Research review
Feeding development of the preterm infant

Providing adequate feeding support to preterm infants is challenging. This review describes the underlying evidence behind practices that promote successful human milk feeding and breastfeeding at NICU discharge.

Medela: Comprehensive solutions for human milk and breastfeeding

For more than 50 years Medela has strived to enhance mother and baby health through the life-giving benefits of breastmilk. During this time, the company has focussed on understanding mothers' needs and infants' behaviour. The health of both mothers and their infants during the precious breastfeeding period is at the centre of all activities. Medela continues to support exploratory research into human milk and breastfeeding, and incorporates the outcomes into innovative breastfeeding solutions.

Through new discoveries surrounding the components of human milk, the anatomy of the lactating breast and how the infant removes milk from the breast, Medela has developed a set of solutions to support Neonatal Intensive Care Units (NICUs) in providing human milk and improving breastfeeding.

Medela understands the challenges of providing human milk in the NICU. There are challenges from the mother's side to reach an adequate milk supply and from the infant's side to ingest the milk; plus there are issues of hygiene and logistics when meeting these challenges. The portfolio Medela offers is directed towards obtaining human milk, promoting human milk feeding, and supporting all infants in achieving breastfeeding as early as possible.

Medela aims to provide the most recent, evidence-based knowledge to support breastfeeding and human milk use in the NICU. The goal of the innovative, research-based products, together with the educational materials, is to overcome the difficulties associated with human milk provision in the NICU.

Scientific research
Medela strives for excellence in scientific research – an attitude that has enabled the company to develop advanced breastpump and breastmilk feeding technologies. Medela works with experienced medical professionals and seeks collaboration with universities, hospitals and research institutions worldwide.

Products
Helping mothers to express milk is Medela's core competency. This includes careful and hygienic collecting of breastmilk in BPA-free containers. Easy solutions for labelling, storing, transporting, warming and thawing – all help to safely manage precious human milk. And for human milk to reach the infant, Medela has developed a range of innovative products for different feeding situations.

Education
Within Medela, research and education are closely linked. Medela connects clinicians and educators in ways that lead to professional growth, exchange of knowledge and interaction with the broader scientific community.

To put available solutions, their functionality and their interaction into the context of the overall hospital processes and evidence-based decision making, Medela has developed a series of research reviews. The reviews are available for NICU processes in which human milk and breastfeeding play a significant role. These include feeding development of the preterm infant, human milk logistics and infection control of human milk.

Feeding development of the preterm infant

Abstract

Breastfeeding is the ultimate goal for the preterm infant and mother pair. Preterm delivery, however, creates a unique set of challenges, making it difficult to breastfeed initially. The preterm infants' progression to breastfeeding is often complicated by neurological and gastro-immaturity and underlying medical co-morbidities. Mothers can also experience multi-faceted issues initiating, building and maintaining lactation during this earlier stage of breast development. Evidence-based practices that support the development of breastfeeding in the NICU, and likewise practices that enable mothers to provide an adequate volume of milk for their preterm infant, are discussed in this review. Future research investigating feeding at the breast in the NICU remains imperative to help mothers and infants overcome these early feeding challenges.

Table of contents

Introduction

Globally the importance of breastfeeding is unanimously agreed upon and is reflected by the World Health Organization recommending exclusive breastfeeding (Table 1) for the first six months of life [1]. Breastfeeding however is advantageous beyond its nutritional benefits [2]; it protects the infant against infection, regulates and enhances the infant's and mother's physiological systems and facilitates bonding of the mother-infant pair [3]. At birth, early sucking contact creates the first bond, enabling the mother to provide colostrum for her infant [4]. Over the first few weeks postpartum, the mother's milk supply increases ensuring optimal growth and development of her infant. This picture is somewhat different after preterm delivery. Imperative development, which normally occurs late in gestation, is interrupted and instead, must be accelerated in the postnatal environment. At birth, the mother and infant pair are often separated immediately, creating a particularly challenging scenario, especially when it comes to breastfeeding and human milk feeding.

For the mother, initiating and maintaining lactation at an earlier developmental stage can be difficult; whereas for the preterm infant, oral feeding and breast-feeding at an immature developmental state is equally problematic. Since the provision of human milk is especially important in the first months of life after preterm birth [5], mothers and preterm infants alike require support to overcome these early difficulties.

This research review aims to provide the neonatal intensive care unit (NICU) professional with an in-depth understanding of the benefits and physiology of breastfeeding in term and preterm infants; the challenges that preterm infants and their mothers face when breastfeeding and human milk feeding; and the evidence-based interventions required to overcome these challenges. With an ultimate aim of providing the NICU professional with a means to maximise the use of human milk and support breastfeeding as early as possible, this review offers a comprehensive outline of the entire feeding pathway – from optimising milk pumping protocols for pump-dependent mothers, to early nutrition and breastfeeding in preterm infants.

Table 1 – Adapted from the World Health Organization feeding definitions

Feeding practice	Requires the infant receives
Exclusive breastfeeding	Breastmilk – (including milk expressed or from a wet nurse) as the exclusive source of nourishment
Predominant breastfeeding	Breastmilk (including milk expressed or from a wet nurse) as the predominant source of nourishment
Complementary breastfeeding	Breastmilk (including milk expressed or from a wet nurse) and solid or semi-solid foods
Breastfeeding	Breastmilk (including milk expressed or from a wet nurse)
Bottle-feeding	Any liquid (including breastmilk) or semi-solid food from a bottle with nipple/teat

The benefits of breastfeeding

The benefits of breastfeeding have been consistently documented in term and preterm infants. The composition of milk protects the infant from infections, provides optimal growth and development, and improves long-term health outcomes for both the mother and her infant. This protection is particularly important for the preterm infant.

Nutrition and protection

As the sole source of food for term infants, breastmilk provides both optimal nutrition (fat, lactose, protein and macronutrients) to support growth and development, and complete protection (biochemical and cellular components) against infection. The composition of preterm milk is different to term milk in that it contains higher energy, lipids, proteins, nitrogen, immunoglobulins, anti-inflammatory elements and some minerals and vitamins [6–8]. Regardless of the lactation stage, human milk provides important protective and developmental advantages to preterm infants [7, 8].

Infants who receive human milk have significant improvements in their nutritional status, infectious and chronic disease control, gastrointestinal maturation, and neurodevelopment compared to formula fed infants [7, 8]. In particular, preterm infants who receive human milk have a reduced risk of necrotising enterocolitis (NEC), enteral feed intolerance, chronic lung disease, retinopathy of prematurity, neurodevelopmental delays and re-hospitalisation [9–16]. Developmentally, breastfeeding is also advantageous for a number of reasons; in term infants, breastfeeding is associated with improved neurodevelopment and behaviour ratings, decreased rates of infections, and a reduced risk of obesity and type 2 diabetes into adulthood [2, 10, 17–21] It is for these benefits that human milk is recommended for all preterm infants [22].

