

SYSTEMATIC REVIEW

The Impact of Pasteurized Donor Human Milk on the Growth of Preterm Infants: A Systematic Review

Nur Syahirah Mohd Khalid¹, Hamizah Ismail², Norafiza Zainuddin¹

¹ Department of Biomedical Science, Kulliyah of Allied Health Sciences, International Islamic University Malaysia, Bandar Indera Mahkota, Jalan Sultan Haji Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.

² Department of Obstetrics & Gynaecology, Kulliyah of Medicine, International Islamic University Malaysia, Bandar Indera Mahkota, Jalan Sultan Haji Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.

ABSTRACT

Introduction: Pasteurized donor human milk (PDHM) is currently the best alternative for preterm (premature) babies as producing a sufficient milk supply in the early weeks can be difficult for new mothers. However, there are conflicting results on the impact of donor human milk (DHM) on the growth of preterm infants. **Aims:** This systematic review aims to thematically investigate the impact of pasteurization on the nutritional components of DHM and to thematically determine the correlation between PDHM and its effect on the growth and development of preterm infants. **Materials and methods:** A comprehensive literature search was conducted using PubMed, Scopus, and Cochrane Library on original research articles published from January 2017 to April 2023. We illustrated the screening and selection outcomes in a PRISMA flowchart and assessed the quality of the selected articles using Crowe Critical Appraisal Tool. **Results:** Four of 130 articles met the inclusion criteria. Correspondingly, two main themes were identified from the selected articles, which include nutrient composition of donor milk and short-term growth outcome. **Conclusion:** To get rid of any potentially harmful bacteria that could infect a premature newborn, it is reasonable to conclude that DHM requires pasteurization. Thus, there is now less of the milk's natural nutritional components—protein, fat, antioxidants, cytokines, immunoglobulins, lactoferrin, and insulin-like growth factor—in the liquid. The short-term growth of preterm infants may be slightly impacted by the pasteurization of DHM, which also lowers some of its nutritional value.

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Corresponding Author:

Norafiza Zainuddin, PhD

Email: znorafiza@iium.edu.my

Tel : +609-5705258

INTRODUCTION

Infants' nutritional needs must be met daily, particularly if they are preterm since nourishment is essential for the healthy growth and development of their organs. The overall objective in the NICU is for the preterm babies to achieve a daily weight increase of around 15 g/kg/day to simulate the development that takes place within the uterus during the third trimester of pregnancy. Consequently, to achieve this targeted daily weight increase, they should receive about 3.4-4.2gm/kg/day of daily protein intake and caloric intake of 110-135 kcal/kg/day (1). However, despite the various benefits human milk can give to a preterm baby, preterm dietary requirements, notably for protein, calcium, and phosphate, are not met by unfortified human milk (2). Additionally, even when preterm newborns are given human milk with milk fortifiers, the prevalence

rate of extrauterine growth restriction (EUGR) remains significant.

Donor human milk (DHM) is extensively utilized and recommended by the World Health Organization (WHO) as an alternative source of milk when mother's own milk (MOM) or mother's breast milk (MBM) is inadequate rather than formula milk. This may be attributed to its ability to lessen the severity of necrotizing enterocolitis. Pasteurized donor human milk (PDHM) is a precious resource provided by certain hospitals and is only used for the smallest or sickest infants who would benefit the most. This includes preterm infants, as well as infants with intestinal or heart problems.

There are conflicting results on the impact of DHM on the growth of preterm infants. After conducting a retrospective study of 209 very low birth weight (VLBW) infants to determine the association between the type of infant nutrition which is mother's own milk and DHM with the growth outcome of preterm, Bajwa et al. (3) concluded that the long-term growth potential of infants fed with DHM is marginally higher than that of

infants fed with MOM. Conversely, Madore et al. (4) and Montjoux-Régis et al. (5) discovered that newborns fed largely with DHM were related to reduced development outcomes compared to those infants fed with MOM. However, Giuliani et al. (6) discovered that there was no significant difference between infants fed with MOM and DHM groups, in terms of clinical outcomes and preterm infants' growth.

