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Cytomegalovirus Transmission to Preterm Infants via Breastmilk: Issues in Research and Practice

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Breastmilk, with all of its bioactive, immunological, anti-inflammatory and nutritive components, is generally believed to be the most beneficial form of nourishment for human infants. However, breastmilk is also a common mode of cytomegalovirus (CMV) transmission to infants. While term infants infected with CMV via breastmilk rarely exhibit any outward signs of illness, preterm infants can present with a variety of signs and symptoms, some quite serious, related to CMV infection. How to approach this clinical issue is both complex and controversial.

Women who have had CMV at some point in their lives are seropositive for CMV antibodies. During pregnancy and lactation, CMV reactivates in a woman's breasts and reproductive tract, causing asymptomatic infection with viral shedding in the mother's breastmilk, cervical secretions and urine. Term infants can acquire CMV infection from breastmilk through what is thought to be a natural immunization process.[1] Infants receive CMV antibodies from their mothers during the third trimester of pregnancy such that at the time of birth, they have a form of passive immunity to the virus. CMV-infected term infants will shed the virus in urine and saliva, but are generally asymptomatic for the infection.

Researchers hypothesize that preterm infants miss the transmission of maternal antibodies to CMV.[2] Thus, when preterm infants — who are by nature physically immature and vulnerable — acquire CMV postnatally via breastmilk, they are at greater risk than term infants of exhibiting symptoms of the disease.[3]

Distinctions among asymptomatic infection, symptomatic infection and a severe CMV sepsis-like syndrome in preterm infants have evolved through clinical studies and case reports. Asymptomatic infection is the most common scenario in term and preterm infants: the infant sheds CMV in urine and saliva but otherwise shows no signs or symptoms of illness. In studies reporting symptomatic infections in preterm infants, infants present with a variety of laboratory and/or clinical conditions.

In a 2010 systematic review, Kurath et al[4] examined the short and long-term outcomes of preterm infants who become infected with CMV via maternal breastmilk. As with most meta-analyses or systematic reviews, studies evaluated varied in methodology, testing procedures, populations and outcomes. Kurath and colleagues' analysis of 26 prospective studies suggests the majority of women of childbearing age are CMV-positive with more than three-quarters of CMV-seropositive women shedding the virus in their breastmilk. CMV infection occurs at a rate of approximately 20% in preterm infants receiving breastmilk from CMV-positive mothers. Additionally, a small percent (median rate of 3.7% or mean of 9.3%) of preterm infants of breastfeeding seropositive mothers develop symptomatic CMV infection. Symptoms vary widely in terms of severity and can include one or more of the following: hepatitis, pneumonia or pneumonitis, neutropenia, thrombocytopenia, elevated liver enzymes, hepatosplenomegaly, gray pallor, fever and hyberbilirubinemia.[5-8] The most commonly reported single symptom is neutropenia alone without other indications of illness.[9,10] In studies reporting symptomatic infections in preterm infants, the infants generally recover spontaneously without evidence of long-term consequences.[4,9,11,12]

Of greatest concern to researchers, health care providers and parents is a severe CMV sepsis-like syndrome evidenced by a very small percent of preterm infants. This analysis by Kurath and colleagues suggests a median of less than 1% of preterm infants of CMV-positive mothers will demonstrate symptoms of severe infection. Of note, Kurath et al do not report any deaths in infants with breastmilk-acquired CMV. In a separate review of multiple clinical and case studies, Hamprecht et al [5] reported very similar results and infant outcomes. Their total sample size was over 1000 infants. Unlike Kurath et al, they identified two infant deaths in one study by Cheong,[13] both deaths occurred in infants with NEC and CMV.

In 1998, Vochem et al[14] identified in five preterm infants with breastmilk-acquired CVM a pattern of more acute illness now known as sepsis-like symptoms or syndrome. These infants exhibited apnea, bradycardia, distended abdomens and gray pallor. Later studies reported similar and additional clinical findings in infected infants, many of whom were extremely low birth weight.[5,6,9,13] However, despite the severity of sepsis-like infections, almost all infants recovered and were discharged home.[5,9]

Shortly after CMV was first reported in breastmilk in 1967,[15] researchers began publishing reports of the effects of breastmilk freezing and pasteurization on CMV. In 1982 Friis and Andersen reported freezing breastmilk significantly reduced the virus in

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breastmilk.[16] The same year Dworsky et al[17] investigated the effects of pasteurization and freezing on CMV in breastmilk. In the Dworsky study, CMV was destroyed completely by Holder pasteurization (heat treatment at 62°C for 30 minutes) but only reduced by freezing. The authors expressed concerns, just as important today as it was then, about the effects of temperature treatment on the immunological properties of human milk.

Breastmilk pasteurization and freezing studies increased in the literature in response to reports of preterm infants with breastmilk-acquired CMV infection. In an attempt to preserve the beneficial properties in human milk, Hamprecht et al[18] compared the effects of Holder pasteurization, short-term pasteurization (5 seconds at 72°C) and freezing at -20°C on CMV-positive breastmilk. Both methods of pasteurization destroyed the CMV, but breastmilk enzymes were also significantly reduced. The authors recommended more study to find the pasteurization temperature at which CMV could be inactivated and breastmilk preserved. Study continues on pasteurization[19] but as Hayashi[20] points out, it is not always practical in a clinical setting.

However, freezing breastmilk is common practice in neonatal intensive care units. Breastmilk is often stored in the freezer for later use or per protocol to reduce CMV transmission. In 2011, Hayashi et al[20] reported a 4.3% CMV transmission rate in preterm infants receiving previously frozen milk from seropositive mothers. Other researchers also report lower rates of breastmilk-acquired CMV transmission in infants fed primarily frozen breastmilk. In Taiwan, where 95% of mothers are seropositive for CMV and all breastmilk is frozen before use, Jim et al[21] found a 15% CMV transmission rate by seropositive mothers to their preterm infants. In Japan, another country where breastmilk is routinely frozen, Yasuda[22] reported 10% CMV transmission via breastmilk with no infant exhibiting clinical symptoms.

While freezing breastmilk seems to reduce CMV transmission, its effects are not entirely benign. The notion that "freezing breastmilk preserves the biochemical and immunologic quality of the milk…" (p. 529)[18] is often taken out of context and repeated. However, this assertion is not consistent with current evidence regarding important breastmilk components and properties. For example, freezing breastmilk kills or significantly reduces cellular components, including macrophages and lymphocytes.[23] Freezing also reduces antioxidants[24] and immunoglobulins IgG, IgM and IgA.[23] This information along with recent breastmilk discoveries such as stem cells[25,26] and the specific immunologic actions of breastmilk lymphoid T and B cells[27,28] should be included in discussions about freezing, pasteurizing or withholding breastmilk for preterm infants.

Studies of CMV transmission via fresh – not previously frozen or pasteurized – breastmilk suggest outcomes similar to those previously discussed. Miron et al[11] in 2005, studied 70 preterm infants fed fresh breastmilk from CMV sero-positive mothers. These researchers reported a 5.7% CMV infection rate with all infants recovering. In 2009 Capretti et al[2] studied 80 infants ≤32 weeks and ≤1500 grams fed fresh breastmilk. CMV transmission occurred in 35% of infants exposed to CMV-positive milk. In this study, 11.5% of infected infants had mild sepsis-like symptoms but all infected infants had positive outcomes with no neurosensory deficits at two years.

The study by Capretti and associates included an additional variable that could have influenced results: immunoglobulin therapy. The neonatal unit's treatment policy for infants less than 28 weeks included IVIGMA therapy at birth. IVIGMA contained variable titers of anti-CMV antibodies. Nineteen study infants less than 28 weeks received IVIGMA; only one developed CMV. In comparison, three of five infants less than 28 weeks who did not receive IVIGMA became infected with CMV. Capretti et al hypothesized the administration of IVIGMA may have helped the very preterm infants compensate for the lack of maternal antibodies they would have received in utero if they had delivered at term.

This is not the first mention in the literature of immunoglobulin therapy to prevent breastmilk CMV transmission: a thin thread of this idea runs through the literature from beginning to end. As early as 1983, Yeager et al[8] recommended the administration of CMV immunoglobulin to preterm infants if the connection between the lack of maternal antibodies and CMV infection could be confirmed. In a later report, Mosca and associates[29] used intravenous immunoglobulins in preterm infants less than 34 weeks receiving CMV-positive breastmilk. In their study, five of 20 exposed infants were CMV infected, but none had any clinical signs or consequences of infection. Lastly, in 2010 Kurath and Resch concluded, "passive immunization with either HCMV monoclonal antibodies or immune globulins might be a case of debate for high-risk low birth weight infants"[30] (p. 680).

Capretti et al[2] concluded the benefits of giving fresh breastmilk outweigh the risks of CMV infection in most preterm infants. For the past 40 years, when interventions for breastmilk-acquired CMV were proposed, they have centered on treating or withholding breastmilk. The discussion of immunoglobulin therapy could shift the focus from treating breastmilk to treating the infant. The more we understand about breastmilk-acquired CMV and breastmilk itself, the closer we come to a comprehensive appreciation of all the relevant issues and options.