Despite its benefits, the nutritional composition of human milk cannot completely meet the high nutrient demands for preterm infant growth especially in infants born very low birth-weight (<1500 g) [7, 15]. Human milk must be fortified with protein, nutrients, vitamins and minerals to ensure optimal growth and development of the preterm infant while still deriving the benefits of human milk [23].

Regulation and enhancement of physiological systems

The provision of human milk through breastfeeding provides important regulation and enhancement of the mother-infant pair. Suckling has evolved to enhance regulation of physiological systems of both the mother and her infant improving the survival of the infant in harsh environmental conditions [3]. Close body contact between the mother and infant during the early postpartum period enhances and regulates the newborn's temperature, respiration, acid-base balance [3] and soothes the infant [24]. During sucking, the close body contact helps prolong the lactation period and may help adapt the mother's gastrointestinal tract to meet increased energy demands during lactation [3]. Breastfeeding increases the mothers attention to her infant's needs [24], accelerates uterine involution after birth, reduces the risk of haemorrhage, helps the mother re-gain her pre-pregnancy weight and decreases the risk of ovarian and breast cancer [25]. Breastfeeding also significantly reduces the risk of acute otitis media [10] and promotes normal oral facial growth of the infant [26], including improved dentition, perioral and masseter muscle activity [27] and palatal growth [28]. In particular, breastfeeding facilitates a bond between the mother and infant pair. Skin-to-skin contact and tactile stimulation of the nipple, including the act of sucking, result in the release of oxytocin, a critical component of the milk ejection reflex (Figure 1), creating a bond between the mother-infant pair [4]. Oxytocin release increases blood flow to the mother's chest and nipple area, rising the temperature of the skin and creating a warm and nurturing environment for the infant [4]. Breastfeeding also provides long-term anti-stress effects; during each breastfeed mothers experience a reduction in their blood pressure and cortisol levels [29, 30] and lower rises in cortisol in response to physical stress compared with bottle-feeding mothers [31]. Breastfeeding mothers are more likely to be calmer and more social than other women of similar age who are not breastfeeding or pregnant [29, 30]. In fact, mothers having newborns skin-to-skin immediately after birth spend more time with their infants, interact more with them during breastfeeding [24] and breastfeed longer [32]. Although this scenario is different for mothers of preterm infants due to their physical separation and other medical issues, skin-to-skin contact is still associated with increased milk production and earlier onset of lactation in mothers and improved physiological stability in preterm infants [33–36].

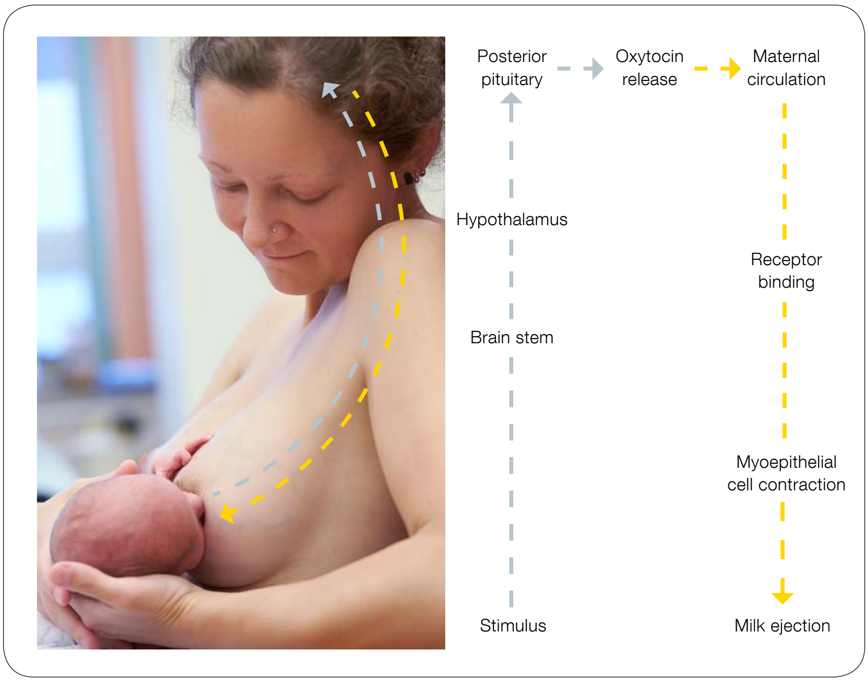

Figure 1 – Milk ejection reflex
In response to a stimulus, oxytocin is released from the posterior pituitary into the maternal circulation. Oxytocin binds to the receptors on the myoepithelial cells surrounding the alveoli. These cells contract and force milk out of the alveoli into the ducts towards the nipple.

The physiology of breastfeeding

Breastfeeding is a complex process requiring maturation, learning and conditioning of the mother as well as the infant. To successfully feed at the breast, the infant needs to be neurologically and physically able to coordinate sucking, swallowing and breathing in response to the flow of milk from the mother's breast.

Tongue movement and vacuum

During each breastfeed, milk ejection is triggered by the release of oxytocin from the posterior pituitary, resulting in the transient delivery of milk to the suckling infant [4]. A breastfeed is therefore made up of periods of milk removal, nutritive sucking (NS), where milk flow rates vary; and non-nutritive sucking (NNS), periods devoid of milk flow with the occasional swallow of saliva. NNS is commonly observed at the beginning of the breastfeed and is believed to be used by the infant to stimulate a milk ejection [37–39], however it has also been measured in the middle and end of a breastfeed [40, 41].

Tongue movement is of major importance to breastfeeding; it must remove milk from the breast and safely clear milk to the pharynx prior to swallowing. *In utero*, foetal tongue movement has been observed from 14 weeks gestational age, with consistent, mature tongue movement observed from 28 weeks gestation [42]. Utilising synchronised ultrasound and vacuum measurements during breastfeeding, the importance of mature tongue movement and vacuum for milk removal during breastfeeding has been demonstrated [41, 43–45].

From day 3 postpartum, term breastfeeding infants have shown a consistent pattern of tongue movement during milk removal (NS) [41]. The infant attaches to the breast by creating a baseline vacuum (mean: –64mmHg) that elongates the nipple and places it within 5 to 7mm of the hard-soft palate junction. At this point, the tongue evenly compresses the nipple, and the posterior part of the tongue is in contact with the hard palate. No milk flow occurs while the tongue is in this resting point. As the tongue lowers away from the hard palate, the nipple expands in size and moves closer to the hard-soft palate junction. As the tongue lowers, vacuum increases in strength and milk flows from the nipple into the oral cavity. When the tongue reaches its maximally lowered point, the strongest vacuum is applied (peak vacuum mean: –145mmHg). As the tongue rises, the nipple is evenly compressed again, vacuum reduces to baseline and milk is cleared from the oral cavity under the soft palate to the pharyngeal area, for swallowing (Figure 2) [43].

