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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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USE OF HUMAN MILK FORTIFIERS IN PRETERM INFANTS – STRATEGIES, BENEFITS AND CLINICAL SIGNIFICANCE: A LITERATURE REVIEW

Alicja Stryczek-Schlusche *(Corresponding Author, Email: alicja.stryczek@gmail.com)*
University Clinical Hospital in Opole, al. W. Witosa 26, 45-401 Opole, Poland
ORCID ID: 0009-0005-3033-1083

Oliwia Gugała
University Clinical Hospital No. 2 PMU in Szczecin, Powstańców Wielkopolskich 72 St, 70-111 Szczecin, Poland
ORCID ID: 0009-0002-4081-4140

Kamil Nowak
Specialist Hospital No. 4 in Bytom, al. Legionów 10, 41-902 Bytom, Poland
ORCID ID: 0009-0001-2539-3360

Hanna Paszkiewicz
5th Military Hospital with Polyclinic in Cracow, Wrocławska 1-3, 30-901 Kraków, Poland
ORCID ID: 0009-0007-6536-3311

Patryk Kowalczyk
10th Military Research Hospital and Polyclinic, Independent Public Healthcare Centre in Bydgoszcz, Powstańców Warszawy 5, 85-681 Bydgoszcz, Poland
ORCID ID: 0009-0009-7303-8185

Bartłomiej Trzciński
10th Military Research Hospital and Polyclinic, Independent Public Healthcare Centre in Bydgoszcz, Powstańców Warszawy 5, 85-681 Bydgoszcz, Poland
ORCID ID: 0009-0007-1309-0470

Igor Winogrodzki
Military Institute of Aviation Medicine, Krasińskiego 54/56, 01-755 Warsaw, Poland
ORCID ID: 0009-0009-0751-6636

Aleksandra Magdalena Furczyńska
Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland
ORCID ID: 0009-0009-3165-8247

Filip Bracichowicz
Military Institute of Aviation Medicine, Krasińskiego 54/56, 01-755 Warsaw, Poland
ORCID ID: 0009-0008-6661-5450

Aleksandra Gęsińska
Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź, Poland
ORCID ID: 0009-0005-6062-4995

ABSTRACT

In Poland, 7–8% of newborns are born preterm, a condition linked to a range of health complications. Adequate nutrition plays a vital role in caring for preterm infants, fostering growth and development and helping prevent metabolic complications. Although breast milk is the optimal source of nutrients and immunological factors, its composition may not fully meet the increased nutritional demands of preterm infants. In such cases, human milk fortifiers (HMFs) are used to provide additional protein, energy, minerals, and vitamins. This article reviews the different types of HMFs, their nutritional composition, and the guidelines for their use. The benefits of fortification are also presented, including improved weight gain, better bone mineralization, and prevention of nutritional deficiencies. HMFs are well tolerated and safe, and their use constitutes an important element of enteral nutrition in preterm infants.

KEYWORDS

Preterm Infants, Breast Milk, Preterm Formula, Fortification of Human Milk, Prematurity, Low Birth Weight Infants, Nutrition

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Introduction

Preterm birth, defined as delivery before completing 37 weeks of gestation, remains a major challenge in modern neonatology. In Poland, about 7–8% of all live births are preterm [1]. These infants face a heightened risk of various health complications, including respiratory failure, gastrointestinal immaturity, neurological disorders, ophthalmic issues, and higher mortality rates. Providing proper nutrition is crucial for creating the best environment for continued growth and development. Proper nutritional support not only fosters adequate growth and physical development but also helps prevent complications linked to prematurity [1]. This review looks at the most up-to-date information about when, how, for how long, and in what way HMF is used, highlighting new methods and pointing out areas where more research is needed.

Importance of Human Milk and Nutritional Needs of Preterm Infants

Breast milk is a crucial component of infant nutrition. It contains immune-active components such as B and T lymphocytes, neutrophils, macrophages, and immunoglobulins. Additionally, human milk provides beneficial bacteria that colonize the infant's gut, aiding digestion, vitamin production, and the development of innate immunity [2]. Preterm infants have increased nutritional needs for energy, protein, calcium, phosphorus, and iron. Mother's own milk and donor human milk (DHM) alone may not meet these demands, potentially leading to nutrient deficiencies and impaired growth and development [3,4]. While breast milk is regarded as the gold standard for neonatal nutrition, its composition may not fully meet the needs of preterm infants. Human milk fortifiers (HMFs) are commonly employed to improve growth and developmental outcomes in this population [5,6].