Concluding Remarks

The survival of very premature infants presents challenges in neonatal care that did not exist forty years ago. The majority of reports of acute and serious CMV illness are clinical cases of extremely low birth weight infants born before 28 weeks gestation. Kurath and colleagues point out it is often difficult to distinguish between complications related to prematurity and complications from CMV infection.[4] However, research evidence suggests the actual risk of severe, symptomatic CMV infection is very low, even in very immature infants.

At the time postnatal CMV came of interest, techniques for milk pasteurization were well established; thus, they were logical interventions for study and practice. Since that time, human milk science has expanded exponentially. This new information obligates more comprehensive analyses of temperature treatments on human milk or withholding fresh milk from preterm infants. Prophylactic immunoglobulin therapy might also warrant further consideration. Undoubtedly, additional research is needed before clinicians and researchers come closer to a consensus on the issue of CMV transmission via breastmilk.

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Initiating and Maintaining Human Milk in the NICU: A Literature Review of Best Practices

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Introduction

Human milk is recognized as the gold standard for infant nutrition. Expert opinion acclaims the many health benefits of human milk for healthy newborns and especially for infants born prematurely.[1] In the last decade, a plethora of research studies have substantiated the health benefits of human milk for premature infants. These studies have shown that mother's milk provides protection from a host of prematurity-specific morbidities and their long term consequences. Mother's milk has been designated a "medicine" that both nourishes and protects fragile premature infants.[2]

Unfortunately, prematurity does not always allow infants to feed at the breast. As a result, mothers find it necessary to employ breast expression techniques that allow them to provide sufficient volumes of breastmilk for their infants. This provision of human milk requires a coordinated effort between mothers wishing to express their milk and the clinicians who provide care to them. Clinicians find it necessary to search for evidence-based technology and practices that will ensure mothers provide an adequate supply of human milk for their infants.

This paper is written for all clinicians who work with pump-dependent mothers. It is meant to provide a literature review of best pumping practices that help to ensure pump-dependent mothers initiate and maintain adequate volumes of human milk for their premature infants. A review of the normal lactation process will first be presented.

Irene Zoppi currently serves as a Clinical Education Specialist for Medela, Inc. In this role, she acts as a vital resource for groups assisting breastfeeding mothers and infants. She has been frequently interviewed on radio and online regarding breastfeeding issues for mothers and clinicians. Zoppi spent many years caring for new families in antenatal, labor and delivery, postpartum and NICU settings and was involved in direct patient care and family-based education. She has extensive experience teaching in a variety of nursing education programs where she consistently received the Outstanding Lecturer title awarded by her students. She produced a video presentation on nursing students' involvement in Community Health Nursing for the National League for Nursing. Ms. Zoppi, an IBCLC since 2000 and former 1st Lieutenant in the Army Nurse Corps, has authored numerous continuing educational programs for health professionals on topics ranging from breastfeeding support to evidence-based practices on the use of human milk. She has been instrumental in developing hands-on education for clinical staff regarding breastpump technology. Irene graduated from Boston University with a master's degree in Parent Child Health Nursing and is a member of Sigma Theta Tau. This article was provided by Medela.

Initiation of Milk Volumes: the normal process of lactation

All females have the capacity to lactate, to provide a species specific nutrition for their infants after delivery. This process originates during pregnancy, under the influence of a variety of hormones. A woman's breast undergoes changes to ductal and glandular tissue in preparation for the provision of nutrition after delivery.[3] This hormonally controlled process, referred to as Secretory Differentiation or Lactogenesis I, occurs irrespective of the mother's decision to provide human milk for her infant after birth.

After the delivery of the placenta and the sudden decline in circulating progesterone, serum prolactin levels rise resulting in an increase in maternal milk volume. Termed Secretory Activation or Lactogenesis II, this onset of copious milk production occurs normally between 36 and 96 hours after birth and occurs, again, irrespective of the mother's decision to provide human milk for her infant. This initial increase in volume happens in the absence of a sucking infant or milk expression.[4]

After the onset of copious milk production, milk synthesis continues if milk is removed either by a healthy suckling infant or by mechanical expression. Involution of the milk secreting cells results, however, if milk is not removed. Milk stasis within the breasts occurs resulting in over-distention or engorgement. Thus, if the mother chooses not to provide human milk to her infant, she simply does nothing; her milk supply will gradually decrease or "dry-up." When an infant is born prematurely and unable to feed from the breast, the mother will need to rely on mechanical measures to repeatedly empty her breasts. Repeated and effective milk expression after Lactogenesis II will continue to drive milk synthesis.

What happens if infants are born prematurely?

However, pump-dependent mothers with premature infants appear to experience multiple lactation difficulties. This assumption is supported by numerous studies that indicate mothers of premature infants are at greater risk for delayed Lactogenesis II and or low milk volume than mothers with healthy term infants.[2,5,6,7,8,9]

Cregan's work (2002) with preterm mothers concluded that many preterm mothers experience a compromised initiation of lactation resulting in low milk production in the early days post birth. Hill's study (2005) demonstrated that pump-dependent mothers of premature infants were more likely to produce

Table 1

Checklist of Best Practices for Pump Dependent Mothers
✓ Assist mother to initiate pumping as soon as possible after delivery.
✓ Have a hospital-grade, double electric pump available for mother.
✓ Instruct mother to pump a minimum of 8 times daily until target volumes are reached.
✓ Instruct mother to initially pump for 15 minutes until milk volumes increase.
✓ Once milk volume increases, instruct mother to pump for 2 minutes after last droplets are noted.
✓ Assess for risk factors associated with delayed lactogenesis.
✓ Guide mother to begin a daily pumping journal.
✓ Provide pumping target volumes for mother.
✓ Assess breast shield fitting daily during 1st two weeks after birth.
o Outfit each hospital pump with breast shield sizing information.
✓ Support bedside pumping.
✓ Assist with frequent skin-to-skin care.
✓ Help with transition to infant tasting breast milk.

less milk in the early days post birth along with reduced milk volumes as they continued to express milk. Schanler and colleagues (2005) also witnessed pump dependent mothers struggle to maintain milk volumes for their premature infants.

Several risk factors have been identified that pose a risk for delayed Lactogenesis II.[8,10,11,12] Risk factors such as diabetes mellitus, preterm labor, pregnancy induced hypertension, excessive maternal blood loss, prolonged bed rest, maternal stress during labor and delivery, an unscheduled Cesarean delivery, obesity, and the use of selective serotonin re-uptake inhibitors (SSRIs) pose risks for any breastfeeding mother, but so commonly occur in mothers who give birth prematurely. Assessment for these lactation risk factors should be included when providing lactation support for mothers of premature infants.

Although insufficient volume of milk is commonplace among preterm mothers, Meier (2007, 2010) and Spatz (2004) contend that many occurrences may be avoided if mothers receive instruction and individualized care regarding best clinical practices during both the initiation phase (Lactogenesis II) and maintenance phase of lactation. The following paragraphs describe these best practices. A quick reference list (Table 1) identifies these practices.

Initiation and Maintaining Milk Volumes: Best Practices

The first two weeks post-birth represents a critical period in lactation for all breastfeeding mothers. Due to the complex endocrine, anatomic and biochemical changes occurring during this first two week period, breastfeeding needs to get off to a good start. For the healthy term breastfeeding baby, this requires frequent feeding at the breast in the range of 8 to 12 times per day. In the absence of a healthy term breastfeeding baby, the mother of a preterm infant is at risk for diminishing milk volume; her milk supply may decrease and be insufficient to meet the nutritional needs of her infant. Hill (2005) cites decreasing maternal milk volume as the reason many NICU mothers are unable to meet their lactation goals.

Table 2

Criteria for Correct Breast Shield Fit	
C	Centered nipple which moves freely in the tunnel
O	Only little or no aerola tissue pulled into the tunnel
M	Motion of the breast is gentle and rhythmic with each cycle of the pump
F	Feels comfortable pumping
Y	You find a well-drained breast. If an area of the breast still feels full or a bit firmer, the milk duct in that area of the breast may not be empty.

Getting Started: When and How

Studies indicate[15,16,17] mothers of premature infants should initiate milk expression as soon as possible after delivery. Hill (2001) demonstrated correlation of early breast expression and milk volumes during 2-5 days postpartum. Furman (2002) demonstrated that mothers who initiated milk expression within 6 hours of delivery were more likely to continue lactation beyond 40 weeks. Spatz (2004) recommends mothers begin milk expression within the first 6-12 hours after birth. A pilot study[17] of 20 mothers who delivered VLBW premature infants and began milk expression within 1 hour of delivery produced significantly more milk during the first 7 days after birth than mothers who initiated milk expression between 1 and 6 hours after delivery.

The use of a hospital-grade, double electric breast pump has been recommended for pump dependent NICU mothers to help them achieve adequate volumes of breast milk.[14,18,19,20] Meier (2010) states, "A breast pump is fundamental to a mother's ability to produce milk, and it is critical that NICU mothers receive the most effective, efficient, comfortable, and convenient breast pump available" (p 34). Mothers should be instructed to pump at the same frequency that duplicates the breastfeeding frequency of a healthy term infant. This frequency is required to drive continued milk production. The more milk is removed from the breast either by a healthy baby or by a breast pump, the more milk will be made. This is known as the supply and demand principle of continued lactation. Spatz (2004) and Rodriquez et al (2005) recommend mothers pump every 2 to 3 hours each day. Walker (2010) suggests pumping eight or more times in twenty-four hours. Participants in Parker's study (2011) were instructed to pump at least eight times in twenty-four hours.