During NNS, term breastfeeding infants demonstrate a similar pattern of tongue movement to NS. As the tongue lowers, vacuum strength increases, the nipple expands in size to a lesser extent than during NS, and moves closer to the hard-soft palate junction. As the tongue is maximally lowered, no milk flow is observed and the size of the intraoral cavity is smaller. The tongue returns to the hard-palate in a similar fashion to that of NS. During NNS, the infant's suck rate is significantly faster than during milk removal (NS) [39, 43].

Unlike their term counterparts, preterm infants do not show a consistent pattern of tongue movement or vacuum during breastfeeding. Instead, preterm infants born at less than 30 weeks gestation, initially rely predominantly on compression to remove milk during conventional bottle-feeding. At first these

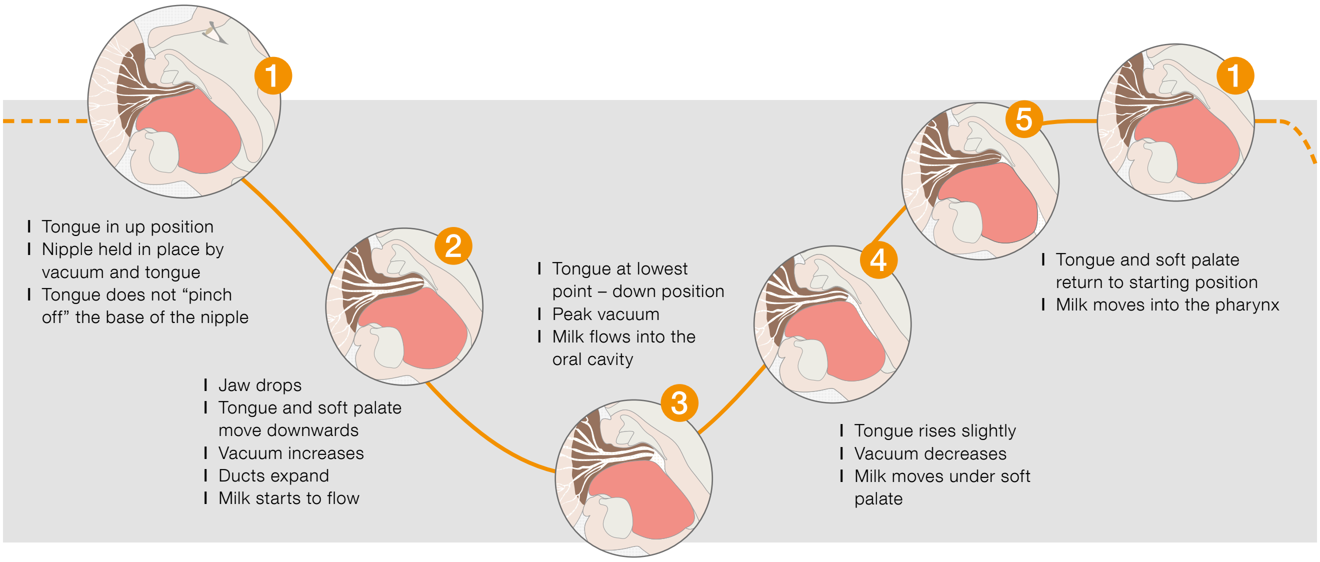

Figure 2 – The suck cycle [43]

infants use a disorganised pattern of compression without vacuum. However, with increasing age and experience, they begin to use vacuum and reduce their use of compression to remove milk. As their vacuum increases to a level similar of a term infant, preterms become more efficient and effective feeders in that they are able to prolong their suck bursts, increase their milk transfer rates (mL/min) and complete their bottle-feeding session in a shorter period [46].

Preterm infants between 32–36 weeks gestation also have been shown to use weak vacuums in combination with irregular sucking, averaging 2–3 sucks per second [47, 48]. With increasing age, these infants apply stronger vacuums and show improvements in the duration of each suck and in milk transfer rates [48]. Although studies assessing breastfeeding in preterm infants are limited, clinically it has been noted that they have difficulty maintaining a latch to the breast, they apply weak vacuums, have inconsistent and short suck burst patterns, and often fall asleep at the breast [49, 50]. Preterm infants are subsequently often fed at the breast using a nipple shield to assist in maintaining a latch to the breast [51], making outcomes of feeding directly at the breast unclear for preterm infants.

Preterm infants also perform NNS; this usually refers to sucking on a pacifier or finger and is significantly associated with earlier attainment of oral feeding skills [52]. Tongue movement during NNS on a pacifier has been shown to differ from tongue movement during NS on a bottle in a preterm infant case study. During NS there was greater movement of the anterior and posterior tongue than during NNS [53]. Future research clarifying the mechanism in which NNS assists preterm infants attain earlier oral feeding skills may be beneficial for devising NNS suck training programmes for these infants.

Suck-swallow-breathe coordination

For successful breastfeeding, the infant must not only remove milk from the breast, but also coordinate swallowing and breathing to allow safe transport of the milk from the infant's oral cavity to the digestive system – all whilst maintaining good cardiopulmonary stability [54]. During breastfeeding, term infants are able to simultaneously suck and swallow milk, but must cease breathing briefly (for approximately 0.5 seconds) to swallow [54, 55]. Compared to NNS, during milk removal NS respiratory rates (40–65 breaths per minute) are lower [40, 55], heart rate is higher (140–160 beats per minute) and oxygen saturation remains unchanged (99%), demonstrating excellent coordination by the infant [40].

Term breastfeeding infants are able to adapt their suck-swallow-breathe coordination to the rapidly changing milk flow rates encountered at milk ejection [40]. They must briefly pause their breathing to swallow, and are able to do this during both the inspiratory and expiratory phases of respiration [56–58]. They are able to rapidly extend their suck bursts in periods of high milk flow [40] and also change their ratios of sucking to swallowing and breathing during periods of NS and NNS. For example, although previous reports have commonly suggested a pattern of 1:1:1 to be optimal; that is, for every suck, they may also exhibit one swallow and one breathe, it has since been noted that 1:1:1 ratios rarely occur. In fact ratios vary from 2:1:1 and 3:1:1 [59] up to 12:1:4 [40] during milk flow (Figure 3). The range of ratios observed during breastfeeding is most likely explained by variation in milk flow that occurs at and between milk ejections [40].

