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ORIGINAL ARTICLE

Nutrition

The impact of donating milk on the health of milk donors and their infants: A systematic review and meta-analysis protocol

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Abstract

Objectives: Breast milk is the recommended nutritional source for newborns and has been associated with decreased morbidity in low-birth-weight and preterm infants. In situations where breast milk is not available, donor breast milk is an alternative. Milk banking is becoming increasingly common worldwide to meet this need. Although the benefits of donor breast milk for the recipient infant are well established, the health impact on the breast milk donor and the infant of the breast milk donor is an area of current research. We aim to synthesize and evaluate the available evidence regarding the impact of donating breast milk on the health, lactation, and well-being of the breast milk donor, and the health and growth of the infant of the breast milk donor.

Methods: We will search electronic databases, grey literature, and the websites of relevant international organizations. We will include studies that involve lactating women and their infants, healthy or with health conditions, who donate breast milk, without restrictions on study date, language, or study design. If sufficient homogeneity exists between studies, we will complete meta-analyses. We will evaluate the risk of bias using the Risk of Bias tool or the Cochrane Risk of Bias in Non-Randomized Studies tool. We will evaluate

the overall certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach.
Conclusion: In this systematic review and meta-analysis, we will summarize the current literature regarding the effects of human milk donation on human milk donors and their infants.

KEYWORDS
human, lactation, postpartum period, reproductive physiological phenomena

1 | INTRODUCTION

Infants born prematurely, defined as less than 37 weeks gestation, are at increased risk of morbidity and mortality.[1] There were 15.2 million cases of neonatal preterm birth in 2019, and preterm birth remains a leading cause of death worldwide during the neonatal period.[1] The risks associated with preterm birth include respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, retinopathy of prematurity, and intraventricular hemorrhage and are dependent upon the degree of prematurity and the extent of low birth weight.[2–5]

The recommended nutrition source for preterm infants is breast milk. Breast milk is beneficial to the growing infant, protecting against the development of bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, and sepsis.[6–12] When maternal milk is insufficient, unavailable, or contraindicated, the American Academy of Pediatrics, World Health Organization (WHO), and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommend that these infants receive donor human milk (DHM).[13–16]

The use of DHM is increasing.[17] The number of milk banking facilities is increasing worldwide, and banked human milk is now available in more than 65 countries.[18,19] Most DHM banks are located in high-income countries, but few operate in low- and middle-income countries.[19,20]

Maternal benefits of breastfeeding one's infant include decreased risk of breast and ovarian cancer, lower risk of developing type 2 diabetes, and longer lactational amenorrhea.[21] Although these benefits are established, it is not clear if donating breast milk offers the same advantages to the lactating person. Similarly, although the benefits to the infants who receive donor milk are well studied, it is not clear if donating breastmilk leads to adverse health or growth outcomes for the infant of the breastmilk donor. No systematic review on this topic has been completed to date.

In this WHO-commissioned systematic review and meta-analysis, we aim to identify, synthesize, and evaluate the available research regarding the impact of donating milk on the health, lactation, and well-being of the breast milk donor and the health and growth outcomes of the infant of the breast milk donor.

What is Known

- Donor human breast milk provides numerous health benefits to developing infants when maternal milk is not available.
- Human milk banking is becoming increasingly common worldwide to meet the demand for human breast milk.
- There has been no systematic review published to date regarding the effects of human milk donation on the donors or their infants.

What is New

- In this systematic review and meta-analysis, we will summarize the current literature regarding the effects of human milk donation on human milk donors and their infants.

2 | METHODS

This systematic review will be conducted following the standard guidelines of Cochrane Collaboration and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[22] This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on March 26, 2024, and was published (PROSPERO IDs: CRD42024529222, CRD42024528803).

3 | ELIGIBILITY CRITERIA

3.1 | Type of population

We will include studies that involve lactating women donating breast milk and their infants. There is no unified definition of human milk donation, but we will use the definition adopted by the European Milk Bank Association: "DHM is breastmilk that has been expressed by a mother and provided freely to a (human milk donor bank) to be fed to another mother's child."[23] We will include studies involving lactating women who

are healthy and those with health concerns (body mass index [BMI] outside the healthy limits, acute illness, chronic illness, suboptimal birth outcomes including preterm delivery, bereavement, and delivery of a low-birth-weight infant). We will also include studies involving infants of lactating women who are healthy or with health concerns. We will include studies irrespective of how the human milk was donated, for example, a relative, an anonymous donor, through a nonprofit human milk bank, a for-profit human milk bank, and so on. We will exclude studies that involve human milk donation between family members where donated milk was not processed in a milk bank. We will exclude studies on animal milk and synthetic milk created in the laboratory setting.

