at approximately 3, 12, and 24 hours of postnatal age.

Appendix G: Information Flyer for Nurses, Midwives, and Residents



Hi, my name is Cynthia French MS CRNA, I'm a nurse anesthetist at Yale New Haven Hospital and a PhD candidate at University of Connecticut. My dissertation is titled '**Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life**' and has been approved by the Human Investigation Committee at Yale University and we will begin data collection soon.

Purpose: The primary purpose of this study is to assess breastfeeding and neonatal neurobehavior in 51 neonates whose mothers have received a continuous epidural infusion of bupivacaine (local anesthetic) and hydromorphone (narcotic) for labor pain in comparison with 51 neonates whose mothers have not received epidural analgesia.

Participants: **Healthy multips with previous breastfeeding and a desire to breastfeed again. Healthy babies with no complications of pregnancy.** Infant breastfeeding behaviors will be measured using the LATCH breastfeeding assessment tool, and neurobehavioral responses (central nervous system function) will be measured with the Neurologic and Adaptive and Capacity Scoring System (NACS). Assessments will take place at approximately 3, 12, and 24 hours of postnatal age.

Recruitment on Labor and Birth: Rachel Rachler CRNA, Angelique Garay CRNA and Zach Walton MD will recruit and consent the patients.

Nurses, midwives and residents can alert a study team member of a possible candidate for the study based on the inclusion criteria.

Call: Rachel and Angelique 688-2676; Zach Walton MD Anesthesia Workroom

Your support is appreciated so much, thank-you!

If you have any questions or want to discuss this further please contact Cynthia French MS CRNA 307-699-2410

Appendix H: Text for Nurses and Midwives for Speaking With Prospective Subjects

For the Labor and Delivery Nurses

Cynthia French is a nurse anesthetist at Yale and PhD candidate at UConn. Her study is looking at labor epidural analgesia and its effect on breastfeeding initiation in the first 24 hours. The study will compare babies born to mothers who had no medication for pain during labor and mothers who had epidural analgesia for labor pain. Would you like to talk with a co-investigator about the study? They could explain it to you and you can decide if you want to participate.

Appendix I: Oral Information for Prospective Participants

Text to be used when obtaining informed consent:

My name is _____ and I'm a _____ (CRNA, Resident, Fellow) at Yale. One of the nurse anesthetists at Yale is a PhD candidate at UConn and she is doing a study to find out if medication used in epidurals for labor has an effect on babies ability to initiate breastfeeding in the first few hours after birth. We are asking you if you would participate in this study that will compare babies born to mothers with no pain medication during labor and babies born to mothers who used epidural medication for pain relief during labor.

Your participation is entirely voluntary and you can withdraw at any time without the care you are receiving being affected.

If you agree to participate Cynthia French or a nurse will observe a breastfeeding session at approximately 4, 12 and 24 hours depending on when the baby feeds. The nurses on the postpartum unit observe breastfeeding as part of the normal care you receive. We will coordinate with the postpartum nurse to observe breastfeeding at the same time, so there will be as few interruptions as possible during this very special time for your family.

After the breastfeeding assessments are done, information about your labor and delivery such as types of medication used, babies Apgar scores, and weight will be reviewed and deidentified, meaning your name is not linked with the information.

Again your participation is entirely voluntary and you can withdraw at any time without the care you are receiving being affected.

Appendix J: Written Informed Consent Form

HIC#: 1407014373

**COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH
PROJECT
200 FR. 4 (2014-2)**

YALE UNIVERSITY SCHOOL OF MEDICINE - YALE-NEW HAVEN HOSPITAL

Study Title: Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life

Principal Investigator: Keun Sam Chung MD
Funding Source: Departmental

Non-Medicated Group Form

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at if labor epidural medications and mother has received affect breastfeeding and neurobehavior of infants. Medications we give through epidural cross the placenta and the literature is unclear if the epidural medications depress the baby making the baby sleepy which can make it difficult for the baby to latch on to the nipple and breastfeed successfully. Breastfeeding has many health benefits to mothers and infants and if epidurals depress feeding in infants it's important we know this.

