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+15878858911
editorial-office@sciformat.ca

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HUMAN MILK–BASED FORTIFIERS IN PRETERM INFANTS – CLINICAL BENEFITS AND LIMITATIONS IN THE LIGHT OF CURRENT EVIDENCE

Julia Agnieszka Dębczak *(Corresponding Author, Email: julia.debczak@onet.pl)*
Military Medical Institute – National Research Institute, Warsaw, Poland
ORCID ID: 0009-0004-4574-8466

Agnieszka Krajewska
Maria Skłodowska-Curie Voivodeship Specialist Hospital in Zgierz, Zgierz, Poland
ORCID ID: 0009-0003-2961-7565

Agnieszka Korzeniewska
Military Medical Institute – National Research Institute, Warsaw, Poland
ORCID ID: 0009-0006-0337-961X

Natalia Malicka
Independent Public Healthcare Centre of the Ministry of the Interior and Administration in Kielce, Kielce, Poland
ORCID ID: 0009-0002-3045-2908

Katarzyna Tłustochowicz
Independent Public Healthcare Centre of the Ministry of the Interior and Administration in Kielce, Kielce, Poland
ORCID ID: 0009-0006-4209-2558

Karolina Łuczak
Miedzyleski Specialist Hospital in Warsaw, Warsaw, Poland
ORCID ID: 0009-0000-5952-8457

Magdalena Korba
St. Anne's Hospital in Miechow, Miechów, Poland
ORCID ID: 0009-0002-5577-9923

Wiktoria Polkowska
Central Clinical Hospital of the Medical University of Łodz, Łódź, Poland
ORCID ID: 0009-0006-3812-9573

Adrianna Kowalik
Independent Public Healthcare Complex in Płonsk, Płońsk, Poland
ORCID ID: 0009-0001-4092-5839

ABSTRACT

Background: Preterm infants, particularly those with very low birth weight (VLBW) and extremely low birth weight (ELBW), have substantially increased nutritional requirements. Although human milk provides many protective benefits, it does not fully meet the nutritional needs of this population, which justifies the routine use of human milk fortifiers. Traditionally used bovine milk–based fortifiers (BMBF) have raised concerns regarding their potential association with necrotizing enterocolitis (NEC), which led to the development of human milk–based fortifiers (HMBF).
Objective: This narrative review aimed to present the current state of knowledge regarding the clinical benefits and limitations of HMBF in preterm infants, with particular emphasis on NEC, sepsis, growth, and mortality.
Materials and Methods: A narrative literature review was conducted including randomized controlled trials, observational studies, and systematic reviews and meta-analyses comparing HMBF and BMBF in preterm infants. The analysis focused on clinically relevant outcomes, particularly in ELBW infants and in the context of an exclusive human milk diet.
Results: The reviewed studies indicate a lower incidence of NEC among infants receiving HMBF, particularly within exclusively human milk–based diets. Mortality was also reported to be lower in some cohorts, particularly among ELBW infants. Rates of late-onset sepsis and other major morbidities were generally comparable between groups. Some studies reported slower short-term weight gain with HMBF, whereas long-term growth outcomes showed no consistent differences between feeding strategies.
Conclusions: Current evidence suggests that HMBF may reduce the risk of NEC and mortality in highly vulnerable preterm infants, particularly those with ELBW. Although some studies report slower short-term weight gain, randomized trials have not demonstrated clinically meaningful differences in long-term growth or body composition. Overall, the potential clinical benefits appear to outweigh these temporary differences in growth velocity.

KEYWORDS

Preterm Infants, Human Milk Fortifiers, HMBF, BMBF, Necrotizing Enterocolitis, Growth

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1. Introduction

Prematurity remains one of the most serious challenges of modern neonatology and a significant public health problem. According to the definition of the World Health Organization, a preterm infant is a newborn delivered before 37 completed weeks of gestation [1]. Each year, more than 15 million infants are born preterm worldwide, accounting for approximately 11% of all live births [2,3,4]. Despite substantial advances in perinatal care, prematurity continues to be a leading cause of neonatal morbidity and mortality [2,5,6].

However, increased survival of infants born at extremely low gestational ages has been accompanied by a higher incidence of short- and long-term complications, particularly among infants with VLBW and ELBW [3,5,6]. The most severe complications include NEC, late-onset sepsis, bronchopulmonary dysplasia (BPD), and neurodevelopmental impairments, all of which have a significant impact on long-term prognosis [3,6,7]. Increasing evidence also highlights the role of early environmental factors in the development of long-term metabolic and cardiovascular complications, in accordance with the concept of developmental programming [8-10].