3.2 | Type of intervention and comparator

We will assess studies that involve breast milk donation. Breast milk donation will be divided by postbirth periods including colostrum, transitional, and mature milk. The quantity and duration of milk donation will be recorded when available, as the over-donation and exploitation of donor mothers is a potential ethical concern associated with human milk banks.[24,25]

We will consider studies with comparison groups of lactating individuals who have not donated breast milk and studies with a comparison group who never breastfed. The absence of a comparison group, however, is not an exclusion criterion for the study.

3.3 | Type of studies

Randomized controlled trials are the ideal study design to answer our study question, but we anticipate that there may not be available data to answer the question of interest. Therefore, we will not restrict the study design and will include observational, quasi-experimental, and randomized controlled trials. We will, however, exclude case reports, case series, and opinion pieces.

3.4 | Types of outcomes measures

Articles must report any of the following outcomes to be included in the study:

Primary outcomes

1. Breast milk donor health outcomes
   a. Acute illness (defined as any illness requiring an acute visit to a healthcare facility; inpatient or outpatient care) during the donation period (episodes per duration of follow-up).
   b. Chronic illness (defined as a condition lasting at least a year, which either limits daily activity and/or requires continuous medical attention/incidence).[26]
   c. Nutritional outcomes.
      i. Weight loss (6 months postinitiation of donation)
      ii. BMI (at 6 months postinitiation of donation)
      iii. Abnormal BMI (at 6 months postinitiation of donation)[27]
      iv. Micronutrient deficiencies
   d. Psychosocial outcomes.
      i. Incidence of postpartum depression (defined as experiencing symptoms of change in sleep, interest, guilt, energy level, mood, concentration, anxiety, appetite; thoughts of hurting oneself or others for >2 weeks).[28]
      ii. Incidence of postpartum psychosis (defined as experiencing psychotic symptoms in the postpartum period, including delusions or hallucinations).[28]
      iii. Incidence of anxiety.

2. Health outcomes of infant of breast milk donor:
   a. All-cause morbidity: any acute illness (defined as any illness requiring an acute visit to a healthcare facility as an inpatient or outpatient) during donation period (episodes per duration of follow-up-Incidence).
   b. Tolerance.
      i. Incidence of vomiting in infant
      ii. Incidence of diarrhea in infant
   c. Adverse events/effects: growth faltering or failure to thrive during first year of life (yes or no).[29]
   d. Infections during first year of life: gastrointestinal (incidence: illness episodes during the first year of life).
   e. Infection during first year of life: respiratory (incidence: illness episodes during the first year of life).
   f. Other infections during the first year of life including central nervous systems infection (incidence: illness episodes during the first year of life).
   g. Micronutrient deficiencies: Vitamin B12 defined based on serological markers (yes or no).
   h. Micronutrient deficiencies: iron deficiency based on ferritin and hemoglobin level (yes or no).
   i. Micronutrient deficiencies: zinc deficiency defined based on serum zinc level (yes or no).
   j. Micronutrient deficiencies: Vitamin A deficiency based on serum retinol levels (yes or no).
   k. Micronutrient deficiencies: Vitamin D deficiency defined based on serum vitamin 25-OH-Vitamin D3 levels (yes or no).
   l. Developmental outcomes: Bayley score at 1 and 2 years of age (continuous outcome).

m. All-cause mortality during infancy (yes or no).

Secondary outcomes

1. Breast milk donor's lactation outcomes
   a. Milk supply (mL/day), mean.
   b. Pumped milk feeding (for infant of breast milk donor).
   c. Breastfeeding exclusivity for infant of breast milk donor for first 6 months (yes or no).
   d. Breastfeeding duration (include both donated milk and for donor's own infant).
   e. Incidence of mastitis (yes or no).
2. Breast milk donor's well-being.
   a. Length of lactational amenorrhea (days).
   b. Prevention of harm.
      i. Incidence of breast cancer development (yes or no; postdonation at longest follow-up visit).
      ii. Incidence of ovarian cancer development (yes or no; postdonation at longest follow-up visit).
      iii. Incidence of postpartum hemorrhage (yes or no).
      iv. Incidence of type II diabetes (yes or no; postdonation at longest follow-up visit).
3. Growth outcomes of infant of breast milk donor.
   a. Weight for age Z scores (at 6 months and 1 year of age) (continuous outcome).
   b. Length for age Z score (at 6 months and 1 year of age) (continuous outcome).
   c. Weight for length Z scores (at 6 months and 1 year of age) (continuous outcome).
   d. Head circumference at 1 year of age (continuous outcome).
   e. Underweight at 1 year of age (weight for age Z score less than −2, Yes or No).
   f. Stunted at 1 year of age (height for age Z score less than −2, Yes or No).
   g. Wasted at 1 year of age (weight for length Z score less than −2, Yes or No).