In contrast, preterm infants commonly have difficulty coordinating the suck-swallow-breathe reflex before 34 weeks postpartum due to their neurological immaturity and other medical issues [60]. Infants suffering from respiratory problems such as respiratory distress syndrome or chronic lung disease, requiring oxygen supplementation [61], display lower suck vacuums, poorer suck frequencies and shorter suck burst durations during bottle-feeding [47, 62, 63].

Premature infants, studied from 32 weeks postmenstrual age, initially swallow during prolonged respiratory pauses (apnoeas) during bottle-feeding. As they mature to 36 weeks postmenstrual age, they tend to decrease the proportion of apnoeic swallows and increase their swallows at the start of inspiration or end of expiration, where air flow is minimal [48, 64]. This has not been studied during breastfeeding in preterm infants. Similarly, a suck-swallow-breathe ratio of 1:1:1 or 2:2:1 has been previously considered optimal and a good indicator of mature coordination during bottle-feeding [46]. However, as these patterns have not been measured during breastfeeding, it cannot be assumed that these ratios are generalisable to preterm infants at the breast.

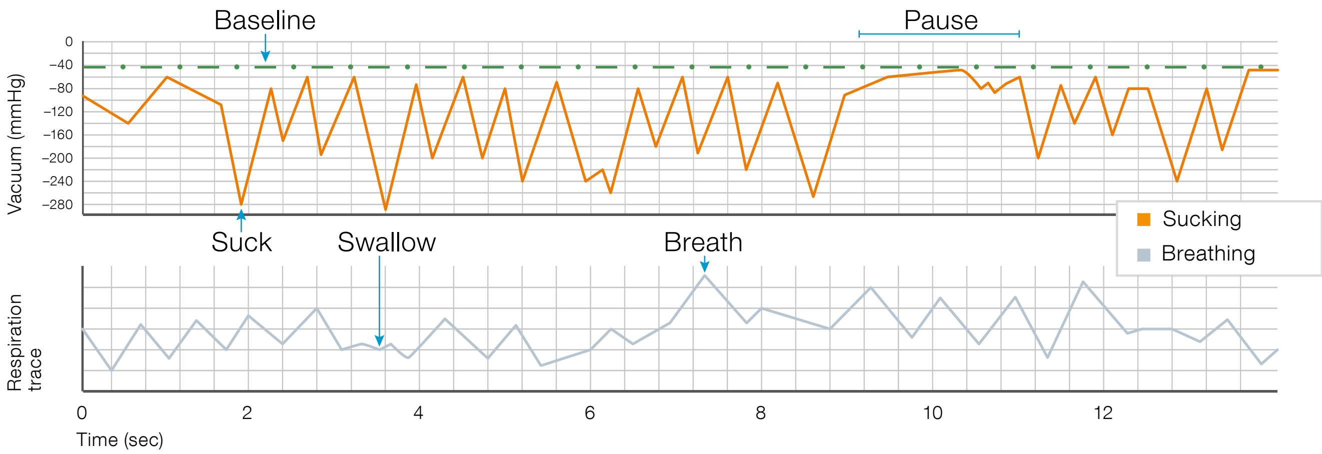

Figure 3 – Example of a synchronised trace of a suck-swallow-breathe pattern [40]

Neurodevelopment

Cerebral and brainstem pathways involved in oral-motor function, swallowing [65] and breathing [66] undergo critical development during mid to late gestation and in the first year postpartum. Myelination of the brainstem first appears at 18–24 weeks gestation. At 20–24 weeks gestation, the roots of cranial nerves and intramedullary roots of cranial nerves for oral-motor function are myelinated, corresponding with *in utero* jaw and tongue movements [42]. Rapid development of brain tissues and peak synaptogenesis of the medulla occurs at 34–36 weeks gestation, coinciding with the time in which the suck-swallow-breathe reflex is considered safe and coordinated [67]; although one study has demonstrated safe breastfeeding in preterm infants aged between 29 and 36 weeks gestation [68]. By 40 weeks gestation, myelination of the reticular formation, nucleus ambiguous and nucleus tractus solitaries in the brainstem occurs; enhancing mastication, swallowing and respiratory control, and therefore the coordination of the suck-swallow-breathe process necessary for breast and bottle-feeding [60]. Myelination of the subcortical and cortical regions involved in swallowing coincides with the appearance of more variable sucking and swallowing patterns at 1 month postpartum [69].

Preterm infants are born prior to these key neurodevelopmental milestones that usually occur in mid to late gestation, affecting their ability to oral feed initially. Preterm infants are required to rapidly catch up in growth and neurodevelopment in the postnatal period [70]. As one third of brain growth occurs in the last 6 to 8 weeks of gestation, preterm infants born at 32 weeks, for example, have 35 % less brain volume postpartum than their term counterparts. For these infants, the remaining growth must occur after birth [70]. As the most rapid brain growth usually occurs with the accumulation of docosahexaenoic acid (DHA) and arachidonic acid (AA) from the placenta in the last trimester [71], the provision of human milk is particularly important. Milk of preterm mothers contains 20 % more medium chain fatty acids (DHA and AA) than term milk [72, 73].

Challenges to feeding in the NICU

Figure 4 – Example of skin-to-skin care

Breastfeeding is a partnership between mother and infant. As such, problems on one side will also have an effect on the other. The arrival of an infant prematurely poses unique feeding challenges that need to be considered on an individual basis, for the mother, infant and healthcare professional.

Challenges to the mother

Mothers of preterm infants often experience difficulties initiating lactation due to their premature stage of breast development, lack of infant sucking contact, emotional issues resulting from preterm delivery and poor access to appropriate equipment and timely support [74]. As a result, many mothers of preterm infants are initially pump-dependent. Nearly all mothers of preterm infants in the NICU experience significant stress, anxiety and lack of sleep during the first weeks after delivery, which can further compound the initiation and maintenance of lactation [75, 76]. Stressful situations, such as those caused by the separation of the mother and infant, and lack of appropriate support for milk expression, can temporarily disrupt the milk ejection reflex by inhibiting the amount of oxytocin released [77] and subsequently the amount of milk that can be delivered to the infant or removed by the pump [78]. Supporting mothers of preterm infants to initiate lactation and encouraging skin-to-skin care (Figure 4) as often as possible are the first critical steps in improving feeding outcomes for the mother and infant pair.

Challenges to the infant

Preterm infants also face hurdles when oral feeding initially [61]. Due to their neurological and gastro-immaturity and underlying medical complications such as hypotonia, gastro-oesophageal reflux and chronic respiratory disease [79], it is often difficult for preterm infants to breastfeed initially. Instead they must often rely on parenteral and enteral nutrition. Preterm infants generally attempt oral feeding around 32 to 34 weeks gestational age or once their cardiopulmonary status is considered stable [61]. This however, varies significantly depending on the infant's gestational age at birth, birth-weight, existing medical conditions and healthcare institution [61, 80]. Since attainment of independent oral feeding is a key criterion for discharge from hospital for preterm infants [81], developing oral feeding skills as early as possible is critical.