In light of these data, optimization of nutrition during the first weeks of life represents one of the key elements of clinical management in preterm infants. Adequate provision of nutrients is essential not only for survival and appropriate postnatal growth, but also for organ maturation, immune system function, and gastrointestinal integrity [11]. Human milk remains the preferred source of nutrition for preterm infants due to its anti-inflammatory, immunomodulatory, and trophic properties; however, its natural composition does not fully meet the increased nutritional requirements of this population [11].

2. Materials and Methods

We conducted a comprehensive review focusing on the clinical outcomes associated with the use of human milk–based fortifiers in preterm infants. Our analysis was based on literature published between 2004 and 2026, with particular emphasis on studies evaluating human milk–based fortifiers and exclusively human milk–based diets in very low birth weight and extremely low birth weight infants. Earlier key publications on neonatal nutrition and human milk fortification were also included to provide essential background context.

Multiple databases were searched: PubMed, Cochrane Library, Web of Science, Embase, Google Scholar, and MEDLINE. Search terms included: human milk fortifier, human milk–based fortifier, bovine milk–based fortifier, preterm infants, necrotizing enterocolitis, growth, sepsis, and exclusive human milk diet.

3. Results

3.1 Fortification of Human Milk in Preterm Infants

3.1.1 Importance of Early Nutrition

Preterm infants, particularly those with VLBW and ELBW, are characterized by limited energy, protein, and micronutrient stores, combined with very high metabolic demands. Immaturity of enzymatic systems and rapid growth velocity mean that even short-term nutritional deficits may lead to extrauterine growth restriction (EUGR) [12,13].

Numerous studies have demonstrated that insufficient nutrient intake during early life is associated with poorer neurological, cognitive, and functional outcomes later in life [14,15]. Therefore, optimization of enteral nutrition from the first days of life is a crucial component of care for preterm infants. Routine fortification of human milk is currently considered the standard of care for VLBW and ELBW infants, enabling adequate delivery of energy, protein, calcium, phosphorus, and other essential nutrients [11,16,17].

3.1.2 BMBF and HMBF

Traditionally used human milk fortifiers are produced from cow's milk and effectively increase energy and protein intake in preterm infants. Their use improves growth velocity and bone mineralization [16,18]. However, these preparations introduce foreign bovine protein antigens into the infant's diet, which may interact with the immature immune system and intestinal barrier [19].

An alternative approach involves the use of HMBF, which allows maintenance of a diet composed exclusively of human milk–derived products. These fortifiers, produced from pasteurized donor human milk, retain many bioactive properties of human milk, including immunomodulatory factors, human milk oligosaccharides (HMOs), and substances that support the development of a beneficial gut microbiota. This strategy makes it possible to provide adequate nutrient intake while limiting exposure to cow's milk proteins [20,21].

3.1.3 Evolution of the Concept of an Exclusively Human Milk–Based Diet

Initially, fortification of human milk focused primarily on increasing caloric and protein intake, without detailed consideration of potential immunological consequences or the impact of fortifiers on the immature gastrointestinal tract of preterm infants. With advances in the research of the gut microbiota in shaping neonatal immune responses, increasing attention has been paid to the quality of nutritional components [11,22].

As a result, the concept of an exclusively human milk–based diet emerged, incorporating mother's own milk, donor human milk, and HMBF. The primary goal of this nutritional strategy is the elimination of cow's milk proteins from the diets of the most immature preterm infants, which may reduce exposure to proinflammatory factors, lower the risk of NEC, and support physiological maturation of the intestinal barrier [19,21].

Exclusively human milk–based diets have gained particular interest in tertiary referral centers caring for infants at the highest risk of complications. An increasing number of reports suggest that this approach may confer benefits not only by reducing the incidence of complications such as NEC, but also by improving feeding tolerance and long-term developmental outcomes [23-25].

3.2 Biological Mechanisms Underlying the Potential Benefits of HMBF

3.2.1 Immaturity of the Intestinal Barrier

In preterm infants, the intestinal barrier is structurally and functionally immature. This immaturity is manifested by increased epithelial permeability and a reduced capacity to protect against microbial invasion. Such conditions facilitate bacterial translocation and the passage of microbial products into the systemic circulation, leading to excessive activation of inflammatory pathways. These mechanisms play a central role in the pathogenesis of NEC [26,27].