Simultaneously pumping both breasts reduces the time mothers spend while pumping. One study (Hill, 1996) suggested that milk volumes may be increased with simultaneous pumping.

No research evidence exists to recommend how long an individual pumping session should last. It is frequently recommended that during the Initiation Phase of lactation, mothers should pump for approximately fifteen minutes. After the onset of Lactogenesis II, mothers should be instructed to pump for two minutes after the last droplets are noted (Meier 2010). This ensures all available milk has been expressed and the high fat milk has been removed. A well-drained breast will more rapidly synthesize breast milk than a breast that is partially drained.[24] Kent (2008) recommends mothers pump using Maximum Comfort Vacuum (MCV), the highest yet comfortable vacuum setting of the pump while expressing milk. Research has demonstrated this allows a mother to pump more efficiently; she will pump more milk in less time.

Hand expression has been mentioned to aid in the retrieval of the small quantities of colostrum produced during the initial stages of lactation. Morton (2009) demonstrated greater volumes of colostrum in mothers who performed hand expression 5 times a day combined with use of a double, electric breast pump more than five times a day in the first few days after birth. Ohyama (2010) found gentle manual expression during the first 48 hours was the best way to obtain small quantities of produced colostrum.

A recent study by Meier (2011) demonstrated increased volumes of expressed milk when mothers utilized a breast pump suction pattern that mimicked the unique sucking action of the healthy term infant.

Meier (2010) recommends mothers be given volume targets they should achieve during the first two weeks of pumping. During this initial phase of lactation, identification and treatment for insufficient milk volumes is critical. Meier (2010) refers to this transition period from Lactogenesis II to a milk volume sufficient for exclusive breastfeeding as "coming to volume." Providing target volumes helps identify pumping issues that need modification. Achieving ideal pumped volumes of 750-1000ml per twenty four hours within the first two weeks after birth is correlated with adequacy of breast milk for the infant over the entire NICU stay.

Spatz (2004) and Meier (2007, 2010) also recommend mothers document daily pumping sessions and collected milk volumes in a journal or diary. Keeping a milk volume record enables mothers and clinicians to identify milk volume issues early so that interventions can by instituted to rectify any problems. Bedside clinicians are able to guide and support mothers' pumping efforts when they review the daily pumping logs with them.

Breast shields, the portion of the breast pump collection kit that comes in direct contact with the mother's breast, nipple and areola areas, require careful fitting to the mother's anatomy. A breast shield that is either too large or too small may cause injury to the mother or impede breast milk drainage leading to the eventual down regulation of a mother's milk supply. Meier (2010) recommends daily assessment of breast shield sizing during the two week "coming to volume" period. Zoppi [this author] (2011) refers clinicians to the use of an acronym; COMFY as a simple tool to emphasize criteria to correctly fit breast shields (Table 2). Zoppi recommends outfitting all breast pumps within the hospital setting with laminated cards detailing these fitting guidelines. Kent et al (2011) described an increase in efficiency of removing milk when breast shields were warmed before use.

Pumping directly at the infant's bedside instead of a designated pumping room provides the mother the opportunity to visit with her infant as she pumps (Meier 2007). The mother may find it more pleasurable to watch and even speak to her infant as she pumps. It also provides an opportunity for the bedside clinician to detect and correct any improper pumping technique used by the mother.

Another non-pharmacologic technique cited in the literature that enhances physiologic stability and breastfeeding behaviors of preterm infants in the NICU is skin-to-skin holding or kangaroo care. Numerous studies[2,13,14,16,31,32] have demonstrated that mothers were able to express significantly more milk after a skin-to-skin episode with their infant.

The next step in the lactation process for NICU mothers and their infants is nonnutritive sucking at the breast or tasting breast milk (Spatz (2004), Meier (2007). This is accomplished by having the mother position her infant skin-to-skin on her breast after she pumped her breasts. Tasting drops of breast milk during a scheduled gavage feeding allows the infant to associate breast milk with his feeding. Nonnutritive sucking can be initiated after the infant has been extubated. It has been shown to improve the transition to direct breastfeeding, shortens the period of pump dependency for mothers and is associated with longer breastfeeding rates.[33]

Summary

Breast milk is undeniably the best nutrition for premature infants. The process of initiating and maintaining adequate volumes of breast milk to meet the nutritional needs of the premature infant requires dedication from mothers and a commitment on the part of bedside clinicians to teach, support and provide up to date evidence on best practices. Many mothers find the challenges of pumping milk for their premature infants overwhelming. They struggle with many issues and have to overcome many obstacles to be successful. Yet many mothers find the process of milk expression for their preterm infants rewarding and empowering.[34]

Bedside clinicians can make a tremendous difference in the pumping experiences of pump dependent mothers challenged to provide expressed milk for their premature infants. Clinicians need to be knowledgeable about current best pumping practices and integrate them into the care they provide to pump dependent mothers.

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NICU Support of the Breastfeeding Mother of Twins and Higher Order Multiples

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Introduction

Human milk (HM) feeding has long been recognized as the optimal method of feeding for nearly all infants. For the subset of infants hospitalized for prematurity, the receipt of HM may be crucial. Human milk plays a significant role in decreasing morbidity and improving gastrointestinal function, absorption of nutrients, visual acuity and long-term neurodevelopmental outcomes. Mothers of premature infants are often challenged in their attempts to provide HM for their infants. Therefore, premature infants are at greater risk than their full term counterparts of not being fed enough human milk or not being fed human milk at all.

A group of mothers known to be at high risk for premature delivery are those experiencing multi-fetal pregnancy. Due to a myriad of conditions, these mothers are at greatest risk for delayed onset of lactogenesis II, insufficient milk supply and even lactation failure. Breastfeeding and lactation support becomes critical in assisting mothers to provide human milk for their infants.

It is imperative that health care professionals in the antenatal healthcare and neonatal intensive care settings be knowledgeable and supportive of breastfeeding and human lactation. In addition to providing guidelines, this paper will address the unique challenges faced by health care professionals as they educate and support the breastfeeding mother of twins and higher order multiples (HOM).

Background

Multiples births were steady at about 2% of all births in the United States from about 1915 through the 1970s.[1,2] Beginning in the early 1980s, the incidence of twin, triplet and HOM birth escalated dramatically.[3,4] This may be due to a number of factors including an aging population and artificial reproductive technology. In its January, 2012 Data Brief, the National Center for Health Statistics reported that in 2009, 1 in every 30 babies was a twin compared to 1 in every 53 babies in 1980.[5] Triplet /+ births have been reported at just over 150 per 100,000 births.[6] Some have called this "an epidemic of multiple pregnancies."[7] The rise in the proportion of infants born prematurely or at low birth weight has become a significant public health concern. (Table 1.) Because they comprise a much larger portion of infants born prematurely and at lower birth weights, twins, but not triplets, have impacted trends of perinatal health indicators.[8]

Table 1. Gestational age and birthweight characteristics by plurity: United States, 2009*

	All Births	Single-tons	Twins	Triplets	Quadru-plets	Quintu-plets and higher order multiples[1]
Number	4,130,665	3,987,108	137,217	5,905	355	80
Percent very preterm[2]	2.0	1.6	11.4	36.8	64.5	95.0
Percent preterm[3]	12.2	10.4	58.8	94.4	98.3	96.3
Mean gestational age in weeks (SD)	38.6 (2.5)	38.7 (2.4)	35.3 (3.6)	31.9 (3.9)	29.5 (4.0)	26.6 (4.6)
Percent very low birthweight[4]	1.5	1.1	9.9	35.0	68.1	86.5
Percent low birthweight[5]	8.2	6.4	56.6	95.1	98.6	94.6

*Adapted from the 2009 CDC/NCHS, national vital statistics System[6]
1 Quintuplets, sextuplets, and higher order multiple births are not differentiated in the national data set.
2 Very preterm is < than 32 completed weeks of gestation.
3 Preterm is < 37 completed weeks of gestation.
4 Very low birthweight is < 1,500 grams.
5 Low birthweight is < 2,500 grams.

Evidence for HM feeding of premature and low birth weight infants is overwhelming. The use of HM in the NICU has been prioritized by major organizations including The American Academy of Pediatrics, The National Institutes for Child Health and Development, and The Academy of Breastfeeding Medicine. Percentages of infants receiving any breastmilk during their NICU stay and of those being discharged receiving any breastmilk are now benchmarked in hospital NICUs. Given the rise in multiple birth and prematurity, health care professionals can do much to support and guide these high-needs infants and their mothers to initiate and sustain HM feeding.

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NICU Support During the Antepartum

A number of support measures can be provided during the antepartum by NICU staff and other health care professionals. Many mothers of multi-fetal pregnancies are hospitalized on bed rest for extended periods during the antepartum. These mothers often beseech interaction, thus providing abundant opportunities for perinatal education.

