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Introduction

When a human infant is born prematurely, they are unable to receive the adequate nutrient and mineral requirements from parenteral or enteral sources that would have been provided to them in most intrauterine states. Preterm infants have low birth weights as the majority of fetal weight gain occurs in the third trimester. Term infants can also be growth restricted at birth for reasons pertaining to placental challenges such as pregnancy induced hypertension, arterial venous anastomosis as in to twin transfusion syndrome, or when severe maternal malnutrition exist. While not necessarily preterm, the products of these gestations will need similar nutritional supplementation for growth and healthy neurodevelopment as the preterm infant. The goal of many neonatal advanced practice nurse providers is to maintain growth rates similar to the uterine environment and often times in the face of critical illnesses or challenges. When adequate nutrition is not administered, extra-uterine growth restriction occurs. Growth restriction has been directly correlated to the decreased structure and function of the central nervous system, specifically when the restriction is during critical periods development such as the neonate period. The central nervous system deficits are irreversible (Ziegler, 2011). Growth goals that have been established for the preterm neonatal period is a weight gain of 15 g/kg/day, occipital frontal circumference growth of 0.5cm/week and length increases of 1 cm/week (Georgieff, 2005). The ability for a preterm infant to grow and have similar organ development at intrauterine rates requires they receive increased amounts of protein, fat, and minerals when compared to newborn term infants. To establish these goals, daily protein intake should be 3.4-4.2gm/kg/day and caloric intake of 110-135kcal/kg/day, with the degree of prematurity directly indicating nutritional needs on the higher side (Arslanoglu, Moro, & Ziegler, 2010). In addition to monitoring weekly measurements of preterm infants, serum lab work can be

useful as indicators for growth and used to guide fortification of feedings. Serum sodium, chloride, calcium and phosphorus requirements are necessary to monitor as the premature infant will quickly develop defects following umbilical cord clamping exacerbated by their immature kidney functioning. Trends in prealbumin, BUNs, and alkaline phosphate levels are also used as indicators of protein status and markers of bone health respectively. Extra-uterine growth restriction has a direct correlation to neurodevelopment challenges and is therefore an area of importance to providers caring for these vulnerable infants. Excluding parenteral nutrition, the ways in which neonatal care units provide growth restricted infants these requirements are by enteral administration via a naso/orogastric tube of own mother's breast milk (OMM), donor breast milk (DBM), and preterm formulas (PF).

Human Milk

The literature supports improved neurodevelopment, cardiovascular health, and decreased risks of cancer and other infectious incidences when infants are breastfed or provided OMM (Gomella, 2009 and Arslanoglu, 2010). The properties of human milk (HM) that make it superior for immunologic protection and developmental benefits include live cells, enzymes, and immune factors (Georgieff, 2005). In addition to immunologic properties, HM is higher in fat than PF, a benefit for premature infants, but low in protein and sodium which are both essential for the somatic growth of premature infants. Pumped HM is also considered an inexpensive option for families and health care systems.

OMM produced from mothers of preterm infants and term infants differs in its nutritional qualities. The mother of an infant delivered preterm produces milk that has a higher content of protein, chloride and sodium for the first 1-2 weeks, up to the first month postpartum. This richer

preterm HM is a natural fortification for the underdeveloped neonate (Zeigler, 2011 & Gross, David, Bauman, & Tomarelli, 1980).

Donor milk

Multiple sources state the majority of breast milk donated to milk banks is from mothers of term infants (Lindemann, Foshauge, & Lindemann 2004); therefore, the widely accepted assumption is the protein content is not adequate to sustain or grow a preterm infant as it is from term mothers. While OMM has a variable amount of protein content regardless of the mother's gestiation, DM is "less variable, but lower in protein content" than any OMM (Zeigler, 2011). In addition to the differences of preterm milk and term milk, protein content also decreases throughout the course of lactation (Arslanoglu, Moro, & Ziegler, 2010), therefore donors who's own infants are now four or five months old will produce a less nutrient rich milk. DM also undergoes a process OMM does not which is a pasteurization process, most often Holder pasteurization. Holder pasteurization is the heating of milk to 62.5 degrees Celsius for 30 minutes. DM is then cultured and frozen to -20 degrees Celsius before being dispensed (Human Milk Banking of North America, 2011). Human milk oligosaccharides and long-chained polyunsaturated fatty acids are two immune factors that are maintained in DM throughout Holder Pasteurization process (Bertino et al., 2008). Human milk oligosaccharides work with the immune system and are responsible for prebiotic functioning and protection of intestinal infections and long-chained polyunsaturated fatty acids assist with immunological protection of the gastrointestinal track (Arslanoglu, Ziegler, & Moro, 2010). While these factors are maintained, fractions of many immunologic factors such as sIgA, IgA, lactoferrin, lysozyme, lymphocyte, lipase, and alkaline phosphatase are lost in the intense heating process. While not

utilized as frequently and less studied, a shorter pasteurization process exists which is heating to 72 degrees Celsius five times, each time for 15 seconds (Heiman & Schanler, 2006).

