Cell Reports Medicine

CellPress
OPEN ACCESS

Preview

More evidence: Mothers' own milk is personalized medicine for very low birthweight infants

Paula P. Meier[1,*]
[1]Rush University Medical Center, Chicago, IL, 60612, USA
*Correspondence: paula_meier@rush.edu
https://doi.org/10.1016/j.xcrm.2022.100710

"Human milk sources and fortification: Impact on fecal microbiota and calprotectin in premature infants" highlights improved outcomes in predominantly mothers' own milk-fed versus predominantly pasteurized donor human milk-fed VLBW infants, regardless of fortifier type. Research and practice implications are reviewed.

"Human milk sources and fortification: Impact on fecal microbiota and calprotectin in premature infants" adds to recent studies comparing health outcomes in exclusively human milk-fed (EHM; no commercial formula) very low birthweight (VLBW; <1,500 g birthweight) infants as a function of proportions of mothers' own milk (MOM) and pasteurized donor human milk (PDHM) received during the neonatal intensive care unit (NICU) hospitalization. Kumbhare et al. randomized EHM-fed VLBW infants to receive either human- or bovine-derived fortifier and compared gut microbial colonization, gut inflammation, and oxidative stress at four post-birth time points. Findings revealed that the *type* of human milk (MOM versus PDHM) was more important than type of fortifier in shaping gut microbiota and minimizing gut inflammation.[1]

The finding that high MOM intake was associated with significantly better outcomes joins two recent observational cohort studies of EHM-fed VLBW infants,[2,3] which compared health outcomes for predominantly MOM-fed versus predominantly PDHM-fed infants. Taken together, the three studies found that predominantly MOM-fed infants had better clinical outcomes,[1,3] healthier microbiome colonization[1,2,3] including potential modulation of the negative impact of antibiotic exposure,[1,3] and improved metabolic/metabolomic profiles[2] than primarily PDHM-fed infants. Furthermore, predominantly PDHM-fed infants had slower and/or impaired growth,[1,3] including higher rates of head circumference measures below the third percentile,[3] higher rates of bronchopulmonary dysplasia[3], and altered pyrimidine and steroid pathways.[2] Although these studies were limited by relatively small sample sizes and observational designs, the convergence of findings adds to clinical concerns that high-dose PDHM may be an inadequate long-term supplement for low-dose MOM in VLBW infants. These findings have important implications for future research, clinical quality improvement initiatives, and efforts to prioritize the availability of MOM in the NICU.

Compared with commercial formula, high-dose MOM through to NICU discharge reduces potentially preventable complications of prematurity and their associated costs.[4,5] These complications, which include necrotizing enterocolitis (NEC), late-onset sepsis, bronchopulmonary dysplasia, neurodevelopmental problems, and rehospitalization, predispose VLBW infants to lifelong health and educational problems and increase costs for families, institutions, and society at large.[5] With the exception of NEC reduction, these improved outcomes are unique to MOM but are often inappropriately generalized to PDHM and to the broader category of EHM.[6]

As shown in these studies, EHM feeding can translate into high-dose PDHM with minimal MOM. For example, the Ford et al. study[3] divided a cohort of 125 EHM-fed VLBW infants into two groups based on receipt of <50% or >50% MOM and found a bimodal distribution. The <50% group received an average of 14% MOM during the NICU hospitalization, whereas the >50% group received 91% MOM. Thus, studies of EHM feedings (e.g., inclusion criterion, independent variable, dependent variable) may minimize the beneficial impact of MOM and inflate the effect of PDHM, depending upon the relative proportions of each. Similarly, quality improvement initiatives that benchmark *receipt* of EHM may show high rates of EHM but low rates of MOM, leading NICU care providers to conclude that they are "doing a great job," but PDHM may be the predominant type of EHM feeding. A priority for research and practice is the separate reporting of MOM and PDHM proportions within the EHM metric.

The same human- and bovine-based fortifiers are used for both MOM and PDHM, and they are based on studies of MOM, not PDHM. Slower and/or impaired growth with predominantly PDHM feedings is a well-known outcome in VLBW infants.[6,7] Fortification strategies for PDHM have focused primarily on *super fortification* with exogenous protein because MOM has the lowest protein content among mammals.[6] Although macronutrient content in MOM and PDHM is similar, the mechanisms by which the infant metabolizes and absorbs nutrients are likely different.[6] PDHM involves the reduction and/or eradication of MOM-borne digestive enzymes, MOM microbiota, and alterations in metabolic components and pathways.[1,2,3,6] Additionally, mothers who deliver preterm produce MOM that is higher in multiple bioactive components than PDHM from mothers of term infants, especially during the early weeks post-birth.[6] Many of these *personalized* medicine components target growth and may have a programming effect including growth factors, adipokines, micro RNAs, oligosaccharides, the MOM microbiome, the gut metabolome, and others.[6]

Refaunation of PDHM with MOM is a promising strategy that colonizes PDHM with MOM microbiota,[8] but it is not yet sufficiently tested for widespread clinical use. Given the increased use of PDHM as a supplement to MOM in VLBW infants, prioritization of a PDHM fortifier is a research priority.