Because hospitalization often occurs in high risk settings where neonatal intensive care services are readily available and strategically located, NICU clinicians who will care for these infants have relatively easy access to the mothers and their families. A multidisciplinary team comprised of NICU and antenatal unit staff, neonatologists, lactation consultants, perinatal educators, occupational therapists and registered dietitians may be assembled to assess medical and educational needs. A systematic approach to the delivery of healthcare education geared specifically to individual and family needs may significantly improve outcomes. Expectations for delivery, early infant care and feeding are topics that should be addressed. If possible, a trip to the NICU with explanations of equipment and procedures may be very helpful to select mothers when performed in a gentle and thoughtful manner.

There is a wide variation in populations relating to rates of breastfeeding initiation in multiples. These range from 40-90% in twins alone.[9] Mothers expecting multiples may not consider breastfeeding purely due to logistical concerns. Therefore, research-based information about the importance of human milk-feeding should be provided. Breastfeeding education during the antepartum will allow mothers of multiples to make informed decisions and to approach infant feeding with more confidence.

Mothers of multiples are more likely to become pump-dependent. Therefore, preparation and anticipation for milk expression should be addressed. Pump-dependent mothers of premature infants are at risk for low milk volumes and discontinuation of HM feeding.[10,11] Preparation for HM feeding might include discussion and demonstration of hospital grade electric breast pumps and accessories, frequency and duration of milk expression, expectations of volume, storage, transport and feeding of HM to premature infants. Becoming familiarized with these elements prior to the birth of their babies will reduce fear and facilitate more positive outcomes.

Along with education regarding breastfeeding and infant nutrition, an assessment of maternal prenatal nutrition should be conducted. Mothers of multigestional pregnancies should have specific goals for daily caloric and nutrient intake given that they are at greater risk of micronutrient deficiency.[9] Attention to specific nutritional needs during multi-fetal pregnancies has been associated with improved neonatal outcomes[12] and increased initiation of breastfeeding.[13]

Early Postpartum: The First Few Days

Mothers of multiple infants are faced with all of the usual challenges experienced by mothers of singletons. However, a unique set of impediments affect multiples over singletons. Coupled with the increased potential for prematurity and its associated feeding difficulties, mothers of multiples often must deal with a variety of physical and psychological issues.

In the early postpartum, a mother may be besieged with infirmity related to pregnancy or the intrapartum. Serious illness (such as pregnancy-induced hypertension or HELLP syndrome), weakness due to heavy blood loss or bed-rest induced cardiovascular / muscular de-conditioning, surgical recovery, medication therapy and other physical stressors are often the case.

The psychological impact of caring and concern for multiples may be more than a mother can handle in the first few days and weeks. Mothers may be troubled with issues of separation, anxiety, grief and indecision. For example, the process of maternal / infant attachment may be at risk due to geographic separation. Mother is separated from her infants and her infants may be separated from one another due to differing needs in the level of intensive care.[14]

In situations where there has been a loss of one or more of the infants, a bereaved mother of multiples must cope with making decisions about disposition of remains. Concurrently, she may be struggling with anxiety, worry and conflict regarding attachment to the surviving infant(s).[15] Feelings of guilt often plague newly delivered mothers as they question whether there might have been something more they could have done to extend the gestational period.

Because these physical and psychological issues are associated with poor milk production and late onset of lactation, breastfeeding support provided by post-partum and NICU caregivers must begin as soon as possible after birth.

Begin Lactation Support as Soon as Possible after Delivery

For all mothers, the first 14 days post delivery is a critical period for the establishment of milk production.[16] It is imperative that pumping and manual expression of milk be initiated ASAP after delivery of premature infants. The combination of hand (manual) expression with breast massage and pumping has been shown to increase milk production and is highly recommend by practitioners[17] and by the Human Milk Banking Association of North America (HMBANA) as best practice.[18] Use of a hospital grade pump with small collection containers (such as those manufactured by Medela) will allow for optimal collection of milk. Although there are several types of hospital grade pumps, one in particular is able to provide a specific pattern of stimulation known to be closely associated with optimal subsequent milk volumes when used in the post delivery stage of lactogenesis I.[10,16] In situations where mother is too weak or ill, hands-on pumping support may be required to facilitate early initiation. Caregivers may hold breast shields in place and operate the pump. This may be done easily while mother is resting in side-lying position.

As soon as even a few drops of colostrum can be obtained, it should be fed to the infants orally by any means appropriate to their care. Ideally, colostrum should be given in the order it was expressed. Oropharyngeal administration of colostrum should be considered for those infants of extremely low birth weight who are not yet able to begin enteral feeding.[19,20] Mothers may be instructed on this relatively simple yet extremely important method of providing care to the baby. Not only is frequent oral mucosal coating of colostrum medically significant in reducing or avoiding intestinal inflammation, but also psychologically important to the mother in terms of her ability to care, interact and bond with her babies. Skin-to-skin mother care initiated as soon as possible after delivery will also facilitate milk production and attachment for these at-risk mothers.

Later Post-partum: The First Few Weeks

Mothers of multiples are often breast pump dependent for several weeks or even months. A hospital grade electric breast pump is recommended for long-term breast milk expression.[21] Insurance companies will often pay for the rental of a hospital-grade breast pump during the infant's hospitalization and until direct breastfeeding is well established. Intensive support for human milk feeding will be required during the infants entire hospital stay.[22] Following maternal discharge from the hospital, the role of the NICU staff becomes the primary source of education and support for the family of multiples. The family may be struggling with time constraints, stress, challenging infant feeding schedules and the psychological implications discussed earlier.

One of the obstacles of HM feeding for mothers of multiples vs singletons, is the distribution of expressed breast milk to their infants in cases where maternal milk supply is an issue. Mothers may have difficulty determining whether to give all HM to the sickest infant, to rotate exclusive HM feedings or to distribute available milk evenly amongst all. The NICU staff can assist mother in making these often difficult and critical decisions. An inverse dose-response relationship between the amount of human milk received and short or long-term morbidity has been demonstrated. The higher the doses of human milk, the lower the risk of health problems to the infant.[10] Furthermore, there is evidence of critical periods for human milk feeding where infant formula should be avoided. These may be the first 14 or 28 days of extra-uterine life, depending on the gestational age of the infant.[10] NICU staff diligence in supporting the breastfeeding mother of multiples can reduce the need for having to make these tough decisions regarding milk distribution.

Another decision that NICU staff can assist mother in making is the dietary choice of HM fortifier. If the infants are at very low birth weight and extremely premature, chances are that HM fortifier will be necessary. The NICU team should consider the use of human milk-based HM fortifier for these infants. Exclusive HM infant diets are associated with less morbidity and significantly lower rates of necrotizing enterocolitis (NEC) compared to those diets which include bovine milk-based products.[23] Furthermore, the use of human milk-based HM fortifier may reduce the cost of medical care by preventing NEC.[24] Although expensive, mothers may wish to consider this option and should be educated about its benefits and availability.[25]

There are a number of other measures NICU staff may employ to support mothers of multiple premature infants in their effort to provide human milk over the weeks of hospitalization.

- Have a NICU policy in place that will guide the staff in supporting these mothers. The staff needs to be consistent in giving advice.
- Encourage mothers to provide as much infant care as possible when they are visiting the NICU.
- Keeping the infants together in a cluster may help with attachment. If possible, co-bedding may facilitate attachment for the mother and reduce the level of stress for the infants. This may improve physiologic stabilization and assist with the initiation of breastfeeding.[26]
- Encourage mother to pump near her babies; create a cozy environment (low lights, relaxed positioning).
- Encourage skin-to-skin positioning in dark quiet areas where mom and babies can relax. When an infant is quiet and alert, encourage mother to hand express drops of milk onto its lips and tongue.
- Keep an eye out for post partum depression. These mothers are at greater risk.
- Be sure there is a support network available to her. Emphasis must be placed on intensive support and encouragement for the continuation of HM feeding throughout an infant's hospital stay.[22] Consider a support group for breastfeeding in the NICU.
- Recommend upper body massage therapy. This may facilitate milk ejection, thus greater volume when performed during milk expression.
- Lactation consultant services should be available daily and milk volume assessments should be monitored. Check function of mother's breast pump periodically.

Approaching Discharge

Length of hospitalization is a risk factor for HM feeding of premature babies. In one study, length of stay was found to be the most important factor influencing breastfeeding in premature singletons. The longer the hospitalization, the more likely the infant would be discharged formula feeding.[27,28] However, in a subgroup of multiples, lower gestational age (and thus longer hospitalization) significantly increased the probability of being breastfed.[27] Another study determined that multiple birth was a predictor of human milk feeding discontinuation by post-partum week 12.[28]

Pump dependency may last well beyond hospital discharge. Breastfeeding mothers need to know that their infants may not be fully capable of efficient milk transfer via exclusive direct breast feedings until they are close to or even beyond the time when they would have reached full term gestational age. Mothers will need help in planning for continued milk expression at home while bottle or alternate methods of feeding will likely be required for some or all of the infants.