Processes are in place and regulated in an attempt to ensure the safety of DM. Donors of milk are routinely tested for cytomegalovirus, HIV, and Hepatitis B and C before donating and throughout the process to confer safety for the already immuno-suppressed preterm infant who will receive the DM. The possibility for viral transmission exists even if the donor serum is negative at the time of donation. Finally, the process of pasteurization presents possible bacterial contamination of DM, therefore all samples are cultured for colonization prior to distribution (Lindemann, Foshaugen, & Lindeman, 2003).

Fortification

All HM, OMM or DM, is inadequate in the amounts of nutrients for the premature infant. Standard practice is to fortify HM with human milk fortifier (HMF) when enteral feedings have been advanced to 100ml/kg/day. HMFs, currently extracted from cow's milk, contain protein, carbohydrates, fats, and essential vitamins and minerals which afford providers the ability to keep volumes of feedings in a range of 150-160ml/kg/day (Zeigler, 2011). Current research is ongoing for the development of an HMF from human milk called Prolacta.

Gut Maturation and Necrotizing Enterocolitis

Preterm infants are not born with mature intestinal tracks, necessitating the need for slow advancements in enteral feedings along with the use of total parenteral nutrition. Throughout the history of neonatology, feedings were withheld and advanced slowly as the risk of necrotizing enterocolitis (NEC) was realized (Zeigler, 2011). NEC is an inflammatory process of the bowel in response to an intolerance of a substrate in the bowel lumen for reasons still unknown to

providers. The bowel wall becomes damaged and, in severe stages, perforates leaking intestinal contents into the peritoneum, a life threatening event. The field of neonatology now agrees the way to mature the gut, increase motility, and promote microbial properties is to provide small amounts of HM, OMM or DM consistently for the first few days to a week to prime the intestinal track. These small feedings, called trophic feedings, are not utilized by the baby as essential nutrition and parenteral nutrition continues to be utilized for administration of protein, fats, and essential minerals. The immunologic properties of fresh OMM are absorbed by the infant's mucosal track which is called passive immunity, something pasteurized milk is less able to do secondary to decreased amounts of IgA. Benefits of trophic feedings with OMM are two-fold, intestinal maturity and immunologic protection.

DM is widely used by neonatal care units when OMM is unavailable and before PF is considered as the risk of NEC is higher for premature infants receiving PF. Infant receiving DM who are born on the edge of viability will receive DM for up to 6-8 weeks before they are switched to PF around 32 to 34 weeks postmenstral age. This makes them vulnerable to the negative neurodevelopment effects of extra-uterine growth restriction. The increasing usage of DM necessitates an in-depth understanding regarding the benefits and consequences of its use. A literature search on the subject of DM for optimal growth of preterm infants was surprising as *current* research on the topic was limited. This lack of substantiated evidence in the literature suggests the side effects of DM many not be fully realized by providers and necessitates the need for further studies.

Literature Review

In a randomized control trial published in 2005, Schanler et al. compared infants under 30 weeks gestation receiving exclusively OMM and infants who were supplemented with DBM or PF when OMM was not available. A wide variety of short term outcome data were analyzed including length of stay (LOS), infectious rates, including NEC, growth rates, and rates of skin to skin contact between the mother and infant. To clarify, all subjects received some amount of OMM, which was a limitation of this study because it is not clear how much OMM the subjects received before being supplemented. The results could be confounded as the protective benefits of OMM hid some outcome effects of the supplementation; however, the authors do point out the amount of OMM received was not statistically different between the DM and PF groups. When the control group, exclusive OMM, was compared to the DM and PF groups, infection rates were improved, including decreased incidences of NEC, fewer gram negative cultures, shorter LOS, and less severe staging of ROP rates, supporting common opinion that OMM is best for premature infants. Another important factor the authors point out is the similar characteristics of the subjects' mothers who provided enough OMM. They were older, had a higher SES, and visited their infant more, perhaps a confounding variable of the health of their infant regardless of the supplementation use for enteral feedings. When DM was compared to PF there were no differences in outcomes of NEC, LOS, or death. Slower weight gain was noted in the DM group. This difference was so drastic, the principle investigator along with the attending neonatologists switched 17 infants from the DM group to the PF before the end of the study. No difference in OFC occurred throughout the three groups, however both DM and PF groups lagged behind OMM group for length. It was also noticed that DM group needed higher sodium supplementations and both the DM and PF groups needed higher oil or protein supplements

when compared to the control OMM group. In the study design, the authors point out Enfamil Human Milk Fortifier and Similac Human Milk fortifiers (likely the hospital contract changed mid-study) are added to the OMM and the DM when the infants reached 100ml/kg/day of feeding volume. The PF used was Enfamil Premature Formula, also specialized for premature requirements. The DM was pumped from mothers of premature infants. This is an interesting difference as most studies on DM do not specify the characteristics of the mother donating. Some milk banks do keep DM pumped from mothers of preterm infants separate and sell it to hospitals as preterm DM. This only seems to legitimize the results of this study further. Perhaps making this a more thorough study would be inclusion of serum markers of growth between the two groups.