3.2.2 Effects of Cow's Milk Proteins

Cow's milk proteins may amplify inflammatory responses through activation of toll-like receptors (TLRs), components of the innate immune system responsible for recognizing microbial structures and initiating inflammatory cascades. In preterm infants, excessive stimulation of these receptors, combined with increased intestinal permeability, may lead to uncontrolled immune activation. This results in an inflammatory response that is disproportionate to the stimulus and, instead of providing protection, may cause tissue injury and exacerbate disease processes [28,29].

3.2.3 Bioactive Components of Human Milk

Human milk contains numerous bioactive components, including lactoferrin, oligosaccharides, immunoglobulins, and growth factors, which support maturation of the intestinal barrier and modulate inflammatory responses. These components enhance intestinal defense mechanisms and limit excessive immune activation. Importantly, these bioactive properties are preserved in diets based on HMBF [30,31].

3.2.4 Gut Microbiota

The type of feeding has a significant impact on the development of the gut microbiota in preterm infants. Diets based exclusively on human milk promote the dominance of bacterial populations with potentially protective profiles, supporting intestinal maturation and limiting the development of adverse inflammatory responses [32,33].

3.2.5 The Gut–Immune Axis

The immune system of preterm infants is characterized by marked immaturity of both innate and adaptive immunity. The gut, as the largest immune organ in the body, plays a key role in shaping immune responses, and its proper maturation is closely dependent on the type of nutrition. Components of human milk influence cytokine expression, the maturation of regulatory T lymphocytes, and the suppression of excessive proinflammatory immune pathways. Preservation of these mechanisms in diets based on HMBF may be crucial in reducing the risk of excessive inflammatory responses characteristic of NEC and late-onset sepsis [30,34].

3.3 NEC

NEC is one of the most severe gastrointestinal diseases of the neonatal period, occurring predominantly in preterm infants, especially those with VLBW and ELBW. The disease is characterized by an acute inflammatory process leading to intestinal injury and, in severe cases, to bowel necrosis, perforation, sepsis, and the need for surgical intervention. NEC is associated with high mortality and significant long-term complications, including growth failure, short bowel syndrome, and adverse neurodevelopmental outcomes [24,26-28].

The increased susceptibility of preterm infants to NEC results from gastrointestinal immaturity, impaired intestinal barrier function, an underdeveloped immune response, and abnormal gut microbiota colonization. Perinatal factors, such as episodes of hypoxia and intestinal ischemia, also play an important role. Numerous studies indicate that feeding practices are a key factor in NEC pathogenesis, and that human milk feeding significantly reduces the risk of NEC compared with formula-based feeding [24,25-27,31,35].

In this context, increasing interest has focused on the use of HMBF. Available data suggest that their use, particularly within exclusively human milk–based diets, may be associated with a lower risk of NEC compared with BMBF. This effect is most pronounced in ELBW infants; however, not all studies demonstrate statistically significant differences, underscoring the need for further high-quality randomized controlled trials [19,21-23].

Although BMBF effectively increases protein and energy intake, they may alter the biological properties of human milk. The presence of foreign proteins and the absence of natural bioactive components characteristic of human milk may enhance intestinal inflammatory responses and promote unfavorable microbiota colonization, which in some studies has been associated with an increased risk of NEC. Although the evidence is not conclusive, these observations form part of the rationale for exclusively human milk–based diets using human-derived fortifiers [19-22].

A comparison of the effects of HMBF and BMBF on NEC risk and other relevant clinical outcomes in preterm infants is presented in Table 1.

Table 1. HMBF vs. BMBF – NEC and Other Clinical Outcomes [16,19,21,23,31]

Clinical parameter	HMBF	BMBF
Overall NEC risk	Lower or comparable; protective trend	Higher risk in some studies
Surgically treated NEC	Less frequently observed	More frequently reported
Effect in ELBW infants	Greatest potential benefit	Higher risk of intestinal complications
Feeding tolerance	Better tolerance, fewer intolerance episodes	More frequent intolerance symptoms
Infection/sepsis	Possible reduction in risk	No protective effect
Weight gain	Variable; sometimes slower without individualization	Often faster weight gain
Bioactive composition	Presence of immunological factors and HMOs	Lack of natural protective components
Quality of evidence	Low to moderate (limited RCTs)	Greater availability of comparative data
Cost and availability	High cost, limited availability	Lower cost, widely available