As the infants approach hospital discharge, it is important for NICU staff to recognize additional challenges faced by mothers of multiple premature infants. These challenges can affect HM feeding outcomes. Infants of multiple gestations are often staggered in their hospital discharges. This can place emotional and physical strain on the mother and her family. Travel to and from the hospital coupled with the fatigue associated with full time infant care may wear a mother down. Fear of emotional disconnect in claiming the infants as her own may also complicate the process and anticipation of discharge for mother.[14] NICU staff must recognize these feelings and be able to address them with mother. The need for help and assistance at home should be emphasized.

Resources for Patient and Staff

There are a number of breastfeeding and general resources available for mothers of multiples and healthcare professionals alike. These include, but certainly are not limited to, the following:

- Twins to Quints: The Complete Manual for Parents of Multiple Birth Children, Edited by Rebecca L. Moskwinski, MD, (2002, Harpeth House Publishing)
- National Organization of Mothers of Twins Clubs, Inc. (A support group for parents of twins and higher order multiples), http://www.nomotc.org
- Multiples: More of Everything. Two volume video set, Injoy Birth and Parenting Education, 2009. 7107 La Vista Pl. Longmont, CO 80503

- Human Milk Banking Association of North America (HMBANA), https://www.hmbana.org

In Conclusion

NICU staff is in a unique position of influence over new parents whose infants are hospitalized for extended periods. The provision of HM is a critical element in the health and health care of infants, yet it remains a highly vulnerable matter. Knowledge and support of breastfeeding and human lactation should be a basic requirement for all members of hospital and community healthcare teams. During the Third Annual Summit on Breastfeeding, it was suggested that The Joint Commission, the largest health care accrediting body in the United States, require all hospitals who provide perinatal care, to meet the UNICEF/World Health Organization's Ten Steps to Successful Breastfeeding.[29] Although neonatal intensive care units may be exempt from some of its elements, patient and staff appreciation of the ten steps would undoubtedly spill over and influence best practice of human milk feeding in the NICU.

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Reducing Morbidity and Necrotizing Enterocolitis: The Interface of Human Milk with the Preterm Infant Gastrointestinal System

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Introduction

> Breast milk is very important if your baby is born early or is sick. Breast milk can help your baby get better faster and develop properly. The nurses or lactation consultant can help you learn how to pump your milk if your baby cannot breastfeed.
>
> – *The Joint Commission – Speak up: What you need to know about breastfeeding.*[1]

Recently, the Joint Commission joined medical, nursing and other professional organizations, the CDC and the US Surgeon General in publically promoting the benefits of human milk for all infants. The evidence supporting the use of human milk in the NICU is both extensive and compelling: laboratory and clinical research demonstrate the value of human milk in reducing multiple disease states of the preterm infant including necrotizing enterocolitis (NEC), chronic lung disease, retinopathy of prematurity, and infections.[2-10] Against this backdrop of information and data, it is easy to lose sight of the most critical and consistent element in all of these diseases: the interface of human milk with the infant gastrointestinal system.

Protective Function of Human Milk in the Preterm Infant GI System

At the time of birth, the preterm infant's gastrointestinal system is anatomically and physiologically immature. As the infant develops, tight junctions between the cells of the intestinal mucosa close, reducing the risk of invasion by pathogens in the environment.

In a 2009 study, Taylor, Basile, Ebeling, and Wagner[11] investigated the effects of human milk feeds on preterm infants' gut permeability in the first month of life. Intestinal permeability can be accurately measured by the ratio of lactulose to mannitol in infants' urine. In this study, infants who received mother's milk were found to have better tight junction closure with less gut permeability when compared to infants who received little or no human milk. Conversely, exclusively formula-fed infants demonstrated a 2.8-fold higher composite median lactulose/mannitol ratio when compared with those who received any mother's milk. These results suggest formula feedings may be associated with delayed closing of tight junctions, predisposing preterm infants to gastrointestinal morbidities including NEC.

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The gastrointestinal tract has a dual purpose of absorbing nutrients and protecting the organism from invasion of environmental pathogens. This protection begins in the lumen of the GI tract with functional barriers like mucus and commensal (or protective) bacteria and continues into deeper layers of the mucosa with cells specific to immune response and regulation of inflammation.

The human gastrointestinal tract is comprised of several layers of functional substances overlying the intestinal epithelial absorptive cells, commonly referred to as enterocytes. At the apical end of the enterocyte, several layers of coatings protect the epithelial cells from harmful microbes. The glycocalyx is a thick, mucin-rich glycoprotein matrix lining the entire gastrointestinal system. Together with the mucus layer, it forms a sticky gel-like barrier that lubricates and protects the intestine.[12,13] Embedded within the mucus layer are antimicrobial inhibitors that help regulate gut colonization.[13] Lastly, a biofilm of symbiotic bacteria develops at the interface with the intestinal lumen. All three layers work in concert to protect the infant from pathogenic bacteria.[13]

Gut permeability is one of multiple developmental limitations of the preterm infant's immature gastrointestinal system, all of which can contribute to an increased risk of feeding intolerance as well as short and long-term morbidities. Other aspects of the preterm gastrointestinal system related to immaturity include a need for rapid cellular growth and turnover[14] decreased peristalsis,[10,15,16] decreased gastric acid,[15] decreased proteolytic enzymatic activity,[15,16] altered intestinal mucus,[14-16] and an immature inflammatory response.[13]

According to Wagner et al,[14] amniotic fluid and human milk are sources of multiple growth factors important to the continuum of fetal-infant gut development and maturation. Like amniotic fluid, human milk promotes gut maturation by supplying epidermal growth factor as well as other trophic factors. After birth, human milk assumes the role of exogenous source of bioactive substances stimulating cell growth and repair through the synergistic actions of cytokines, insulin-like growth factors, transforming growth factors a and b, insulin, erythropoietin and vasoactive endothelial growth factor. Wagner et al hypothesize trophic factors in human milk also enhance the development and function of the intestinal mucus barrier.[14] By promoting growth of enterocytes, tight junctions and the mucus barrier, human milk contributes to the overall functioning and integrity of the infant gastrointestinal system.

Human milk provides other benefits related to immaturity of the neonatal gastrointestinal tract. Human milk increases peristalsis, thereby decreasing the build up of toxins and pathogens in the intestinal lumen.[16,17] Additionally, milk lipases breakdown triglycerides into anti-microbial free fatty acids promoting an acidic gastric environment essential for nutrient degradation.[13] These are just a few of the numerous protective functions of human milk in the preterm gastrointestinal tract.

The Role of Human Milk in Reducing the Risk of NEC and Other Morbidities

Several studies have demonstrated the protective effects of human milk for preterm infants against the risk of sepsis and NEC.[4,8,9,18,19] Research by Meinzen-Derr and colleagues[20] evaluated the impact of the dose and total percent of human milk over a short period of time in a large population of infants. Their findings suggested an inverse relationship between human milk feedings during the first 14 days of life and the risk of NEC or death over hospital stay. Increasing cumulative and proportional amounts of human milk in the first 2 weeks was associated with increased survival time in which the infant was free of NEC. Infants who developed NEC or died after the first 2 weeks were fed less human milk and had a lower mean daily volume of human milk than infants who survived free of NEC.

In a separate prospective cohort clinical study, also of ELBW infants, Sisk et al[21] evaluated the impact of low (<50% of total feeds) and high (>50% of total feeds) doses of human milk. Their results indicated a six-fold decrease in the risk of NEC in infants receiving at least 50% human milk feedings in the first 14 days of life. For mothers who did not plan to provide milk for their infants, this information could positively influence their decisions about initiating pumping.

Human milk is a well-known source of multiple anti-infective agents including secretory IgA, lactoferrin, lysozyme, macrophages and free fatty acids.[13,17] These agents work in concert to inactivate, destroy or bind to specific microbes, preventing their attachment to mucosal surfaces.[22] At the same time, human milk contains lactic acid bacteria, primarily bifidobacteria (also referred to as lactobacillus bifidus). These protective commensal bacteria become part of the gut microflora and influence inflammatory and immunomodulary processes.

The significance of a healthy gut microbiota cannot be understated. Commensal bacteria prevent the overgrowth of pathogenic bacteria, acidify the gut, ferment lactose, break down lipids and proteins, and produce vitamins K and biotin.[10,15-17] Colonization of the infant's GI tract begins at the time of birth with exposure to the mother's vaginal flora or skin flora, depending on mode of delivery.[23] Colonization continues with exposure to the environment and is heavily influenced by type of infant feeding.