In a prospective observational study of infants born under 32 weeks gestation, researchers compared the growth of infants fed <20% OMM, more than 80% OMM, and those fed 20-80% OMM with the supplementation being DM. Standard fortification was used for both OMM and DM when feedings reached 100ml/kg/day. Using statistical significance values of $p < 0.05$, results indicated a mean weight gain of 5.1g/kg/day lower for infants fed less than 20% OMM. Infants receiving 20-80% OMM had growth rates of 4.8g/kg/day lower and those fed >80% OMM reached growth rates similar to intrauterine amounts of 15gm/kg/day. While this was a small, single hospital study, without randomization and minimal controls, it does show results consistent with other studies. The conclusion was properties of DM were insufficient to grow premature infants at intrauterine rates (Montjauz-Régis, Cristini, Glorieux, Vanpee, and Casper, 2010).

A meta-analysis of seven studies, five of which were randomized control trials, were reviewed to compare the use of OMM, pasteurized DM, and PF for outcomes of death, NEC,

infection and growth for premature and growth restricted infants. True meta-analysis was not possible as the outcome variables for growth were not standardized across the studies. For the trials evaluating growth, it was concluded that there was a tendency for improved early postnatal weight gain, increased OFCs, and skin fold thickness, but no gains in length for those fed formula. Three of the studies evaluated the risk of NEC and concluded presumed cases of NEC were not statistically significant; yet, confirmed rates of NEC were statistically lower for subjects fed DM compared to PF. A combined risk difference of the 3 studies was determined to be 5.4%, meaning 18.5 premature infants would need to be given donor milk instead of formula to prevent one case of NEC. While this is a recent review, the studies were published in the 1970s and 1980s which is problematic as the field of knowledge for nutrition in neonatology has improved since that time. The studies that evaluated DM did not include DM that was fortified with HMF, a practice now standard. Thus interpretation of results must be done carefully when comparing unfortified DM to PF. Another important factor to consider is the variable outcome criteria for the studies used, making analysis difficult (Boyd, Quigley, & Brocklehurst, 2007).

A Cochrane database review compared DM to PF to evaluate growth of premature infants and low birth weight infants, born less than 37 weeks gestation and weighing less than 2.5kg at birth respectively. Studies included eight randomized controlled trials, including Schanler, et al. from 2005 as outlined previously in this paper. Schanler et al. remains the only study to date comparing fortified DM to formula, the others use unfortified DM. Schanler et al. is also the only study within the last decade, all others included in this analysis were from the 1970 and 1980s. This meta-analysis concluded short term growth rates were higher for those fed formula verses DM. Long term outcome data was analyzed and failed to show a difference in growth

rates or neurodevelopment outcome. This analysis indicated the incidence of NEC is statistically increased in those fed formula over DM (Quigley, Henderson, Anthony, & McGuire, 2008).

Implications

The trials frequently cited in the literature, excluding one, are considered dated material in modern neonatology, specifically with the changes in nutrient goals for premature infants. Proponents of DM may argue that growth rates and development will not matter if the infant suffers mortality secondary to NEC and therefore argue that OMM and DM are the only suitable options for premature infants. However, as stated in the meta-analysis by Boyd and colleagues, 18.5 infants will need to receive DM to save one from death due to NEC. This risk-benefit can be a difficult for providers to weigh. Rather, the practice should perhaps be to give all infants OMM or DM through the first 14 days of life or first 14 days of feedings, when NEC is most likely to occur and then switch to PF to focus energies on growth and development of the infant. This increases the number of infants exposed to DM, something some parents may not feel comfortable with and choose to withhold consent. Again, these conclusions are based on studies that, for the most part, are decades old. It is clear more randomized control trials need to take place before widespread recommendations are given. Currently, multiple neonatal intensive care units are shifting towards increased usage and longer duration of DM feedings when OMM is not available. In addition to the increased cost on the already stressed healthcare system, it is puzzling since the literature review suggests it may not be the liquid silver (OMM being the liquid gold) some believe it to be. Other options for the continued use of DM for this population would be to target fortification individually; meaning all milk is tested for its protein, fat and energy content and fortification is specialized to the individual neonate. Currently, serum markers of protein status such as BUN, albumin and prealbumin are evaluated and a standard

assumption of the qualities of DM is used. Again, this is a labor intensive activity and likely a further expense on an already taxed system. If perfection remains what providers strive for, this is the next modification.

Feeding low birth weight premature infants is a challenging task for the neonatal nurse practitioners responsible for guiding the care of such infants. Forming a partnership with parents is vital for open communication and education surrounding this topic. Honest communication with families regarding feedings and the possible morbidities that threaten preterm infants is essential. Advance practice nurses have the potential to encourage and support maternal pumping of milk. Some situations can preclude the amount of OMM available, regardless of maternal intent to provide, including maternal illness, medications, or breast tissue damage and must be approached with support, sensitivity and care and without judgment. This is a challenging task, but one neonatal nurse practitioners are capable of. It is essential all families are given all the information regarding feeding their premature infants so they are able to make informed decisions as partners in the care of their infants.

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