While learning to oral feed, preterm infants also experience stressful events including oxygen desaturation, bradycardia, apnoeas, choking and aspiration [82–84]. During breastfeeding, and more often during bottle-feeding, the combination of milk flow and immature coordination of the suck-swallow-breathe reflex [85, 86] can trigger involuntary reflexes such as gagging, coughing and spluttering when swallowing [87], particularly in more immature infants [88]. Exposure to stressors such as painful procedures, or lack of maternal contact during hospitalisation is associated with alterations in brain structure at term equivalent age [89, 90].
It is therefore possible that infants who take longer to achieve safe oral feeding and subsequently experience delays in hospital discharge may show similar neurodevelopmental alterations. Certainly poorer oral feeding in term neonates has been linked to reduced neurodevelopmental outcomes at 18 months of age [91]. Tools that can minimise maternal and infant related stress during the initiation of lactation and that support oral feeding in preterm infants have significant potential in improving long-term health outcomes for the infant.

Overcoming feeding challenges in the NICU

Providing preterm infants as much of their own mother's milk as possible and achieving direct breastfeeding should be a NICU priority. Evidence-based solutions are required to address any challenges that might present and interfere with feeding development in the NICU.

Supporting the mother

Supporting mothers *via* early and frequent pumping significantly improves the initiation of lactation after preterm birth. Pumping within the first hour, compared to 6 hours after birth, is associated with increased milk production for the first week and at 3 weeks postpartum [92]. Pumping less than 6 times a day is associated with a reduced milk production compared to mothers who pump more frequently [93]. Double pumping (Figure 5) has also been consistently shown to be more effective and efficient at removing milk than sequential pumping, removing both a higher percentage of available milk and a greater volume of milk [94–96] with a higher fat content [96]. Double pumping, at least 8 times a day (24 hours) is therefore recommended [94, 95].

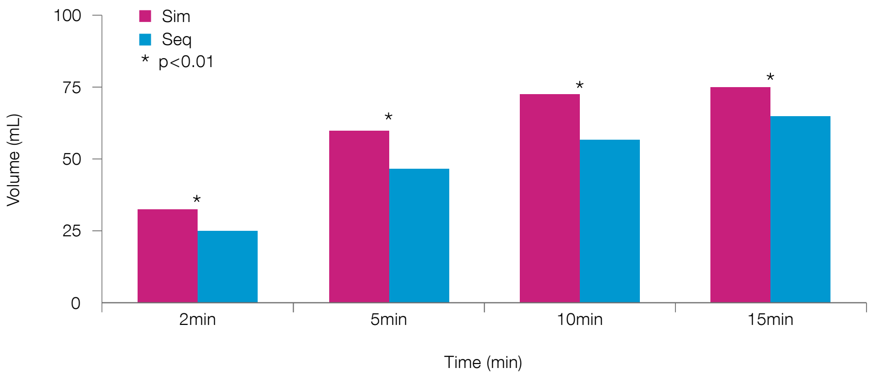

Figure 5 – Expression volumes obtained during double pumping (Sim) compared to sequential single pumping (Seq) [96]

Electric breast pumps work through a combination of suction strength (vacuum) and suction patterns (frequency of cycles per minute). By measuring term infants at the breast and noting that infant sucking patterns change from a rapid sucking pattern prior to milk ejection to a slower and more regular pattern after milk ejection [39, 97], a series of electric pumps were designed to mimic the 2-Phased pattern of stimulation and expression of milk during breastfeeding. These standard two phase patterns included a stimulation phase consisting of a cycling frequency greater than 100 cycles per minute to stimulate a milk ejection, and an expression phase consisting of a slower cycling frequency of around 60 cycles per minute, aiming to facilitate milk removal at the breast [98]. Hospital-grade electric pumps utilising this pattern, at the highest vacuum that is comfortable for the mother, have been demonstrated to be as effective as, and more comfortable during milk removal than single phase electric pumps relying solely on expression [98, 99].

More recently, it has been shown that using a pumping pattern that mimicked a newborn's sucking pattern prior to the initiation of lactation, improved milk removal in pump-dependent mothers. The initiation pattern, used until secretory activation occurred, consisted of 3 phases, varying over fifteen minutes. This included 2 stimulation phases with cycling frequencies of 120 and 90 cycles per minute, as well as an expression phase with cycling frequencies between 34–54 cycles per minute. Mothers using this pattern until initiation, and the standard 2-Phase pattern after initiation, exhibited a significantly greater daily milk production between days 6–13 postpartum, and an increased milk output per minute spent pumping, compared to mothers using only the standard 2-Phase pumping pattern [100].

Other factors that have been shown to assist in milk production include: pumping at the bedside, or in a more relaxed environment to reduce maternal stress [49]; skin-to-skin contact, which is associated with increased production and prolonged lactation [33–36]; non-nutritive sucking at the breast, which is thought to stimulate the release of oxytocin and prolactin and improve milk production; and breast massage during pumping, which is associated with increases in milk volume removed [94, 101] and caloric content of milk [102].

Family centred care can also assist in stress reduction and improve feeding for both the mother and infant [103–105]. Care that encourages parental presence and enables greater family access to the NICU, is associated with improved feeding outcomes in preterm infants. In particular, hospital facilities that allow the parents to stay with their infants are conducive to breastfeeding [103]. Being available at the infant's bedside assists in developing attachment to the infant and gives the opportunity to breastfeed more frequently [104]. Similarly, parental involvement in care is thought to be critical to improving the parents' perception of their infant and reducing parental stress [105].

Supporting the infant

Supporting preterm infants' feeding development is complex. The provision of nutrition is often the initial focus when preterm infants are unable to oral feed initially. Nutritional and feeding practices may depend on gestational age at birth-weight, medical complications, and healthcare institutions. Nutritional support may begin with parenteral and enteral nutrition when the infant is medically unstable or too immature to feed orally (Figure 6). Providing human milk during this period is critical to reducing infection and improving long-term health outcomes. As the infant transitions between enteral and oral feeding, supporting the infant to feed safely and effectively may ensure that the infant is able to be discharged from the hospital as early as possible.