Recent discoveries have clarified the symbiotic relationship of human milk oligosaccharides (HMOs) and lactic acid bacteria in the infant's gut.[22-26] HMOs are complex carbohydrate molecules abundant in human milk. However, human infants cannot digest HMOs, thus their purpose in human milk has been an enigma. In the last few years, researchers have discovered that HMOs in human milk are digestible by specific bifidobacteria in infants' gastrointestinal tracts. In this capacity, HMOs function as prebiotics, feeding and stimulating the growth of commensal bacteria. They also act as decoys or receptor analogs to inhibit binding of pathogens - including rotaviruses - to intestinal surfaces.[24-27]

Human milk reduces the risks of NEC,[2,3,8,9] sepsis,[4,5,8,28] and intestinal disturbances in part by promoting healthy gut microbiota and intact mucosa. Anti-infective agents in mothers' milk (mentioned above) contribute to these layers of protection against infection. However, localized actions do not explain the ability of human milk to reduce the risk of diseases remote from the GI tract, eg, chronic lung diseases, retinopathy of prematurity and disorders which lead to neurodevelopmental delays. These diseases, like NEC, are characterized by a systemic inflammatory response triggered by overproduction and release of pro-inflammatory cytokines, such as Interleukin-8 (IL-8).[10,16,29,30]

Normally, inflammation acts as a healthy defense mechanism to rally immune factors, including leukocytes, to the site of infection or tissue injury. However, preterm infants lack the regulatory mechanisms to keep inflammation in check.[31] Caicedo et al[10] hypothesize the release of IL-8 and other pro-inflammatory factors in the preterm gut can cause an exaggerated inflammatory response, leading to intestinal injury (NEC) as well as damage to other organs. Several human milk components interrupt or downgrade inflammatory processes in preterm infants, including interleukin-10 (an anti-inflammatory cytokine), lactoferrin, epidermal growth factor, transforming growth factor-β, HMOs, soluble CD-14 and insulin-like growth factor.[10,13,31] These factors work synergistically to protect the preterm infant from over-productive inflammatory responses.

In the context of studies we have already examined – those by Taylor, Meinzen-Derr and Sisk in which the early use of human milk had a significant positive effect on preterm infant outcomes – it should be mentioned that many of these protective milk components are at their highest in colostrum.[31] Furthermore, as Meier notes so concisely, it is "during this critical exposure period…that [infant] formula appears to exert an independent, pro-inflammatory effect."[31 (p.222)]

The Confounding Role of Human Milk Fortifiers in Preterm Infant Morbidities

Studies evaluating the efficacy of human milk in reducing the risks of short and long term morbidities are confounded by the need for milk fortification. Once preterm infant feedings progress to volumes greater than 100 ml/kg/day, bovine-based human milk fortifiers are frequently added to human milk – mother's own or donor milk – to enhance nutrients, including protein, calcium and phosphorous. This practice raises questions about the impact of bovine-based fortifiers on preterm infant health.

In a 2009 Cochrane Database Review, Kuschel and Harding[32] analyzed research related to human milk fortification. Noting that current practice, research and clinical ethics have moved beyond the discussion of whether or not to fortify human milk, they recommended further research of fortifier components and comparisons of different fortifier preparations.

The predominant protein in bovine milk and bovine-based human milk fortifiers – casein – has been identified since the 1970s as a chemoattractant to human leukocytes.[33] Leukocytes have specific receptor sites for binding with casein. In laboratory and animal studies, casein activates movement of leukocytes to the casein molecules. Thus, casein is inherently pro-inflammatory, causing activation of mucosal defenses and the release of inflammatory mediators which can progress to NEC, particularly in the presence of pathogenic bacteria.[16,34,35]

A 2010 study by Sullivan et al[36] suggests a diet that includes bovine proteins – including those in human milk fortifiers – can have a significant negative impact on preterm infant morbidity and mortality. Their research examined extremely premature infants whose mothers intended to provide their expressed milk for feedings. Infants fell into two basic groups: 1) those who received mother's milk (or human donor milk if needed) plus a newly developed human milk-based human milk fortifier, or 2) those who received human milk (or preterm formula if needed) plus standard bovine-based human milk fortifier. Results indicated extremely low birth weight infants receiving only human milk products had significantly lower rates of NEC and surgical NEC when compared infants fed a mother's milk-based diet that also includes bovine milk-based products. Furthermore, all cases of surgical NEC and all study deaths related to NEC were in infants who had received bovine-based products.

Perhaps in anticipation of concerns about the cost of using human milk-based fortifiers, Ganapathy, Hay and Kim [37] published a revealing cost analysis in 2011. Using Sullivan's outcomes data, these authors calculated the cost effectiveness of a 100% human milk-based diet comprised of mother's milk and human milk-based fortifier when compared to a diet of mother's milk supplemented with formula and standard fortifier. Their results supported the cost effectiveness of a human milk-based diet; the use of a 100% human milk-based diet could yield a net direct savings of $8,167 per extremely preterm infant.

Concluding Remarks

In this article, we have explored a wide range of topics related to the interaction of human milk, the preterm gastrointestinal system and diseases affecting preterm infants. Of particular importance in this discussion is the evidence supporting the ability of human milk to decrease the risk of many life-threatening morbidities in preterm infants, including necrotizing enterocolitis. As we look to improve practice we must make every effort, from the first day of life, to provide human milk to hospitalized infants.

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Decreasing Ventilator Associated Pneumonia in the Neonatal Intensive Care Unit

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Introduction

Breast milk is the undisputed gold standard for the provision of not only infant nutrition, but also immunological protection. The policy statement from the American Academy of Pediatrics refers to the provision of breast milk as a matter of public health (American Academy of Pediatrics, 2011). Health benefits such as reduced rates of infections including otitis media, upper and lower respiratory infections, gastroenteritis, as well as sepsis and necrotizing enterocolitis have long been reported. As research continues with regards to the immunological properties of breast milk, and especially colostrum, the inclusion of cytokines, secretory immunoglobulin A, and pancreatic secretory trypsin inhibitor (PSTI) have been found to exhibit protective measures on both gastric and oral mucosa (Spatz, & Edwards, 2009). In light of the foregoing, our facility was very committed to providing fresh, never frozen, breast milk to the infants in our Neonatal Intensive Care Unit (NICU) for their first feedings and for the provision of oral care to our babies to aid in the prevention of Ventilator Associated Pneumonia. Our NICU did not have enough breast milk from our pumping moms to provide both so the quest to solve our problem began.

Protecting the Vulnerable

The provision of passive immunity and immunological protection via expressed mother's colostrum is a comprehensive approach to tackling the issue of nosocomial infections in the neonatal population. Extremely low birth weight infants as well as critically ill, ventilated babies, are at risk for developing a multitude of illnesses during their stay in the neonatal intensive care unit.

The Protective Qualities of Colostrum

Colostrum, mother's first milk, provides many beneficial immunological protectors. Secretory IgA, along with other immunoglobulins and cytokines, protect the infant against infectious organisms. PSTI has been shown to have protective qualities on the gastric mucosa. These immune components have been shown to be protective during the first week of life, an especially vulnerable period of time (Araujo, Goncalves, Cornetta, Cunha, Cardoso, Morais, & Giraldo, 2005) (Rodriguez, Meier, Groer, & Zeller, 2009). Furthermore, studies have shown that the concentration of these protective factors, including Secretory IgA, is higher in expressed colostrum during the first week following premature delivery (Araujo et al, 2005) (Dvorak, Fituch, Williams, Hurst, & Schanler, 2003) (Koenig, de Albuquerque Diniz, Barbosa, & Vaz, 2005). The composition of colostrum changes after the sixth day of lactation. Concentrations of immunological components are reduced, while the milk begins to take on a more nutritional focus with its increase in fats and lactose. Once mature milk is established, a blend of nutrients and immunological factors will be noted (Araujo et al, 2005). These changes coupled with the knowledge of the effects of the constituents of early colostrum, point to the need for the provision of colostrum to the smallest and sickest babies.

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Oropharyngeal Administration of Colostrum

Extremely low birth weight and critically ill infants are most often unable to tolerate oral feedings. Through the collective work of many authors, the administration of colostrum via the oropharyngeal route has been suggested as an effective method of providing this life saving milk (Rodriguez, Meier, Groer, & Zeller, 2009) (Rodriguez, Meier, Groer, Zeller, Engstrom, & Fogg, 2010). Cytokines in colostrum stimulate the oropharyngeal-associated lymphoid tissue (OFALT) and gut-associated lymphoid tissue (GALT) which protect the respiratory and gastrointestinal tracts from infectious pathogens (Rodriguez, et al, 2009). This process potentially activates an immunostimulatory cascade protecting against hospital acquired infections including necrotizing enterocolitis and pneumonia.

The Importance of First Feedings of Colostrum and Expressed Breast Milk

Recent research points to the importance of feeding expressed breast milk and especially colostrum as the first feeding to ill babies, especially premature infants. The World Health Organization stresses the importance of colostrum as the first feeding (World Health Organization, 2009). Critical periods in neonatal development have been identified. These times are short, but the provision of human milk is essential in ensuring quality outcomes while reducing catastrophic problems such as necrotizing enterocolitis and other inflammatory-based disease processes such as Chronic Lung Disease (CLD) and retinopathy of prematurity (ROP) (Meier, Engstrom, Patel, Jegier & Bruns, 2010). These health issues can be devastating to the future health of the infant as well as the bottom line of the hospital budget. The provision of early breast milk to the sick and premature infant becomes not only a health benefit and moral obligation, but also a cost saving measure for the present and future care of such infants.