Given the potential of DHM to affect important outcomes for preterm infants, and since uncertainty exists on the impact of PDHM on the growth of preterm infants, an attempt to detect, appraise and synthesize evidence from randomized controlled trials (RCTs), clinical trials, cohort studies, prospective studies and case-control studies is merited. Hence, this review aims to thematically investigate the impact of pasteurization on the nutritional components of DHM and to thematically determine the correlation between PDHM and its effect on the growth of preterm infants.

MATERIALS AND METHODS

Registration and protocol

This systematic review was conducted according to a protocol registered in PROSPERO: CRD42023414535, available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=414535. The protocol was not published in any peer-reviewed journal. The development of the protocol was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2020 (7).

Selection procedure

Articles were reviewed based on their titles, objectives, abstracts, discussions, and research designs to see whether they are relevant to the research subject. In addition, duplicates were also identified and eliminated from the list of relevant articles. Furthermore, each article was evaluated according to the inclusion and exclusion criteria. Finally, the authenticity of the articles was verified using the quality evaluation.

Systematic review process

Identification

A comprehensive literature search was conducted using the open access online databases of Scopus, PubMed, and Cochrane library, and was limited to English language only. Articles were retrieved from the databases using the keywords (preterm infant fed with pasteurized donor human milk, preterm infant, nutritional content of pasteurized donor human milk and hospitalized preterm infant), and MeSH terms, with each potential variant of the terms being taken into consideration. To avoid explicitly incorporating all potential variants into the strategy, truncation was utilized. The asterisk (*) served as PubMed's truncation sign, and its function was to retrieve all the words that include the root (the part of

the phrase that came before the asterisk). In addition, the keywords were used in conjunction with BOOLEAN operators such as AND, OR, and NOT, which were all enclosed in brackets.

The search string used was as follows: (milk, human OR breast milk OR mother's breast milk OR mother's own milk OR maternal milk OR donor milk OR donor human milk OR pasteurized donor human milk OR pasteurized human milk OR unpasteurized human milk OR infant feeding OR fed OR feed* OR milk bank OR breast milk expression OR breastfeed* OR breastfed OR MBM OR MOM OR DHM OR PDHM) AND (infant*, premature, preemie*, neonate*, extremely premature OR infant, low birth weight OR infant, very low birth weight OR intensive care unit*, neonatal OR intensive care, neonatal OR premature birth, neonatal OR hospitalized) AND (low birthweight OR low birth weight OR VLBW OR Prematur* OR Preterm OR pre-term OR infant* OR newborn* OR new-born* OR baby* OR babies OR neonatal intensive care OR NICU) AND (nutrition* OR nutrient* OR nutritional content OR nutritional composition) AND weight NOT enteral feeding* NOT microbiome. In other databases, similar search terms were applied.

Screening

Articles retrieved from the selected online databases were then reviewed for any duplications, and those identified were eliminated from inclusion. Consequently, the titles and abstracts of the articles that were left over underwent an in-depth evaluation. Any articles found to be irrelevant to the aim of this research were dismissed.

Eligibility

Following the initial screening of articles, the inclusion and exclusion criteria were then utilized to determine the eligibility of the remaining full-text articles (Table I). Articles that met all the required criteria were included in this study.

Table I: Inclusion and exclusion criteria for systematic review.

| Inclusion criteria | Exclusion criteria |
|--|---|
| -Studies published in English | -Studies published in other language |
| -Studies published in 2017-2023 | -Studies published before 2017 |
| -Randomized control trials, clinical trials, cohort studies, prospective studies or case-control studies | -Gray literature and hand-searched articles (letters, editorials, systematic review, scoping review and meta-analysis) -Articles that are a chapter of a book, proceeding and dissertation |

Inclusion

Data analysis was performed on the remaining selected papers that satisfied all the standards and earlier assessment.

Data extraction

The final full-text publications' data were evaluated, summarized, and presented in the form of a table for easier viewing. The name of the authors, the year of publication, journal of publication, title of the study, study design and selected participants or sample size were listed in the table. In addition, articles regarding the nutritional component of the DHM and direct human milk, and articles on the association between DHM and the growth of preterm infants were extracted as the main findings.