You have been asked to take part because you have not received any medications during your labor and delivery and you want to breastfeed. It has been suggested that babies born to mothers who had no analgesic medications during labor organize neurobehavior, including those tied to feeding, more rapidly and effectively during the immediate time postpartum. Because you were unmedicated during labor, you and your baby are in the 'control' group, meaning your baby's neurobehavior and breastfeeding assessment scores will be what the epidural analgesic exposed infants neurobehavior and breastfeeding assessment scores will be compared to.

Our aim is to enroll 51 mother and infant pairs who had epidural medications and 51 mother infant pairs that remained unmedicated during labor.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Breastfeeding and Neurobehavior

- Breast milk provides all the necessary nutrients a baby needs and is the preferred choice of pediatricians. You have a desire to breastfeed and we want to do everything we can to help you succeed.
- At YNHH after delivery of a healthy baby, the infant is placed immediately on your breasts for skin-to-skin contact. This early contact between you and your baby has been shown to increase the likelihood of exclusive breastfeeding. Placed skin-skin the baby will instinctively start rooting, finding the breast and

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sucking within the first hour of life. This is the standard of care at YNHH and this study will not interfere with first contact with your baby.

- The first 24 hours after birth is an important time for you and your baby in establishing breastfeeding. It is during this time the medications given through the epidural are being metabolized and cleared in the mother's and baby's circulation. If epidural analgesics has a possibility of preventing early breastfeeding we need to assess breastfeeding when there is still a very small portion of medication left in the blood at 2.5 hours and assess breastfeeding again at 12 hours when the medication is metabolized. This is why we will assess the unmedicated infants at the same time points as the epidural group for comparison.
- At YNHH we use a breastfeeding assessment tool called LATCH. This is the standard of care at our hospital and many nurses through the day will assess your breastfeeding using this tool and enter your score in the Electronic Medical Record. It lets the nurses know if you're having problems breastfeeding that require follow-up and provide you with the support you need.

Description of Procedures

If you agree to take part in this study, you will be asked to allow our research nurse to assess your breastfeeding using the LATCH assessment tool within 3 hours after delivery, 12 hours and 24 hours. The LATCH tool is used by nurses at YNHH and is the standard of care to assess breastfeeding. This will happen whether you participate in the study or not.

As part of the research you will be asked if we can perform a neurobehavior test on your baby. Assessment of the neonate after delivery is evaluated by Apgar scores at 1 and 5 minutes. While the Apgar score evaluates depression of vital function, it is not sensitive to the subtle differences or delayed onset of medications that may depress the neonate. The Neurologic and Adaptive Capacity Score (NACS) was specifically designed to detect if the baby is depressed from the drugs administered to the mother during labor from neonatal depression that may occur with the trauma of birth. It uses 20 criteria to assess 5 general areas: adaptive capacity, passive tone, active tone, primary reflexes and general neurologic status.

The test is similar to the Apgar test in that it takes about 5 minutes, does not require any special equipment, it is not bothersome to the baby, it is simple to perform, and will take place with you present. The research nurse (Cynthia French CRNA), performing the test has been specially trained and certified in neonatal neurobehavior assessment and will provide you with information about each area of test as it is performed with an explanation of the meaning of the evaluation. The NACS will occur at the same time as the LATCH assessment. 2 hours after delivery, 12 hours and finally 24 hours.

The research nurse who is collecting the data will be 'blinded' to which study group you are in. That means she will not know if you and your baby are in the epidural group or the unmedicated group. It's really important you not discuss with Cynthia French that you did not have medication during your delivery.

Risks and Inconveniences

Every consideration will be made to do these tests (LATCH and NACS) without disrupting the new relationship you are developing with your infant. If you are uncomfortable or it's not a good time, let the research nurse know, we have a window of time that the tests can be performed in and can come back.

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There are no physical risks associated with this study. However, there is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Benefits

There is no direct benefit to you and your baby. Information on maternal and fetal drug accumulations after epidural analgesia and determining whether it affects neurobehavior and breastfeeding will be invaluable. You can have satisfaction knowing with the information we receive from this study, we can provide our laboring mothers who want to breastfeed the most accurate and up to date information on epidural analgesia and breastfeeding.