Critical Periods of Exposure to Breast Milk for Premature Infants

Critical periods of exclusive breast milk feedings or as close to exclusive as possible are thought to potentially result in better overall health outcomes for at risk babies than for those babies who received partial feedings throughout their NICU stay. Critical periods of human milk exposure include (Meier, et al, 2010):

Colostrum provision during the transition from intrauterine to extrauterine life
- Stimulates rapid growth of the intestinal mucosa
- Induces digestive enzyme production
- "Replaces" the absence of amniotic fluid swallowing that would have occurred in the intrauterine environment but is absent in premature infants

Early enteral feedings/first feeding exposure
- Exposure to the changing early milk to mature milk causes gastrointestinal changes
- Increased feeding tolerance is noted in premature infants
- Reduces morbidities such as NEC, CLD, and ROP
- Even small amounts of formula during this important stage can alter the colonization process and leave a baby vulnerable

Human milk during the NICU stay
- Earlier discharge was noted among infants who received exclusive own mother's milk
- Lower rates of NEC, CLD, ROP

The Needs of a Unit

Considering all of the research and best practice information available, the need to obtain and provide a mother's own colostrum and breast milk was not only our desire, but a necessity for all of the premature and sick babies in our NICU. We were providing expressed breast milk, but the infants did not have enough available to provide for oral care as well as first feedings and exclusive provision of breast milk to our babies. Pumping education and support were available as well as NICU Lactation Consultants, but babies were still acquiring VAP. The amount of milk necessary to provide needed care and administration was not being met. We needed a solution.

New Pump Technology

We looked to the research conducted by Dr Paula Meier et al at the Rush University Medical Center in Chicago, IL. There is much knowledge surrounding the issue of increasing breast feeding rates and the provision of breast milk through staff education and evidence-based competency and policy development. Our unit had begun a breast feeding/breast milk awareness education campaign in 2008. This campaign, coupled with VAP education and oral care bundles, allowed us to make strides in decreasing our VAP rates. Our unit had not collected VAP rates prior to 2009 but we had two cases in 2009 and two cases in 2010. Our staff and neonatologists were struggling with simultaneously providing breast milk for feedings and oral care. There simply was not enough milk available for the majority of our patients. Education and understanding was evident but we just didn't have the supply we needed.

Dr Meier published work in 2010 surrounding new breast pump suction patterns used in the Medela Symphony pump. Through blinded randomized clinical trials, Dr Meier's research demonstrated that a new pump with breast pump suction patterns that mimic the patterns of newborns during the initiation of lactation were effective in obtaining more milk output (Meier, Engstrom, Janes, Jegier & Loera, 2010).

The Symphony Pump trials sought to discover whether a different pattern of sucking, one mimicking the rapid suck rate followed by an irregular rhythm caused by the small amounts of milk available after delivery, would yield more milk in mothers who were separated from their babies and were reliant upon a pump for the initiation of lactogenesis II (Meier, et al, 2010).

Daily milk output was measured for volume. Daily outputs of over 350 ml were counted as sufficient to attain full and exclusive breastfeeding for premature infants and 500 ml per day for term babies. One hundred and two mothers from a sample group of 105 were able to achieve the minimum 350 ml/day volume needed to produce enough milk throughout the breastfeeding needs of an infant. This new pump was proven to have success at extracting the amount of milk needed by a growing preemie and provide a sustained output of milk that would grow with the needs of the baby. Mothers were comfortable and the pump was felt to be convenient (Meier, et al, 2010).This research was suggestive of increased success and milk availability as well as sustained milk output, so our neonatal team decided to implement the pump.

Implementation of a New Strategy, Changing the Culture

It took the concentrated efforts of our Lactation Consultants and NICU Leadership team to provide the evidence supporting the purchase of new pumps. The potential increased milk volumes, reduction in infections and complications, as well as cost savings associated with these benefits proved enough to suggest a return on investment worthy of action.

We implemented an education plan to establish competencies on pump use and maternal education, utilizing our Lactation Consultants, NICU Leadership, Baby Friendly Committee Members, and NICU staff within our Advanced Clinical Ladder. Previously, our truly engaged and competent nurses and NICU staff who assisted with pump instruction and guidance included a handful of educated and interested staff. Now that we had our Symphony pumps and a dedication to increasing the efficiency of our mother's efforts, we wanted to improve the quality of support offered to our families. By using a team approach to changing the culture of our unit, we were able to build an arsenal of staff that started the education and support but also started the change process by becoming champions for the cause.

Our current policies and procedures were reviewed and changes made to include use of the Symphony pumps and ensure consistency throughout our mother/baby units. VAP bundles including oral care with fresh breast milk were created and staff educated. Education was a key element in the success of our program; the new changes, polices, and bundles needed to be conveyed and buy in secured. Nurses, therapists, and staff needed to understand the science behind the pump, the diligence needed to encourage mothers and support pumping. NICU staff needed to understand why the provision of breast milk was so very important and key to improving the outcomes of our vulnerable infants.

Our conversion to the Medela Symphony Premie+ pumps occurred in August of 2010. The conversion was easy once the commitment had been made. With a variety of educational venues and methods including individual initial education and hands on practice, attendance at group education in a competency fair setting, hands on demonstration by each staff member on setting up the pump, and rounding by our champions, our message, that oral care with breast milk was the gold standard in preventing VAP and a necessary component in quality care, reached the staff and the new pumping was successful. Nurses and NICU staff saw increased milk volumes which now allowed for enteral feedings and oral care.

Outcomes Improved!

Maternal and staff satisfaction followed the conversion to our new pumps. Our Lactation Consultants and bedside staff were motivated to continue assisting mothers with their pumping success. VAP bundles including oral care with fresh colostrum and breast milk were adopted by the majority of the staff. Prior to the use of these pumps, staff were inconsistent in their approach to oral care. Our respiratory staff reported that each nurse had his or her own way of suctioning, providing oral care, and caring for the infants. We know had a policy and the necessary education regarding the importance to provide rationale and reasoning. Many of our nurses reported needing the rationale to inspire them to provide the cares. The respiratory therapists were especially helpful and diligent with providing this oral care and assisting parents to help with cares. Mothers were busy pumping with great success while fathers were bringing valuable bottles of colostrum and milk to the bedside. While our data collection on the actual percentage of increased milk volume is not completed at this time, the change was visibly evident. Numerous bottles of fresh milk were now present necessitating the purchase of a new breast milk refrigerator! A new policy was created to guide staff in labeling and storing fresh milk for the use in oral care. Many bottles of fresh, never frozen milk lined our refrigerator shelves and bottles of milk were frozen in the freezer, ensuring that our tiny babies would have all of the immunity providing milk they needed.

Our unit reported zero VAP cases from the start of our program; previously we had sporadic VAP cases over the year. Staff noted that the oral care with fresh milk was having a positive and visible effect. While we did not have a formal tracking instrument, our breast milk champions and leadership were approached on a daily basis with satisfactory reports of decreased oral secretions, film, and deposits. Babies were tolerating the procedure, families were assisting with cares, and staff members were happy with the instant, noted change. Our previous success with initial pumping was high but we had many mothers who needed supplementation with galactogogues such as Metaclopramide. Following our intense education and Symphony pump implementation, our mothers requiring such help fell from approximately 12% of new mothers to only 4%! We noted this change two months after the implementation of our new stragtegies! There was now enough breast milk for all of the needs of our precious babies.

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New Findings in the Science of Neurodevelopment, Cognition and Human Milk

Jean Rhodes, PhD, CNM, IBCLC

Introduction

Despite improvements in neonatal and perinatal medicine, infants born prematurely have a significantly higher risk of neurological disabilities when compared to infants born at term. According to a 2002 Agency for Healthcare Research and Quality report, half of all extremely low birth weight (ELBW) infants will have a least one significant neurodevelopmental impairment.[1] As with many neonatal outcomes, these risks are inversely proportional to the infant's birth weight and gestational age at birth: the smaller and more preterm the infant, the greater the risk.[1-4]

While effects of early infant nutrition may be subtle, with results not apparent for months or years, studies suggest early nutrition has the potential to influence cognition, behavior and educational performance.[3,5-13] Human milk contains a multitude of physiologically active factors, including essential fatty acids and their derivatives docosahexanoic acid (DHA) and arachidonic acid (AA). These fatty acids are recognized as critical elements in development of healthy cells and tissues in the human nervous system, cardiovascular system and eyes.[7,14-30] Other components of human milk such as growth factors, antioxidants, hormones, anti-infective/anti-inflammatory factors and cholesterol are also involved in healthy human neurological development.[10,12,13,19,31,32] In this article, we will explore some of the recent evidence related to the benefits of human milk in the neurological and cognitive development of infants, particularly preterm infants.

Studies of Cognitive and Neurological Development and Human Milk Feedings

Cognitive and behavioral benefits of human milk have been a subject of inquiry for many years. As early as 1929, Heofer and Hardy[33] evaluated the effects of infant feeding type and duration on physical and mental developmental differences in Chicago school children. Study methods and analyses differed from those seen today; however, results supported the benefits of 4-9 months of exclusive breastfeeding over infant formula feeds.

Researchers of lactation and human neurodevelopment are challenged by a number of methodological issues that influence outcomes, particularly those that influence intelligence measures. Therefore, results are not always consistent.[5,8,34-38]

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However, recent reports continue to add to the body of evidence that human milk improves mental capacity. In 2011 a study by Jedrychowski *et al*[8] reported IQ scores of children born >36 weeks increased with duration of exclusive breastfeeding when compared to partially breastfed children. This study followed subjects for seven years after birth. Intelligence measure gains – in the range of 2-3.8 IQ points, depending on the length of exclusive breastfeeding – were small but statistically significant.