Inter-rater reliability and disagreement

Based on the predetermined inclusion and exclusion criteria, the articles were selected by two reviewers, Nur Syahirah Mohd. Khalid (NSMK) and Norafiza Zainuddin (NZ), with NSMK doing the screening and NZ independently validating the accuracy of the extracted data. Discrepancies during the data extraction and assessment of the risk of bias process were resolved by discussion and consensus among all reviewers, including Hamizah Ismail (HI). NSMK and NZ possessed relevant knowledge in biomedical science, whereas HI is an expert in maternal fetal medicine. Percent agreement was employed throughout this study to deal with the disagreement of the individual judgment.

Quality assessment

The Crowe Critical Appraisal Tool (CCAT) (8) version 1.4 checklist of questions was used to evaluate the research articles' quality and suitability for inclusion in this study. The CCAT is composed of the CCAT Form and the CCAT User Guide which was used together to exclude any possibility of a breach in the authenticity and dependability of the results collected (8). Only articles scoring above 75% were included in this systematic review, since they were deemed to be of sufficiently high quality to warrant inclusion.

RESULTS

Literature search

Initially, a total of 130 articles were identified through database searches utilizing specific keywords. Following

a comprehensive review, six duplicate articles were removed, and 23 potentially relevant articles were selected based on titles. Subsequently, 11 articles were excluded as these articles did not meet the study's aim. The remaining 12 articles were assessed and filtered based on the predefined inclusion and exclusion criteria. Subsequently, eight articles were deemed irrelevant to the research objective. Ultimately, a total of four publications were selected for inclusion in this systematic review (Fig. 1).

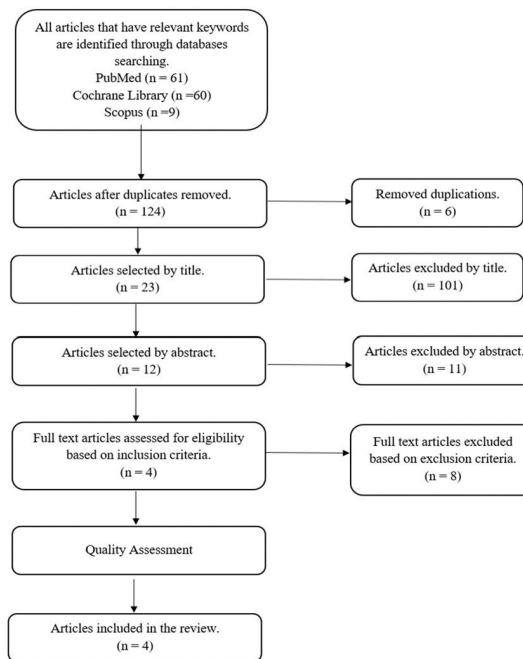


Fig. 1: Flow Diagram of Selection Procedure based on PRISMA 2020

Data selection and study characteristics

The first author, year the article was published, journal of publication, title of the study, study's objectives, study design, country, number of participants that participated in the study, and study method were extracted, summarized, and tabulated in Table II based on the four eligible full-text articles. In addition, the nutritional component of donor human milk and the association between donor human milk and the development of preterm infants have been analysed and extracted.

Table II: Characteristics of included studies.

| Study no. | Author and publication year | Journal of Publication | Types of publication | Title of study | Objective | Study design | Country | No. of participants | Methods |
|-----------|------------------------------|------------------------------|----------------------|---|--|--------------------------------------|---------|---------------------|------------------|
| 1. | Kumbhare, S.V. et al. (2022) | <i>Cell Reports Medicine</i> | Article | Source of Human Milk (mother or donor) is More Important than Fortifier Type (human or bovine) in Shaping the Preterm Infant Microbiome | To evaluate the benefits of targeted HM fortification on body composition outcomes of VLBW infants To determine the influence of targeted fortification on neonatal growth outcomes | Ran- domised clinical trial | Canada | 36 | Qualita- tive |

CONTINUE

Table II: Characteristics of included studies. (CONT.)