Economic Considerations

You will not be paid for your participation in this research study. There is no additional charge to you or your insurance carrier.

Alternatives

The alternative is to not participate in this study and receive the standard of care provided to our mothers and neonates.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and medical record number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The paper files will be converted into an excel spreadsheet on a network server that is password protected that only key individuals have access to. You will be assigned a study ID so there will be no identifiable data linking you. The paper list will be stored in a locked file cabinet in a locked office for 6 months. The paper will be shredded after the 6 months and all that will remain are the study ID numbers with no identifiable data. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 6 months after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

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- Age, weight, height, allergies, medications and health history
- Apgars of the baby, sex, health history, medications, weight at birth and 24 hours. Apgar scores are a worldwide universal test to assess the health of newborn children.
 - Research study records
 - Medical and laboratory records of only those services provided in connection with this Study.

Information about you and your health which might identify you may be used by or given to:

- *The U.S. Department of Health and Human Services (DHHS) agencies*
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator Kuen Sam Chung MD
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR. (e.g. health insurance company, disability provider.)

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and, Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury

HIC#: 1407014373

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine and Yale-New Haven Hospital, do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Kuen Sam Chung MD, at the Yale University School of Medicine, 333 Cedar St, TMP 3, PO Box 208051, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

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Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: _____ (Mother)

Name of Subject: _____ (Infant)

Signature: _____

Date: _____

Signature of Principal Investigator
or

Date

Signature of Person Obtaining Consent

Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Kuen Sam Chung MD 203-737-1818. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

*THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX
HAS BEEN COMPLETED IN THE HIC OFFICE*

THIS FORM IS VALID ONLY THROUGH:

Sept 10, 2015

INITIALED:



HIC#: 1407014373

**COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH
PROJECT
200 FR. 4 (2014-2)**

**YALE UNIVERSITY SCHOOL OF MEDICINE - YALE-NEW HAVEN HOSPITAL
INSTRUCTIONS:**

Study Title: : Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life

Principal Investigator: Keun Sam Chung MD

Funding Source: Departmental

Labor Epidural Analgesia Form

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at if labor epidural medications that the mother has received affect breastfeeding and neurobehavior of infants. Medications we give through epidural cross the placenta. The literature is unclear if the epidural medications depress the baby making the baby sleepy which can make it difficult for the baby to latch on to the nipple and breastfeed successfully. Breastfeeding has many health benefits to mothers and infants and if epidurals depress feeding in infants it is important we know this.

Our aim is to enroll 51 mother and infant pairs to see how much of the epidural medications cross the placenta, assess how well your baby breastfeeds after delivery and evaluate the neurobehavior of your baby. These findings will be compared to a group of 51 mother infant pairs that remained unmedicated during labor.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, and any risks of the procedures. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Breastfeeding and Neurobehavior

- Breast milk provides all the necessary nutrients a baby needs and is the preferred choice of pediatricians. You have a desire to breastfeed and we want to do everything we can to help you succeed. Epidural analgesia has been identified as a barrier to breastfeeding success. One way it does this is the local anesthetic and the opioid drug combination administered in the epidural cross the placenta to the fetus and may depress the necessary reflexes the baby needs to root, swallow and suck which can prevent the baby from latching on to the breast.
- The first 24 hours after birth is an important time for you and your baby in establishing breastfeeding. It is during this time the medications we gave you through your epidural are being metabolized and cleared in the mother's and baby's circulation. The 1/2 life of hydromorphone is 2.5-3 hours. 1/2 life means 1/2 of the drug has been cleared from the blood of you and your baby. If epidural hydromorphone has a possibility of preventing early breastfeeding then we should assess breastfeeding when there is still a

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very small portion of medication left in the blood and assess breastfeeding at 12 hours when the medication is metabolized and compare if there is a difference in success.

- At YNHH we use a breastfeeding assessment tool called LATCH. This is the standard of care at our hospital and many nurses through the day will assess your breastfeeding using this tool and enter your score in the Electronic Medical Record. It lets the nurses know if you're having problems breastfeeding that require follow-up and provide you with the support you need.