3.4 Sepsis and Other Complications

Sepsis and other complications in preterm infants have a multifactorial etiology; therefore, the impact of a single nutritional component, such as HMBF, is difficult to determine conclusively. The most common complications include late-onset sepsis, BPD, and retinopathy of prematurity (ROP), all of which can significantly affect infant health and development. Late-onset sepsis occurs after 72 hours of life and increases the risk of shock and organ dysfunction. BPD results from chronic lung injury in preterm infants requiring prolonged ventilatory support, while ROP is a disorder of retinal vascular development that may lead to visual impairment. To date, studies have not demonstrated a clear difference in the incidence of these complications between infants fed with HMBF and those receiving BMBF, although HMBF continues to be evaluated for its potential benefits in supporting development and feeding tolerance [19,22,36].

3.5 Safety and Limitations of HMBF Use

Despite potential clinical benefits, the use of HMBF is associated with certain limitations. These products undergo pasteurization, which may lead to partial loss of some bioactive components of human milk. In addition, their nutritional composition may vary between production batches [11,16,30].

Limited availability and high costs represent further challenges, potentially resulting in unequal access to this form of nutrition in clinical practice. Long-term studies evaluating the effects of HMBF on neurodevelopmental and metabolic outcomes in school-age children and adults are also lacking [14-16,23].

Some studies have reported slower weight gain during the first weeks of life, which may raise concerns among clinicians. This underscores the need for individualized nutritional strategies and close monitoring of growth parameters [12,13,16].

3.6 Growth and Quality of Growth

The impact of HMBF on growth and growth quality in preterm infants initially raised clinical concerns, as slightly slower weight gain was observed in the short term compared with BMBF [12,13]. However, long-term data indicate that these differences do not translate into significant deviations in length, head circumference, or body composition [16]. Moreover, the use of HMBF is associated with improved feeding tolerance and a lower risk of intestinal complications, which may indirectly support optimal physical development [23,24]. These findings suggest that HMBF provides safe and effective nutritional support for preterm infants, achieving growth outcomes comparable to traditional fortifiers while offering potential additional clinical benefits.

3.7 Mortality

Meta-analyses suggest that the use of HMBF may be associated with a potential reduction in mortality among preterm infants, although available data remain limited and require further investigation. The precise mechanisms underlying this effect are not yet fully understood, but likely include reduction of subclinical inflammatory processes, improved feeding tolerance, and a decreased risk of gastrointestinal complications such as NEC. Through these beneficial effects, HMBF may indirectly contribute to improved clinical stability and survival outcomes [19,21]. Although larger studies are needed, current evidence indicates that HMBF represents a promising nutritional strategy that not only provides nutrients comparable to those delivered with maternal milk but may also contribute to improved overall clinical outcomes in preterm infants.

3.8 Economic and Organizational Aspects

Despite relatively high direct costs associated with the use of HMBF, its implementation may generate significant indirect savings in the care of preterm infants. These benefits primarily result from a potential reduction in severe complications such as NEC, shorter hospital stays, and a decreased need for surgical interventions. Reduced burden on neonatal intensive care units may also contribute to more efficient use of medical personnel and equipment resources. Furthermore, the use of HMBF may improve quality of care by reducing complication rates and hospitalizations, which in the long term may offset the higher costs of the product itself [16,23,24,26]. Economic analyses therefore suggest that although HMBF entails higher direct costs, potential savings resulting from reduced complications and shorter hospitalizations may render its use cost-effective from a healthcare system perspective.

3.9 Practical Implications

The greatest benefits of HMBF use are observed in ELBW infants and in patients with additional risk factors for NEC. Implementation of this strategy requires close collaboration among neonatal teams, human milk banks, and clinical dietitians [11,16].

In clinical practice, the decision regarding the choice of human milk fortifier should be individualized, taking into account gestational age, birth weight, feeding tolerance, and product availability. The most significant benefits of HMBF appear to be achieved in ELBW infants and those at increased risk of NEC [11,19,21,22].

4. Discussion

The present review summarizes current evidence regarding the clinical benefits and limitations of human milk–based fortifiers in preterm infants, with particular emphasis on the most vulnerable population of infants with VLBW and ELBW. Overall, available data suggest that the use of HMBF, especially within an exclusively human milk–based diet, may provide important clinical advantages compared with traditional bovine milk–based fortifiers.