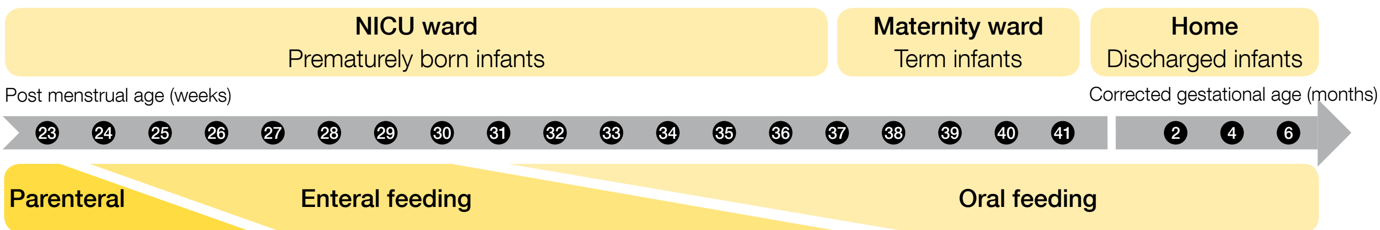

Figure 6 – General schematic showing the progression towards oral feeding

Initial nutrition

Preterm infants have limited nutrient stores at birth and are at risk of accumulating significant nutrient deficits and poor growth. Nutritional goals for preterm infants therefore aim initially to achieve postnatal growth rates and mimic the foetal body composition of infants born at term, whilst avoiding extrauterine growth restriction [106]. This remains a challenging task, especially for infants born very low birth-weight (<1500 g), due to rapid tissue accretion [107].

Parenteral nutrition (PN) is a method of intravenous feeding that fulfils nutritional requirements when normal metabolic and nutritional needs cannot be met by enteral feeding. PN aims to provide adequate nutrients, and in particular protein, to promote anabolism and mimic foetal growth. Almost all premature infants born <1500 g receive PN as the initial feeding for the first few days of life [108].

PN is indicated when feeding *via* the enteral (gastrointestinal) route is impossible or hazardous. As preterm infants are faced with gastrointestinal tract immaturity concomitant with a risk of developing necrotising enterocolitis (NEC), a high incidence of muscular and neurological immaturity, respiratory compromise and other illnesses, PN is recommended immediately after birth [108]. The benefits of PN for more stable infants born >32 weeks gestation is less clear, though it is often used to bridge the gap while full enteral feeds are being established. The average duration of PN until full enteral feeding is achieved is typically 1–2 weeks, although this depends on the degree of prematurity [107].

PN usually includes a mixture of amino acids, dextrose, lipids, vitamins and minerals. An early PN strategy, also known as aggressive PN, refers to the practice of commencing a high dose of amino acids (≥ 2 g/kg/day) as PN within the first few hours of birth [107, 109–112]. This practice has been shown to prevent postnatal growth failure, shorten the duration of exclusive PN and improve long-term neurodevelopmental outcomes. Early introduction of lipids is also safe, and provides a significant source of energy (≥ 2 g/kg/day) immediately after birth. Volumes of PN should increase over the first 3 days post-partum to approximately 150 mL/kg/day, providing a total caloric intake of approximately 100 kcal/kg/day [107]. Colostrum of the infant's own mother, which contains a high concentration of cytokines and other immune agents, may also be beneficial when administered oropharyngeally to extremely low birth-weight infants during the first few days of life. Using colostrum as oral care may stimulate oropharyngeal-associated lymphoid tissue and protect the infant's oral mucosa from infection [113, 114].

Despite the importance of PN, its use remains a balance of risks and benefits. Very low birth-weight infants born small for gestational age have inadequate glycogen stores, are likely to have difficulty maintaining blood sugars and are therefore at risk of hypoglycemia during PN. In addition, the risk of nutrient deficits are high during PN, specifically for micronutrients and vitamins (especially fat-soluble vitamins) [115]. PN is also associated with an oxidant load and hepatic dysfunction, especially with long-term use [116]. Similarly, complications can arise with the use of a central venous catheter, which is typically inserted in the umbilical vein or percutaneously (PICC, peripherally inserted central catheter). PICC is more often associated with risk of sepsis, localised skin infections, thrombophlebitis [117], as well as mechanical complications in relation to venous line placement.

Enteral Nutrition

PN meets the immediate nutritional requirements for preterm infants. However, achieving nutrition enterally (*via* the intestine) using human milk is preferred when possible [15]. The absence of food in the gastrointestinal tract during PN places the infant at risk of digestion and absorption issues. For this reason, early enteral feeding with human milk is normally started within the first week of life to stimulate gut motility and maturation [118].

During enteral feeding, infants are still either too immature or unwell to coordinate oral (suck) feeds. They therefore receive milk *via* tube passed through the nose (nasogastric), or often the mouth (orogastric), into the stomach or upper intestine. There is limited evidence to suggest whether naso- or orogastric is better since concerns exist for both. Nasogastric may partially obstruct breathing during suck feeds, whereas orogastric tubes are more frequently displaced and can subsequently cause aspiration or respiratory compromise during suck feeds [119].

Enteral feeding may be continuous or an intermittent bolus. Continuous feeding is associated with improved feeding tolerance and slower weight gain [120], whereas the bolus feeding method stimulates greater hormonal responses similar to that of adult eating [121]. Since neither of these methods have shown enhanced nutrient absorption, there is limited evidence for one method over the other for feeding [121].

Typically, enteral nutrition is introduced slowly, with gradual decreases in PN and increased loads of enteral feeding. Enteral feeding may be complicated by feeding intolerances, infections, gastrointestinal anomalies and renal function issues, and rapid feed advancements are associated with increased rates of NEC [122, 123]. Trophic feedings have been suggested to be used in small boluses of 1–3mL/kg per feed, not exceeding 15 mL/kg/day [118, 124]. Early introduction of enteral feeding has been associated with reduced time to full enteral feeds and reduced length of hospitalisation. However, time frames for introducing enteral feeding vary widely between institutions [125, 126]. The transition from parenteral to enteral feeds is managed through various clinical factors assessing feeding tolerance. These include abdominal distention and tenderness, gastric residual volumes and residual characteristics, stool output, and clinical conditions [118].

While human milk is strongly recommended for enteral feeding and all oral feeding in the NICU, human milk, whether fresh or frozen, often requires fortification with protein, nutrients, vitamins and minerals [23] to meet the high nutrient demands for preterm infant growth. If own mother's milk is not available or is short in supply, donor milk is often used to supplement enteral feeding [7, 127]. Donor milk is usually lower in protein content compared to own mother's milk and therefore requires a greater level of fortification [7, 128]. If human milk is unavailable, infants are fed preterm formula. Since the nutrient bioavailability is less than that of human milk and formula use is associated with negative clinical outcomes, it is not generally recommended for feeding preterm infants [129]. An exclusive human milk diet, including donor milk and human milk-based fortifier has been shown to reduce the risk of NEC compared to a mother's milk-based diet that also includes bovine milk-based products [130].