| Study no. | Author and publication year | Journal of Publication | Types of publication | Title of study | Objective | Study design | Country | No. of participants | Methods |
|-----------|-----------------------------|---------------------------------------|----------------------|---|---|-----------------------------------|-----------------|---------------------|--------------|
| 2. | Newkirk, M. et al. (2018) | <i>Nutrition in Clinical Practice</i> | Article | Comparison of Calorie and Protein Intake of Very Low Birth Weight Infants Receiving Mother's Own Milk or Donor Milk When the Nutrient Composition of Human Milk Is Measured with a Breast Milk Analyzer | To determine the actual daily calorie and protein intake of VLBW infants receiving enteral feedings of blindly fortified HM (either mother's own milk, MOM or donated breast milk, DBM) using retrospective data on the baseline nutrition content of HM that was established using a breast milk analyzer. | Retro-spective cohort study | USA | 31 | Quantitative |
| 3. | Ginovart, G. et al. (2017) | <i>Advances in Neonatal Care</i> | Article | A Fortified Donor Milk Policy is Associated With Improved In-Hospital Head Growth and Weight Gain in Very Low-Birth-Weight Infants | To evaluate the impact of early human milk feeding (donor milk and/or mother's own milk) with standard fortification on in-hospital growth of very low-birth-weight infants. | Pre-/post retro-spective study | Spain | 182 | Quantitative |
| 4. | Parat, S. et al. (2020) | <i>Nutrients</i> | Article | Targeted Breast Milk Fortification for Very Low Birth Weight (VLBW) Infants: Nutritional Intake, Growth Outcome and Body Composition | To evaluate the benefits of targeted HM fortification on body composition outcomes of VLBW infants To determine the influence of targeted fortification on neonatal growth outcomes | Pro-spective interventional study | Cleveland, Ohio | 127 | Quantitative |

Synthesis

Two main themes of the impact of donor human milk on the growth of preterm infants were identified and are tabulated in Table III. The first theme was nutrient composition of donor human milk, which focuses on reduced protein content, lower calorie content, nutrient insufficiency in DHM provided by mothers of term infants, lower antioxidant capacity, reduced immunoglobulins, reduced cytokines, reduced lactoferrin and reduced insulin-like growth factor. The second identified theme was short-term growth outcomes, highlighting two important aspects which included suboptimal growth in MOM-fed and poor growth in DHM-fed. These two main themes were synthesized due to content of each study that were almost interrelated and should be included in the same category.

Table III: Themes identified in each study.

| Theme | Study | | | |
|---|-------|---|---|---|
| | 1 | 2 | 3 | 4 |
| 1. Nutrient Composition of Donor Human Milk | | | | |
| i. Reduced protein content | √ | | √ | √ |
| ii. Lower calorie content | | √ | √ | √ |
| iii. Nutrient insufficiency in DHM donated by mothers of term infants | | √ | | |
| iv. Lower antioxidant capacity | √ | | | |

CONTINUE

Table III: Themes identified in each study. (CONT.)

| Theme | Study | | | |
|--|-------|---|---|---|
| | 1 | 2 | 3 | 4 |
| 1. Nutrient Composition of Donor Human Milk | | | | |
| v. Reduced immunoglobulins | | | | √ |
| vi. Reduced cytokines | | | | √ |
| vii. Reduced lactoferrin | | | | √ |
| viii. Reduced insulin-like growth factor | | | | √ |
| 2. Short-Term Growth Outcomes | | | | |
| i. Suboptimal growth in MOM-fed | | | √ | |
| ii. Poor growth in DHM-fed | | | √ | √ |

DISCUSSION

This systematic analysis of 130 publications examines how donor human milk affects preterm newborn development, specifically weight gain. Four studies were directly relevant to this study's goals, which were to systematically distinguish the nutritional components of PDHM and to determine the correlation between PDHM and preterm infant weight. These investigations were carried out in many various countries, including Ohio, Canada, Spain, and the United States of America. The US and Canada are in the top 10 countries for preterm births. According to Bronstein et al. (9), increased rates of

obesity, heart disease, and poor health status contribute to stress, which may cause hypertension, spontaneous preterm delivery, and early labour. All the included studies were found to be of moderate to high quality. Moreover, nutrient composition of donor milk and short-term growth outcome are the two main themes that were identified and synthesized for this study.

Pasteurization of donor human milk is a procedure commonly used to guarantee the microbiological safety of donor human milk by eliminating harmful pathogens. Holder pasteurization is the most common method used for pasteurizing human milk. Raw donor milk is heated to a temperature of 62.5°C and held at that temperature for 30 minutes. Holder pasteurization can be done in batch or in continuous method where in batch method individual containers of milk are heated in a water bath meanwhile in continuous method, milk flows through a heat exchanger, allowing for a continuous process of pasteurization. The donor human milk is then rapidly cooled to refrigeration temperature around 4°C to prevent bacterial growth. Additionally, the process of pasteurization, which eliminates certain important immunological and development components, has the potential to adversely affect the immune function and growth potential of children who are dependent on DHM (10).