In another study published in 2011, Quigley *et al*[10] evaluated the relationship of breastfeeding and human milk feeding on cognitive development in both term and preterm infants. In total, 11,879 infants were recruited and followed for five years. The authors adjusted for multiple confounders; beyond the standard confounders such as maternal age, education, socioeconomic status, infant gestational age and birth weight, the analysis adjusted for parents' parenting beliefs and the child's exposure to early learning opportunities.

Their findings suggested longer durations of breastfeeding/human milk feeding had positive effects on cognitive development, particularly in children born preterm. For example, in children born at term, the authors found a 1-2 point difference on three subtests of the British Ability Scales (Second edition) between children who were breastfed for 4-6 months and those who were never breastfed. Children born preterm who were breastfed or received breastmilk for at least 2 months had even greater improvements, with 4-6 point increases, when compared to children who did not receive mother's milk.

This very large study contributes significant weight to the argument that breastfeeding and human milk feeds contribute positively to infant intelligence and cognitive development. Like most studies, maternal IQ – an important variable in predicting a child's intelligence[35,39] – was not measured directly but inferred from maternal education and socioeconomic status. Unlike many previous reports, this study controlled for selected aspects of the home environment including parenting beliefs and the child's exposure to educational opportunities. Comparison of outcomes by gestational age at birth suggests greater cognitive effects of human milk feeds in infants born preterm.

Studies Specific to Preterm Infants

Two studies by Vohr and associates – published in 2006 and 2007[12,13] – followed extremely low birth weight infants until approximately 18 and 30 months corrected age. The authors' objective was to evaluate longitudinally the physical, developmental, neurological, cognitive and behavioral effects (as measured by Bayley Scales of Infant Development) of breastmilk ingested in the NICU. Data were collected on multiple confounding variables including but not limited to socioeconomic status, maternal age, education, marital status, race/ethnicity, infant gestation, gender, and neonatal complications.

In these studies, children who received breastmilk during the NICU stay had better Bayley Scale outcomes at 18 and 30 months than children who were formula fed. Furthermore, after adjusting for confounding variables, analyses indicated that for every 10 mL/kg/day increase of breastmilk, infants demonstrated incremental improvements in Bayley subscale percentile scores and rehospitalization rates. Overall, any breastmilk volumes were better than none with cognitive results sustained if not improved between 18 and 30 months of age.

Previous studies, like those we have just examined, have associated breastfeeding with positive child cognitive development. Other research has suggested cognitive scores in preterm infants might be related to anatomical factors such as head circumference and brain size.[40] A 2010 study by Isaacs and colleagues[32] took the question a step further by examining the relationship between early human milk feeding, measures of intelligence, and brain growth and brain volume in preterm infants. The subjects in this study were part of a larger project conducted many years prior. From 1982-1985, Lucas and colleagues studied 502 NICU preterm infants over the first 30 days of life. All breastmilk feedings were documented then converted into percentages of infants' total feeding intake. Their results showed a dose-response benefit from human milk feeding on infant cognitive development at nine months,[41] 18 months,[42] and 7-8 years of age.[38]

In 2010, Isaacs and associates published a follow up study with 50 from the original 502 infant cohort, now in their adolescent years. All subjects were born at or less than 30 weeks gestation, were previously determined to be neurologically normal, and received primarily expressed mothers' breast milk in the first month of life with some variation as to type of supplement. The authors assessed cognitive and neurological development with Wechsler intelligence scales and brain MRI studies. MRI analysis included total brain volume as well as white matter and grey matter volumes.

Isaacs *et al* found subject mean IQ scores were close to the population average of 100 with no significant difference between girls and boys. However, boys – but not girls – showed a significant proportional relationship between percent expressed breastmilk and IQ scores. The higher the percent of expressed breastmilk, the higher the IQ scores. In addition, total white matter in boys increased with higher percentages of human milk feedings. The authors concluded that, "In all subjects, but most clearly in boys, the effects of breast milk were seen more strongly on white than grey matter in the brain. These data support the hypothesis that one or more constituents of mothers' breast milk promote brain development at a structural level." (p.6)[32]

Components of Human Milk that May Contribute to Improved Cognitive and Neurological Outcomes

Human milk contains a variety of medium and long chain fatty acids, including two essential fatty acids – linoleic acid (LA) and α linolenic acid (ALA) – the human body can't synthesize and must, therefore, get from dietary sources. Linoleic acid is the precursor for the omega 6 polyunsaturated fatty acids; α linolenic acid is the precursor for omega 3 polyunsaturated fatty acids.[43] Of the many fatty acids in human milk, arachidonic acid (AA) from linoleic acid and docosahexanoic acid (DHA) from α linolenic acid are the LCPUFAs most associated with brain, eye and cardiovascular development.[9,14,16-22,24,26,28-30,44-49]

During fetal development, the last 20 weeks of gestation is a critical period of human brain growth and development. Linear growth in brain weight follows a steep slope: approximately half of the brain's volume is obtained in the last 6 weeks of a 40-week gestation. Changes during this time period are dramatic. For example, at 26 weeks gestation the brain will weigh 30% of its expected weight at 40 weeks; at 34 weeks it will weigh 65% of term weight.[50]

Brain growth is concomitant with neurological structural maturation and organization. During the fetal period and extending into infancy, neurogenesis, synaptogenesis, dendritic arborization and neuronal connectivity occur as axons elongate to form the cerebral cortex.[24,50] Of interest to the discussion at hand, 60% of infant brain is lipid, mostly membrane lipid, which requires arachidonic acid (AA) and docosahexanoic acid (DHA) for growth and development.[14,17]

DHA and AA are integral components of brain and nervous system cell membranes. They are also abundant in retinal, endothelial and vascular cells.[19,21,23,24,28,29] During pregnancy, the placenta supplies LCPUFAs to the growing fetus, but after birth, the infant is dependent on exogenous nutritional sources for continued supplies. Preterm infants by nature of their interrupted gestation have the greatest need for LCPUFAs. As we have discussed, human milk is a natural source rich in DHA and AA and their precursors, the essential fatty acids. However, bovine milk has very few LCPUFA[43] and studies of the efficacy of infant formulas with added synthetically manufactured PUFAs are inconclusive at this time.[14,26,51-55]

By virtue of their unsaturated status, long chain polyunsaturated fatty acids are susceptible to oxidative degradation and the formation of eicosanoids associated with a cascade of inflammatory and immune responses. Antioxidants in human milk can suppress degradation of LCPUFAs and reduce inflammation associated with eicosanoids.[19] DHA also down-regulates inflammation associated with serious diseases in preterm infants such as necrotizing enterocolitis and bronchopulmonary dysplasia.[19] These components may work in concert with other anti-inflammatory agents in human milk – for example, interleukin-10 (an anti-inflammatory cytokine), lactoferrin, and epidermal growth factor – to reduce destructive up-regulated inflammatory immune responses in preterm infants.[56-58]

Vohr and colleagues,[12,13] Quigley *et al*[10] and Isaacs and associates[32] identified several components of human milk that may be involved in neurological and cognitive development, including LCPUFAs, growth factors and hormones. Of these, LCPUFAs are most often associated with infant central nervous system development. In addition, Isaacs *et al* also suggested the presence of cholesterol in human milk might contribute to brain development and intelligence. Dietary cholesterol is an important component in the development of myelin membranes and glial cells, both constituents of brain white matter.

Like DHA, cholesterol is an essential structural component of cell membranes in mammals. It is also the precursor of steroid hormones.[59] In human studies, plasma cholesterol levels have been shown to progressively increase in breastfeeding infants and are higher than cholesterol levels in formula-fed infants.[60] Therefore, in addition to brain cell development, there is speculation dietary cholesterol from human milk may program a more healthy cholesterol synthesis later in life.[61]

These findings lend support to the notion that breastmilk promotes brain development and that the mechanisms for this effect are probably related to the interactions between multiple human milk components – DHA, LCPUFAs, growth factors, hormones, cholesterol and others – with neural cell growth and development. Interestingly, at a fundamental level there seem to be differences in the neurocognitive development of preterm children determined by gender. As we noted in the results by Isaacs *et al*, girls and boys have different average brain volumes, different proportions of white and grey matter and different neurodevelopmental responses to human milk feedings.

Concluding Remarks

The science of human neurodevelopment, cognition, infant nutrition and gender intersected in this discussion of the use of human milk for preterm infants. Several recent studies demonstrate neurocognitive benefits of human milk feeds in the NICU for preterm infants and to a lesser extent, advantages for breastfeed term infants. These benefits increase as doses of human milk increase.

Of special interest in this discussion are the roles of LCPUFAs (especially DHA) and cholesterol in human milk. These substances, naturally abundant in breastmilk but not infant formula, are critical to the development of a functional central nervous system and along with other breastmilk components may be involved in suppressing inflammatory processes in vulnerable infants.

It would seem that the neurodevelopmental building blocks provided by human milk work to increase brain volume and thus may allow for increases in IQ and other neurodevelopmental outcomes so elegantly shown by Vohr and colleagues, Quigley and coworkers and many others before them. Thus the studies outlined in this article add to the growing body of evidence to support the use of human milk for preterm infants and begin to provide insights as to how these benefits are conferred to the infant.

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