Nearly all studies and reviews about PDHM begin with "when MOM is not available," implying that lack of MOM is inevitable in mothers of VLBW infants. However, best practices for the use of MOM in the NICU have been published,[9] and a foundation-funded toolkit to improve the use of MOM in the NICU is available for free download and use by NICU providers and families worldwide.[10] A primary reason for lack of MOM in the NICU is that best practices are often seen as optional and/or unachievable within existing institutional resources because PDHM is seen as an adequate alternative. Acquisition of MOM in the NICU requires an infrastructure that includes NICU-specific provider education such as the PROVIDE toolkit,[10] NICU-specific lactation care,[9] and NICU-specific equipment such as effective, efficient, and comfortable breast pumps.[9] These economic investments in MOM acquisition cost less than the acquisition and feeding of PDHM and/or formula, especially when the cost savings of reduced NICU-based morbidities via high-dose MOM are considered.[5] In low- and middle-income countries, the increasing investment in PDHM infrastructure deserves special consideration because lack of MOM is often due to addressable barriers (e.g., remedial with investment) such as lack of skin-to-skin care, lack of breast pumps, and inadequate MOM storage capabilities. The trade-off in investments for PDHM versus MOM for VLBW infants in the NICU should be data-driven, and the cited papers provide compelling evidence to inform these considerations.

DECLARATION OF INTERESTS

P.P.M. has received research funds from Medela, AG and currently serves as a consultant to Medela, AG and to Ferring Industries.

REFERENCES

1. Kumbhare, S., Jones, W., Fast, S., Bonner, C., Jong, G., Van Domselaar, G., Morag, G., Narvey, M., Azad, M.B., et al. (2022). Human milk source and fortification: impact on fecal microbiota and calprotectin in preterm infants. Cell Reports Medicine.
2. Pineiro-Ramos, J.D., Parra-Llorca, A., Ten-Domenech, I., Gormaz, M., Ramon-Beltran, A., Cernada, M., Quintas, G., Collado, M.C., Kuligowski, J., and Vento, M. (2021). Effect of donor human milk on host-gut microbiota and metabolic interactions in preterm infants. Clin Nutr *40*, 1296–1309. https://doi.org/10.1016/j.clnu.2020.08.013.
3. Ford, S.L., Lohmann, P., Preidis, G.A., Gordon, P.S., O'Donnell, A., Hagan, J., Venkatachalam, A., Balderas, M., Luna, R.A., and Hair, A.B. (2019). Improved feeding tolerance and growth are linked to increased gut microbial community diversity in very-low-birth-weight infants fed mother's own milk compared with donor breast milk. Am. J. Clin. Nutr. *109*, 1088–1097. https://doi.org/10.1093/ajcn/nqz006.
4. Meier, P.P. (2019). Human milk and clinical outcomes in preterm infants. Nestle Nutr Inst Workshop Ser *90*, 163–174. https://doi.org/10.1159/000490304.
5. Johnson, T.J., Patel, A.L., Schoeny, M.E., and Meier, P.P. (2022). Cost savings of mother's own milk for very low birth weight infants in the neonatal intensive care Unit. Pharmacoecon Open *6*, 451–460. https://doi.org/10.1007/s41669-022-00324-8.
6. Meier, P., Patel, A., and Esquerra-Zwiers, A. (2017). Donor human milk Update: evidence, mechanisms, and Priorities for research and practice. J. Pediatr. *180*, 15–21. https://doi.org/10.1016/j.jpeds.2016.09.027.
7. Quigley, M., Embleton, N.D., and McGuire, W. (2018). Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst. Rev. *6*, CD002971.
8. Cacho, N.T., Harrison, N.A., Parker, L.A., Padgett, K.A., Lemas, D.J., Marcial, G.E., Li, N., Carr, L.E., Neu, J., and Lorca, G.L. (2017). Personalization of the microbiota of donor human milk with mother's own milk. Front. Microbiol. *8*, 1470. https://doi.org/10.3389/fmicb.2017.01470.
9. Meier, P.P., Johnson, T.J., Patel, A.L., and Rossman, B. (2017). Evidence-based methods that Promote human milk feeding of preterm infants: an Expert review. Clin. Perinatol. *44*, 1–22. https://doi.org/10.1016/j.clp.2016.11.005.
10. Meier P. (2020). PROVIDE: A Training Compendium on Providing Mothers' Own Milk in NICU Settings.