Transitioning to oral feeding
During tube feeding, sucking on a pacifier (non-nutritive sucking) has been associated with improved transition from tube to oral feeding [131]. A Cochrane review has concluded that NNS interventions in preterm infants consistently result in a decreased length of hospital stay, decreased transition time from tube to bottle-feeding, and improved bottle-feeding experiences. Other clinical outcomes have not been consistently observed; including no differences in weight gain, feeding tolerance or age at full oral feeds. Since some positive clinical outcomes, and no negative outcomes have been demonstrated, NNS interventions are recommended for all preterm infants in the NICU [132].

Full oral feeding, on the breast or bottle, is an important criterion for discharge from most NICUs, making the transition from enteral to oral feeding particularly important. Readiness for oral feeding depends on a range of factors including neurodevelopment, behavioural organisation, ability to coordinate sucking, swallowing and breathing, and cardiorespiratory status. Recommendations for feeding readiness based on cardiorespiratory stability irrespective of maturity, age or weight have been suggested [68]. However, depending on the institution, corrected gestational age, infant weight, and developmental assessment criteria are used to determine if infants are ready to begin oral feeding [80, 105, 133]. Methods assessing infant's behavioural cues, such as infant alertness to initiate oral feeding, have been shown to decrease the time of PN to full enteral feeding [105, 134].

Breastfeeding

Oral feeding is recommended to begin with feeding at the breast [103] although current practice varies widely between breast and bottle-feeding of human milk between countries and institutions. Despite breastmilk feedings being encouraged in most NICUs, direct breastfeeding can be overlooked. There is now an increasing body of evidence suggesting that early breastfeeding in the NICU is beneficial, and is associated with an earlier discharge home [135], and an increased rate of human milk feeding in general [136]. Nonetheless, the ability to breastfeed in the NICU depends on the mother's milk production, stress, other family commitments, NICU or hospital facilities and infant stability [68, 137].

As soon as the infant is stable, mothers may be encouraged to hold the infant skin-to-skin, and allow the infant to spend time at the breast. This can occur while the infant is enteral feeding, providing a frequent opportunity to practice feeding at the breast [103]. Developmentally supportive practices that monitor preterm infants' cues and encourage restfulness when the infants show signs of stress and fatigue lead to improved feeding outcomes. Reduction in infant stress by minimising light, noise and handling of the infant, and giving the infant longer rest periods have been associated with improvements in short-term growth, transitioning to oral feeding and earlier discharge from hospital [105].

Traditionally, the transition to oral feeding has been initiated between 32 and 34 weeks gestational age, but sometimes as late as 34–36 weeks age, based on the premise that suck-swallow-breathe coordination is poor before 34 weeks [68]. Although an earlier transition to oral feeding may be more beneficial [68]. During transitional phases, infants may begin with one suck feed per day. At this time, infants may alternate breastfeeding with enteral feeds, allowing the infant to rest between feeds. Infants who do not take their full feed may be tube fed the remaining volume. As infants progress with oral feeding in that they are physiologically stable and are able to complete their allotted volumes, the number of suck feeds per day increases and the number of tube feeds decreases [80]. The challenges of travel and family commitments can make breastfeeding difficult for some mothers. Certainly hospital facilities allowing parents to stay with their infant are conducive to achieving breastfeeding earlier. In cases in which the mother cannot always be available, preterm infants often receive a combination of breast and alternative feeding methods such as bottle-feeding of human milk. In addition, the provision of lactation support, and continuity of care through out the NICU stay and after discharge are beneficial [103].

Figure 7 – Nipple shield in use

Initial feeds at the breast can be difficult for preterm infants due to fatigue, hypotonia and coordination of the suck-swallow-breathe reflex. As preterm infants show improved sucking, swallowing and breathing with restricted flow teats [139], a partially or completely emptied breast after expression may enable the infants to commence sucking at <32 weeks gestation [49], although feeding directly at a full breast has been shown to be safe as early as 29 weeks [68]. Semi-demand feeding has also shown benefits for transitioning to breastfeeding in the NICU population; this involves offering the breast when the infant demonstrates hunger cues and, after a certain time period has lapsed, offering the breast and supplementation if the infant does not demonstrate feeding cues [68]. Using this method in combination with the provision of early and frequent breastfeeding and skin-to-skin care, has been shown to assist in the likelihood of attaining successful breastfeeding earlier in the NICU stay [68].

Skin-to-skin or kangaroo care, refers to the infant being clothed only in a nappy, and being held between the mother's breasts, or on the caregiver's chest, for warmth and stability. Skin-to-skin care is associated with significant benefits during the early postpartum period and when the infant is beginning oral feeds. In particular it improves preterm infant's thermoregulation and stability, and increases the opportunity for the infant to attempt breastfeeding [140]. For mothers, skin-to-skin care is also beneficial as it facilitates their milk supply and assists in earlier attainment and longer duration of breastfeeding [33, 141, 142].

A nipple shield may also facilitate preterm infant breastfeeding (Figure 7). The shield is normally placed over the nipple-areolar surface to assist the infant latch on the breast and minimise nipple pain during breastfeeding. They are also commonly used to help preterm infants attaching to and removing milk from the breast, while learning to oral feed [143]. Premature infants feeding with a nipple shield in the NICU have shown improved milk intake compared to feeding without a shield. Furthermore, after on average 26 days of shield use, there was no negative association with breastfeeding duration after discharge [51]. Term infants in the early postpartum period have shown no differences in milk intake when feeding with and without a shield [144]. The effect of long-term nipple shield use, however, is unknown. Concerns for nipple shield use in terms of milk supply and nipple confusion have been noted in term breastfeeding infants, and therefore monitoring milk intake during shield use has been recommended [143].

Bottle-feeding

In the absence of the mother, infants may be bottle-feeding in combination with breastfeeding and tube feeding. Bottle-fed infants, however, consistently show poorer oxygenation and heart rate, desaturation events, higher body temperature and lower energy expenditure than breastfeeding infants [83, 84, 145, 146]. The presence of nasogastric tubing additionally influences preterm infants' ability to feed. Infants transitioning from enteral to bottle-feeding exhibit three times as many desaturations during bottle-feeding compared to enteral feeding [147], and lower tidal volumes, ventilation, and prolonged desaturations during bottle-feeds with nasogastric tubing in place [148].

Conventional teats used with bottles are designed differently to the mother's nipple: milk flows continuously under the influence of gravity, the rate of flow depends on the size of the teat hole, and the teat is more compressible than the mother's nipple [149]. Breast and bottle-feeding are therefore physiologically different, especially since during breastfeeding milk flows in a transient manner during milk ejections and is not continuously available like it is during bottle-feeding [149]. As a result, infants suck and swallow more frequently, and in a disorganised pattern when feeding from conventional teats. Infants also apply lower vacuums, and different tongue movement patterns [150] and have poorer oxygenation and heart rate, with desaturation events when using a conventional teat [83, 84, 145, 146].