Description of Procedures

If you agree to take part in this study, you will be asked to allow our research nurse to assess your breastfeeding using the LATCH assessment tool within 3 hours after delivery, 12 hours and 24 hours. The LATCH tool is used by nurses at YNHH and is the standard of care to assess breastfeeding. This will happen whether you participate in the study or not.

As part of the research you will be asked if we can perform a neurobehavior test on your baby. Assessment of the neonate after delivery is evaluated by Apgar scores at 1 and 5 minutes. While the Apgar score evaluates depression of vital function, it is not sensitive to the subtle differences or delayed onset of medications that may depress the neonate. The Neurologic and Adaptive Capacity Score (NACS) was specifically designed to detect if the baby is depressed from the drugs administered to the mother during labor from neonatal depression that may occur with the trauma of birth. It uses 20 criteria to assess 5 general areas: adaptive capacity, passive tone, active tone, primary reflexes and general neurologic status. (Appendix B).

The test does not require any special equipment, it is not bothersome to the baby, and it is simple to perform. The test takes about 5 minutes, and will take place with you present. The research nurse (Cynthia French CRNA), performing the test has been specially trained and certified in neonatal neurobehavior assessment and will provide you with information about each area of test as it is performed with an explanation of the meaning of the evaluation. The NACS will occur at the same time as the LATCH assessment. 2 hours after delivery, 12 hours and finally 24 hours.

The research nurse who is collecting the data will be 'blinded' to which study group you are in. That means she will not know if you and your baby are in the epidural group or the unmedicated group. It's really important that you do not discuss with Cynthia French whether or not you had an epidural.

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Risks and Inconveniences

Every consideration will be made to do these tests (LATCH and NACS) without disrupting the new relationship you are developing with your infant. If you are uncomfortable or it's not a good time, let the research nurse know, we have a window of time that the tests can be performed in and can come back..

Benefits

Subjects in this study will benefit from participation because we are performing breastfeeding assessment and neurobehavior test 3 times in a 24 hour time period. Because of the study procedures we may find some of our

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subjects may be having problems breastfeeding or the baby's may have depressed neurobehavior that is impeding breastfeeding that might have gone undetected under normal circumstances. If we detect problems we can alert the postpartum nurses or lactation consultants to assist the subjects which has the potential to improve breastfeeding outcomes.

Information on maternal and fetal drug accumulations after epidural analgesia and determining whether it affects neurobehavior and breastfeeding will be invaluable. You can have satisfaction knowing with the information we receive from this study, we can provide our laboring mothers who want to breastfeed the most accurate and up to date information on epidural analgesia and breastfeeding.

Economic Considerations

You will not be paid for your participation in this research study. There is no additional charge to you or your insurance carrier.

Alternatives

The alternative is to not participate in this study and receive the standard of care provided to our mothers and neonates.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and medical record number. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify you will remain confidential. The paper files will be converted into an excel spreadsheet on a network server that is password protected that only key individuals have access to. You will be assigned a study ID so there will be no identifiable data linking you. The paper list will be stored in a locked file cabinet in a locked office for 6 months. The paper will be shredded after the 6 months and all that will remain are the study ID numbers with no identifiable data. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for 6 months after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Age, weight, height, allergies, medications and health history
- Time epidural placed, time of delivery, length of time of epidural, all medications received during labor.

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- Apgars of the baby, sex, health history, medications, weight at birth and 24 hours. Apgar scores are a worldwide universal test to assess the health of newborn children.
- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.

Information about you and your health which might identify you may be used by or given to:

- *The US. Department of Health and Human Services (DHHS) agencies*
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator Keun Sam Chung MD
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider).

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and, Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine and Yale-New Haven Hospital, do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You

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or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Keun Sam Chung MD MD, at the Yale University School of Medicine, 333 Cedar St, TMP 3, PO Box 208051, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

The primary investigator, Dr Keun Sam Chung may withdraw you from this study if:

-
- Any unforeseen obstetric or neonatal emergency, complication or cesarean section.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

HIC#: 1407014373

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject: Mother

Name of Subject: Infant

Signature: _____

Date: _____

Signature of Principal Investigator
or

Date

Signature of Person Obtaining Consent

Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919 [Add country code, if applicable].