The procedure of pasteurization has a substantial impact on the nutritional composition of the DHM, which was thematically analysed in this research that focuses on eight important aspects including decreased protein content, lower calorie content, nutritional insufficiency in DHM provided by mothers of term infants, lower antioxidant capacity, reduced immunoglobulins, reduced cytokines, reduced lactoferrin and lastly reduced insulin-like growth factor. Macronutrients, which comprises of carbohydrates, proteins, and fats, is essential to the proper development, growth, and generation of energy in infants, therefore it is crucial to make sure that the preterm infants received an adequate amount of macronutrient.

Based on the findings from studies 1, 3, and 4, it has been observed that preterm infants who are fed with DHM tend to receive lower protein content. Appropriate daily intake of protein is crucial for preterm growth since protein is the building block of body tissues, including muscles, bones, skin, and organs (11). Besides, protein is also involved in various metabolic processes, including enzyme production and energy metabolism. Hence, it could be concluded that preterm infants should receive the appropriate amount of protein content to achieve sufficient growth which is supported by Atchley et al. (12) in which they claim that increased protein intake could lead to increase relative weight gain. Fortification strategies, for example, targeted fortification and standard fortification, can be utilized to increase the protein content of DHM, providing infants with the

energy required for optimal growth and development.

Furthermore, based on the results from study 3 and 4, it was revealed that preterm infants fed with DHM tend to receive a low-calorie content. Calories could be defined as the measurement of the energy content of food. According to Ben (13), in comparison, a term infant has a daily caloric need of 100-120 kcal/kg, whereas a preterm infant has a caloric requirement of 110-150 kcal/kg. Based on study 2, using the breast milk analyser, Newkirk et al. (14) had concluded that with the total enteral fluid intake of 150.7 ml/kg, the preterm infants that was fed with predominantly DHM provided about 110.1 ± 9.0 kcals/kg daily, which is quite similar with the calories provided by MOM. However, the DHM-fed would show a significantly lower calorie content than MOM-fed if the total enteral fluid were kept the same for both milk sources (14). Hence, to provide a similar caloric content with MOM-fed, the predominantly DHM-fed should receive a higher intake of total enteral fluid. In addition, according to study 4, it has been identified that there is a presence of nutrient insufficiency in DHM donated by mothers of term infants. The nutrient content of breast milk, including DHM, may differ among people due to several variables, including nutritional status, food, health situations, as well as nursing practices. Gialeli et al. (15) mentioned that donor milk that is primarily derived from mothers of term infant tend to have lower protein concentration and less caloric energy compared to donor milk donated by mothers of preterm infant.

Additionally, when raw donor human milk is heated at 62.5°C during pasteurization, the antioxidant capacity is diminished in comparison to MOM which can be observed in study 1. Other studies have also shown a reduction in total antioxidant capacity after Holder pasteurization compared to untreated milk (16, 17, 18). Due to the imbalance of oxidants and antioxidants that could lead to an increase in the level of free radicals, preterm infants tend to be more susceptible to oxidative stress (Lembo et al. (19). The accumulation of free radicals resulting from the imbalance of oxidant and antioxidant will may cause cellular dysfunction and damage thus influencing the general health of the preterm infants. Furthermore, based on the findings of study 2, the immunoglobulin and cytokine levels of donor human milk after the pasteurization process has been reduced. Holder pasteurization was also shown to decrease IgA by 30% and IgG by 60% previously (20). Both immunoglobulin and cytokines play a crucial role in the immune system. Hence, it is possible that a decrease in immunoglobulin and cytokines influence the growth of preterm infants, as the infant will be unable to fend off potentially hazardous pathogens. Furthermore, a weakened immune system may alter the gut microbiota of the preterm infants, which aids in nutrition absorption and catch-up development capacity (21). Similarly, as shown on Table II, based on study 2,

it can be observed that the lactoferrin and insulin-like growth factors levels are decreased when a donated human milk underwent pasteurization process. As low as 1 g/L of lactoferrin may be found in DHM that is collected postpartum and refrigerated for three months. Nevertheless, pasteurization can further lower baseline lactoferrin by up to 88% (22). The reduction of NEC and sepsis has been associated with lactoferrin, a powerful anti-infective, anti-inflammatory, immunomodulatory, and prebiotic compound in MOM. Hence, reduced lactoferrin in pasteurized milk may affect its benefits to preterm infants.