In particular, preterm infants demonstrate desaturations, aspiration and choking when conventional teats have high or unrestricted flow compared to teats with low or restricted flow [151]. There is increasing evidence suggesting that preterm infants feed more effectively when milk flow is lower, and in particular when infants can control the rate of milk removal [139, 151]. Teats with restricted flow (smaller teat hole) have been shown to improve oral feeding in preterm infants as well as increase milk intake, reduce feed duration and improve tolerance compared to standard flow teats [139]. In particular, these studies have shown the advantage of allowing the infant to regulate milk flow, in that milk was removed only when the infant was actively sucking, compared to conventional bottles where milk flowed continuously under the influence of gravity. These studies have also demonstrated issues associated with vacuum build-up inside of bottles, making milk removal more difficult as the feed progresses when less milk is available in the bottle [139, 151].

Other studies have shown that using a teat designed to release milk only when the infant applied a vacuum over a certain level, has also positive feeding outcomes in term and preterm infants. Instead of restricting flow by changing the teat hole size, a valve allowing milk flow only if the infant applied a vacuum over a threshold level was used. Unlike conventional bottles, the vacuum level required for milk removal was consistent throughout the bottle-feed. Compared to breastfeeding, term infants feeding from the vacuum release teat showed similar patterns of tongue movement [149], suck-swallow-breathe coordination, oxygenation, heart rate and vacuum half the strength of that for breastfeeding to remove milk [152]. Adding to this, jaw and throat movements comparing the vacuum release teat and breastfeeding showed that infants feeding from the vacuum release teat opened their mouth to the same angle, and moved their jaw and throat a similar distance to breastfeeding [153]. In contrast, infants feeding from a conventional teat use a significantly smaller angle, to the point that is

Figure 8 – Supplemental feeding tube device in use

classified as a poor latch [154]. Importantly, with the use of vacuum as the key component to milk removal from the teat, no differences in oxygenation and heart rate between the teat and breast were shown [152].

Using the same principle in preterm infants, a vacuum release teat was designed with the idea that preterm infants when learning to oral feed, increase their use of vacuum, and become more efficient and effective feeders over time [82]. Preterm infants who used the vacuum release teat when their mothers were unavailable to breastfeed, left the NICU 2.5 days earlier than infants who were feeding with a standard teat. In addition, infants who fed from the vacuum release teat were more likely to be breastfeeding in the hospital [155]. As with the term vacuum release teat, preterm infants used a similar tongue movement and vacuum half the strength of breastfeeding when feeding from the preterm teat [156]. The use of vacuum release teats may be potentially advantageous because they enable infants to regulate milk removal in a similar fashion as during breastfeeding [40].

Other types of teats and bottles exist to assist oral feeding infants with special needs such as cleft-lip and palate and hypotonia. Infants with cleft-lip and palate are often unable to form a seal around the breast or conventional teat, and are subsequently unable to, or experience significant difficulty with generating vacuum to remove milk from the breast or bottle [157–159]. Likewise, infants with neurological disorders can experience similar difficulties generating vacuum because of hypotonia [160, 161]. Special needs feeders use a one-way valve membrane between the bottle and teat; this means the teat can be filled with milk before the feed so that no air can enter the teat. In addition, a slit valve on the tip of the teat enables the infant to regulate the rate of milk flow by compression rather than vacuum. The caregiver can squeeze the bottle to provide assistance in the infant receiving milk. Infants with clefts have shown improved weight gain, and may find feeding easier when using squeezable bottles compared to rigid bottles [162, 163].

Alternative methods of feeding

Finger feeding is an option for infants who are unable to suck at the breast. A feeding tube is taped onto a silicon covering that is placed over the caregiver's finger and connected to a milk-filled syringe or reservoir at the other end. The preterm infant is able to receive milk from the tube while sucking on the silicone-covered finger. The finger feeder may be advantageous in avoiding nipple confusion and potentially promoting sucking [164]; however, it may not promote jaw opening, or similar jaw movement when sucking on a finger compared to the breast. While the research into the use of the finger feeder in the NICU is extremely limited, one study has shown that the use of the finger feeder instead of bottle-feeding in the NICU is associated with improved breastfeeding rates as discharge [165].

Supplemental feeding tube devices (e.g. Supplemental Nursing System, Figure 8) are another method that enables the preterm infant to obtain additional milk while sucking at the breast. Supplemental feeding tube devices involve one tube connected to a milk reservoir that sits around the mother's neck, and the other side of the tube taped to the mother's nipple supplementing the infant while breastfeeding. These devices are thought to be advantageous as they give infants the opportunity to feed at the breast, and may assist in stimulating a mother's milk production [166], although no studies have assessed their validity in the NICU.

Cup feeding has been used as an alternative to enteral feeding and other forms of supplemental feeding in the NICU. Cup feeding is thought to enable infants to lap milk, then swallow and breathe, rather than coordinate sucking, swallowing and breathing simultaneously. Various forms of cups or vessels have been used in different institutions. Although cup feeding has shown benefits previously in terms of enhanced exclusive breastfeeding at NICU discharge [167, 168, 169], it has also been associated with milk spillage, a low milk intake [170], as well as no differences in exclusive breastfeeding rates at 3 and 6 months, and a longer hospital stay compared to bottle-feeding [169]. As a result, a Cochrane review does not currently recommended cup-feeding for preterm infants over bottle-feeding [171]. In contrast, a more recent study has shown that cup-fed, late preterm infants have increased exclusive breastfeeding rates at discharge, 3 and 6 months, and no difference in hospital stay compared to bottle-fed infants [172]. Large-scale randomised controlled trials are required to further understand the effect of cup feeding on premature infants.

Conclusion

Human milk feeding and direct breastfeeding are crucial for the optimal growth and development of preterm infants. The initiation of lactation for mothers and the ability to oral feed in preterm infants are challenging after delivery. Evidence-based methods to support the mother and infant are required to ensure successful human milk feeding and breastfeeding at NICU discharge.

For the mother, ensuring optimal milk production is critical; therefore, the NICU should encourage early and frequent pumping after birth; double pumping; access to electric pumps that maximise milk output. The NICU should also provide opportunities to be as close to the infant as possible, including skin-to-skin care and hospital facilities allowing parents to stay with their infant.

Methods to support preterm infants breastfeeding include early and frequent attempts at feeding at the breast, semi demand feeding, skin-to-skin care and using nipple shields to assist with attachment to the breast. Similarly, when mothers are unable to be at the NICU, using teats that enable the infant to regulate milk removal may be conducive to improving suck-swallow-breathe coordination.

Understanding the physiology of breastfeeding and milk removal in term and preterm infants may additionally help mothers and infants to overcome feeding challenges in the NICU. Future research investigating feeding at the breast in the NICU is urgently required to assist in devising breastfeeding and human milk feeding interventions for this population.

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