3.5 | Information sources

Systematic electronic searches will be conducted utilizing PubMed, EMBASE, the Cochrane Central Register for Controlled Trials, Web of Science, CINHAL, Scopus, and WHO Global Index Medicus. There will be no restrictions on publication date, language, or study design in the search strategy. A proposed search strategy is provided in Supporting Information S1: File S1.

3.6 | Other sources

We will also search grey literature including searching Google Scholar and ClinicalTrials.gov for ongoing studies and unpublished dissertations. We will search the websites of relevant international agencies, such as the WHO (including WHO's Reproductive Health Library), UNICEF, Global Alliance for Improved Nutrition, International Food Policy Research Institute, International Initiative for Impact Evaluation (3ie), Nutrition International, Human Milk Bank Association of North America, and European Milk Bank Association. Lastly, the reference sections of previous reviews and the latest published studies will also be searched for potentially eligible studies.

4 | STUDY RECORDS

4.1 | Study selection process

All studies identified in the electronic search will be exported to the software Covidence for screening.[30] Two authors will independently screen all titles and abstracts to identify studies relevant to the research question. Then, those studies identified as relevant will be screened with a full-text review to determine if they are eligible for inclusion. A third author will be available to resolve any conflicts during screening. We will include a list of studies that were excluded after full-text screening and provide detailed reasons for their exclusion.

4.2 | Data collection and management process

Studies deemed eligible for inclusion during the full-text review step will then proceed to full data extraction. Two authors will independently extract data for each study, and any conflicts will be resolved by discussion with the help of the senior author on the team as needed. The following information with be extracted for each study: first author, publication date, study site, study year, study population, intervention, comparison, outcomes, and risk of bias. The risk of bias will be assessed by using the Cochrane Risk of Bias tool for randomized controlled trials, or by using the Cochrane Risk of Bias in Non-randomised Studies-of Interventions (ROBINS)-I tool for nonrandomized studies.[31,32] We will contact the authors if data for exposure or outcomes is missing from reports. For continuous outcomes, if a study does not report a standard deviation (SD) for a mean and this cannot be calculated from the reported data and information is unavailable from authors, we will use an SD reported from a similar study for the same outcome.

5 | DATA SYNTHESIS

We will report a table of the characteristics of the included studies, and a separate table for the summary of findings for the primary outcomes. We will also report narrative summaries of the results of included studies regarding the outcomes of interest. Studies from low- and middle-income

countries will be reported separately from those from high-income countries. We will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the overall certainty of the evidence, using the GradePro software.[33] We will report the results of the GRADE assessment in a table that summarizes the findings for primary outcomes, with each finding characterized as very low, low, moderate, or high certainty.

We will conduct and report meta-analyses when data are available from more than one study and there is sufficient clinical and methodological homogeneity between studies. Meta-analyses will report dichotomous outcomes with relative risk and corresponding 95% confidence intervals. We will report continuous outcomes with mean difference and corresponding 95% confidence intervals. We will calculate the statistical heterogeneity of effect sizes using the χ^2 and I^2 statistics. Funnel plots and regression tests for funnel plot asymmetry will be used to assess small studies and publication bias if/when the meta-analysis includes 10 or more studies. We will use the statistical software RevMan and Stata to complete the analyses.[34,35] We will report findings in a table format, grouped by outcome domains. We will order studies on the certainty of the evidence, with high-certainty evidence at the top of the tables, followed by moderate and low-certainty evidence sources.

6 | SUBGROUP ANALYSES

1. Time of milk donation (colostrum, transitional, and mature milk).
2. Bereavement (donation following perinatal death vs. donation after live birth).
3. Donation after full-term birth versus preterm birth.
4. Donation after birth with normal weight versus low birth weight.

7 | SENSITIVITY ANALYSES

1. Use of fixed effect vs random effect model.
2. Studies with a high risk of bias.

8 | DISSEMINATION

We plan to publish the findings of this review in a peer-reviewed journal.

9 | CONCLUSION

This systematic review and meta-analysis will summarize the current literature regarding the effect of human milk donation on the health, well-being, and lactation of human milk donors, and on the health and growth outcomes of the infant of the breast milk donor. This information will inform the WHO's recommendations for human milk banking.

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CONFLICT OF INTEREST STATEMENT

Dr. Tarah Colaizy is the research director of the research committee of the Human Milk Banking Association of North America (HMBANA). She contributes to this position on a volunteer basis and has never received any honorarium from HMBANA. This proposal was not discussed in the research committee of HMBANA, and HMBANA did not have any role in the design of this study. The remaining authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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