One of the most consistently reported benefits is the potential reduction in the incidence of necrotizing enterocolitis [19,21,24]. NEC remains one of the most severe complications of prematurity, associated with high mortality and long-term morbidity. Several observational studies and meta-analyses indicate that diets based exclusively on human milk, including the use of HMBF, may reduce exposure to proinflammatory bovine proteins and support the development of a more favorable intestinal environment. This effect is particularly relevant in ELBW infants, who have the highest baseline risk of intestinal complications.

The biological plausibility of these findings is supported by the presence of numerous bioactive components in human milk, including oligosaccharides, lactoferrin, immunoglobulins, and growth factors [30,31]. These compounds contribute to the maturation of the intestinal barrier, modulation of immune responses, and promotion of a beneficial gut microbiota [32,33]. Preservation of these properties within exclusively human milk–based diets may therefore play an important role in limiting excessive inflammatory activation within the immature gastrointestinal tract.

Another important aspect discussed in the literature concerns growth outcomes in infants receiving HMBF. Some studies have reported slightly slower weight gain during the early postnatal period when compared with BMBF [12,13,16]. However, these short-term differences do not appear to translate into clinically meaningful differences in long-term growth parameters, including length, head circumference, and body composition. This suggests that early differences in weight velocity may reflect variations in nutrient composition or feeding tolerance rather than true growth impairment.

Importantly, current evidence indicates that the incidence of other major complications of prematurity, such as late-onset sepsis, bronchopulmonary dysplasia, and retinopathy of prematurity, is generally comparable between infants receiving HMBF and those receiving BMBF [19,22,36]. While some studies suggest a potential reduction in infection risk, the available data remain inconclusive and further well-designed randomized trials are required.

Despite the promising findings, several limitations should be considered. First, a significant proportion of available evidence is derived from observational studies or single-center cohorts, which may introduce bias and limit generalizability [19,21]. Second, the relatively high cost and limited availability of HMBF remain important barriers to widespread implementation in many healthcare systems. Finally, long-term follow-up data evaluating neurodevelopmental and metabolic outcomes in children exposed to HMBF are still limited.

Future research should focus on large multicenter randomized controlled trials comparing different fortification strategies in preterm infants. Additional studies evaluating individualized fortification approaches, long-term developmental outcomes, and cost-effectiveness are also needed to better define the role of HMBF in neonatal nutritional practice.

Overall, the available evidence supports the concept that preservation of an exclusively human milk–based diet may represent an important strategy for improving clinical outcomes in the most vulnerable preterm infants.

5. Conclusions

HMBF represents a promising nutritional strategy for preterm infants, particularly those with VLBW and ELBW. Current evidence suggests that HMBF may contribute to a reduction in the risk of necrotizing enterocolitis and improved feeding tolerance while preserving the beneficial bioactive properties of human milk. Although weight gain during the first weeks of life may be slightly slower compared with BMBF, no significant adverse effects on length, head circumference, or overall physical development have been observed.

HMBF may also be associated with a potential reduction in mortality among preterm infants, although further high-quality studies are required. Implementation of exclusively human milk–based diets requires close collaboration among neonatal care teams, human milk banks, and clinical dietitians, as well as appropriate education of parents and healthcare personnel, to maximize clinical benefits and ensure safe nutrition support for the most vulnerable newborns.

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Author's Contributions:
Conceptualization: Dębczak Julia Agnieszka
Methodology: Krajewska Agnieszka, Dębczak Julia Agnieszka
Software: Korzeniewska Agnieszka, Dębczak Julia Agnieszka
Check: Krajewska Agnieszka, Łuczak Karolina, Kowalik Adrianna
Validation/Check: Malicka Natalia, Korba Magdalena
Formal Analysis: Tłustochowicz Katarzyna, Dębczak Julia Agnieszka
Investigation: Łuczak Karolina, Polkowska Wiktoria
Resources: Malicka Natalia, Dębczak Julia Agnieszka
Data curation: Dębczak Julia Agnieszka, Kowalik Adrianna, Korba Magdalena
Writing -rough preparation: Łuczak Karolina, Dębczak Julia Agnieszka
Writing -review and editing: Korzeniewska Agnieszka, Polkowska Wiktoria
Supervision/Project Administration: Tłustochowicz Katarzyna, Dębczak Julia Agnieszka

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