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Keun Sam Chung MD 203-737-1818. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688 [Add country code, if applicable].

***THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX
HAS BEEN COMPLETED IN THE HIC OFFICE***

THIS FORM IS VALID ONLY THROUGH:

Sept 30, 2015

INITIALE

a/l L



Appendix K: Neurologic and Adaptive Capacity Score (NACS)

NEUROLOGICAL AND ADAPTIVE CAPACITY SCORE
IN FULL - TERM NEWBORNS
(AMIEL - BARRIER - SHNIDER)

NAME _____

Date of Birth _____ Chart Number _____

		0	1	2
Adaptive Capacity	1 RESPONSE TO SOUND	absent:	mild:	vigorous:
	2 HABITUATION TO SOUND	absent:	7-12 stimuli:	< 6 stimuli:
	3 RESPONSE TO LIGHT	absent:	mild:	brisk blink or startle:
	4 HABITUATION TO LIGHT	absent:	7-12 stimuli:	< 6 stimuli:
	5 CONSOLABILITY	absent:	difficult:	easy:

TOTAL

ADAPTIVE CAPACITY

		0	1	2
Passive Tone	6 SCARF SIGN	encircles the neck:	elbow slightly passes midline:	elbow does not reach midline:
	7 RECOIL OF ELBOWS	absent:	slow; weak:	brisk; reproducible:
	8 POPLITEAL ANGLE	> 110°	100° - 110°	< 90°
	9 RECOIL OF LOWER LIMBS	absent:	slow; weak:	brisk; reproducible:
Active Tone	10 ACTIVE CONTRACTION OF NECK FLEXORS (from lying position)	absent or abnormal:	difficult:	good; head is maintained in the axis of the body:
	11 ACTIVE CONTRACTION OF NECK EXTENSORS (from leaning forward position)	absent or abnormal:	difficult:	good; head is maintained in the axis of the body:
	12 PALMAR GRASP *	absent:	weak:	excellent; reproducible:
	13 RESPONSE TO TRACTION (following palmar grasp)	absent:	Lifts part of the body weight:	lifts all of the body weight:
	14 SUPPORTING REACTION (upright position)	absent:	incomplete; transitory:	Strong; supports all body weight:
* Primary Reflexes	15 AUTOMATIC WALKING *	absent:	difficult to obtain:	perfect; reproducible:
	16 MORO REFLEX *	absent:	weak; incomplete:	perfect; complete:
	17 SUCKING *	absent:	weak:	perfect; synchronous with swallowing:
General Assessment	18 ALERTNESS	coma:	lethargy:	normal:
	19 CRYING	absent:	weak; high pitched; excessive:	normal:
	20 MOTOR ACTIVITY	absent or grossly excessive:	diminished or mildly excessive:	normal:

TOTAL

NEUROLOGICAL

TOTAL SCORE AT _____ MINUTES OF LIFE

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Appendix L: LATCH Feeding Record

Effect of Labor Epidural Analgesia With Hydromorphone on Neonatal Neurobehavior and Breastfeeding Behavior in the First 24 Hours of Life

Participant Study Id Number _____ Delivery _____

Date/Time: _____

Age in hours and minutes _____

LATCH FEEDING RECORD

Method : BR= Breast F= Formula/ml EBM=Expressed breast milk

Other Feeding Method: Specify _____

Date	Time	Feeding Method	L	A	T	C	H	Total	Comments/Neonate BS Amt BR/F in ml

15 minutes observation sessions

	0	1	2
Latch	To sleepy or reluctant No latch achieved	Repeated attempts Hold nipple to mouth Stimulate to suck	Grasp breast Tongue down Lips flanged Rythmical sucking
Audible Swallow	None	A few with stimulation	Spontaneous and intermittent<24 hrs Spontaneous and freq>24 hrs
Type of Nipple	Inverted	Flat	Everted after stimulation
Comfort of Breast	Engorged Cracked bleeding large blisters or bruising Severe discomfort	Filing Reddened small blisters or bruising Mild/moderate discomfort	Soft Tender
Hold	Full assist	Minimal assist Teach one side mother does other Staff holds mother takes over	No assist from staff Mother able to position and hold baby

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