The short-term growth of preterm infants was evaluated thematically and highlighted on two important aspects which are the suboptimal growth observed in MOM-fed and poor growth outcome in DM-fed preterm infants. MOM-fed preterm infants experienced suboptimal growth, as evidenced by in study 1 meanwhile according to the findings in studies 2,3 and 4 stated that preterm infants fed with predominantly DHM tend to experience poorer growth compared to those fed with other source of milk like formula and fortified. Preterm infants have unique nutritional needs due to their immature physiological systems and increased requirements for growth and development. The impact of pasteurization on the DHM that results in a decreased nutritional component is associated with the poor growth of preterm infant fed with PDHM particularly protein, calorie content, immunoglobulins, cytokines, lactoferrin and insulin-like growth factor.

Macronutrients, for instance, carbohydrate, fats, especially protein are substantial for the growth and development of children particularly preterm infants as macronutrients helps provide energy, aids in micronutrients absorption and supports the immune system (23). Study 1,3 and 4 discovered that there was reduced amount of protein delivered by predominantly DHM feedings meanwhile study 2 found that when DHM was administered in a high total enteral fluid, the infants only received around 110.1 ± 9.0 kcal/kg of calorie content, which is within the minimum amount of calorie recommended for a premature newborn. Bioactive milk proteins can boost nutritional absorption, guard against infections, and support the growth of the immunological and neurological systems of preterm infants. Pasteurization inactivates some of these proteins, giving PDHM differing qualities from raw mother's milk. Furthermore, preterm infants require a higher amount of protein and calorie content to achieve optimal nutrition that will then help maintain a normal extrauterine growth compared to term infants. Thus, a lower amount of protein and calorie content may impact the growth of preterm infants (24, 25).

Pasteurization of donor human milk tends to lower the insulin-like growth factor or also known as IGF -1 (26). It is a major regulator of fetal growth and development

of most organ systems (27). In fact, the insulin-like growth factor is a peptide hormone in which its main responsibility is to stimulate the growth hormone. Subsequently, the growth hormone then stimulates other tissues to produce IGF-1 which in turn causes the tissues to undergo hypertrophy and hyperplasia. Hence, a decrease levels of insulin-like growth factor in the PDHM may affect the growth of preterm infant growth soon. Therefore, the process of pasteurisation could influence some of the nutritious components of DHM, which might, in turn, result in a retardation of the development of premature infants. The findings of inadequate development in PDHM-fed preterm infants imply the potential need for further intervention to meet their short-term growth and nutritional requirements.

CONCLUSION

In conclusion, this systematic review has identified two main themes that are relevant to the aim of the study which includes i) nutrient composition of PDHM, and ii) infant short-term growth outcome. Considering all the findings presented in this systematic review, it is possible to conclude that DHM requires pasteurization to eliminate any potentially dangerous pathogens that could infect a preterm infant. This, in turn, has led to a reduction of nutritional components present in the milk itself such as protein, calorie content, antioxidant, immunoglobulins, cytokines, lactoferrin and lastly insulin-like growth factor. Additionally, part of the nutritional content of PDHM has been reduced because of pasteurization, which has a slight impact on the short-term growth of preterm infants.

On note, we acknowledged the limitation of this review where there could have been studies that fulfilled the requirements that were missed during the selection process such as hand-searched (grey) articles and articles published in languages other than English. Overall, this study has presented some valuable information regarding the impact of PDHM on the growth of preterm infants. Future research should prioritize investigating preterm weight gain as an end measurement to better understand the effects of PDHM on the development of premature infants. Furthermore, it would be beneficial to investigate the correlation between the lactation period of the donor mother and the nutritional composition of the donated milk, and how these factors influence preterm growth. In addition, performing further research that is entirely focused on the nutritional content of PDHM will improve our knowledge of the influence that it has on the growth of premature infants and thus aid in informed decisions regarding the nutritional care of these vulnerable infants.

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