Types of Fortifiers and Principles of Use

HMFs are categorized based on their protein source—bovine, human, or donkey—and their nutrient composition. Single-nutrient fortifiers are primarily used for extremely low birth weight infants [4]. Leading scientific bodies, including the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the World Health Organization (WHO), and the American Academy of Pediatrics (AAP), recommend using HMF for breastfed preterm infants weighing ≤1800 g. Fortification usually begins when enteral feeding reaches 50–100 mL/kg of body weight per day [4].

Comparison of Selected Human Milk Fortifiers Available in Poland [7,8] Table 1

Table 1

Nutrient (per 1g sachet/25 ml milk)	BEBILON HMF	Nestlé PreNAN
Energy	18.1 kJ / 4.3 kcal	18.2 kJ / 4.3 kcal
Fat	0.18 g	0.18 g
DHA	1.2 mg	1.37 mg
Linoleic acid	2.7 mg	8.38 mg
Carbohydrates	0.37 g	0.32 g
Protein	0.33 g	0.36 g
Salt	0.02 g	0.02 g
Vitamin A	58 µg	83.2 µg
Vitamin D	1.38 µg	0.88 µg
Vitamin E	0.88 mg	0.94 mg
Vitamin K	4.09 µg	1.88 µg
Vitamin C	2.97 mg	4.69 mg
Vitamin B1	0.03 mg	0.04 mg
Vitamin B2	0.04 mg	0.05 mg
Niacin	0.57 mg	0.35 mg
Vitamin B6	0.03 mg	0.03 mg
Folic acid	7.5 µg	9.38 µg
Vitamin B12	0.05 µg	0.05 µg
Biotin	0.62 µg	0.82 µg
Pantothenic acid	0.19 mg	0.16 mg
Sodium	8.24 mg	9.18 mg
Potassium	5.75 mg	12.1 mg
Calcium	17.24 mg	18.9 mg
Phosphorus	9.49 mg	11.0 mg
Magnesium	1.25 mg	1 mg
Iron	≤0.01 mg	0.45 mg
Choline	0.19 mg	2.02 mg

Strategies for the Fortification of Human Milk in Preterm Infant:

Start Time of Breast Milk Fortification

The timing for starting human milk fortification in infants is a matter of debate, with no agreement based on high-quality evidence. Early fortification—initiated when enteral feeds reach 20 mL/kg/day or even with the very first feed—has been associated with increased protein intake without raising the risk of adverse events such as NEC or feeding intolerance [12-14]. For example, Shah et al. reported higher protein intake with early fortification [14], and Ginovart noted greater increases in head circumference and weight among infants who received early fortification [14]. However, studies that look at all the research together have not found much or any effect on how much a baby grows, how long they stay in the hospital, or how often they get NEC, when compared to starting formula at a higher amount, like 100 mL per kilogram of body weight each day [12,14]. A Cochrane review found no significant difference in linear growth, head circumference, or time to regain birth weight between early and late fortification groups [12]. As a result, NICU practices differ significantly, and existing evidence is not strong enough to support a single, standardized start time.

Duration of Breast Milk Fortification

The optimal length of fortification is similarly undefined. In most NICUs, babies keep getting fortified until they are close to their full gestational age, usually around 34 to 36 weeks, which matches the time when their growth slows down naturally towards the end of pregnancy [12]. However, in-hospital growth deficits and macro- and micronutrient gaps may justify continued fortification beyond term PMA or after discharge [12]. Post-discharge fortification approaches involve either adding bovine-based transitional powdered formula to expressed breast milk or offering 1–2 bottles daily of post-discharge transitional formula [12]. Continued fortification post-discharge has the potential to reduce postnatal growth failure and support bone mineralization, but decisions must be individualized based on growth trajectory, clinical stability, and caregiver capacity [12].

Fortification Methods: Standard vs. Individualized

Standard vs. Individualized Fortification

Standard fortification (SF) involves adding a fixed amount of multicomponent fortifier to a set volume of human milk, assuming constant protein and energy content [10,11]. While SF improves in-hospital weight, length, and head circumference gains compared with unfortified milk [11], it often fails to meet recommended protein intakes due to natural variability and decline in breast milk protein content over lactation [11]. This limitation contributes to high rates of extrauterine growth restriction (EUGR), reported in up to 58–81% of PTIs at discharge [11]. Such fortification can be used as the first step in the nutrition of premature infants, but over time the needs of a given infant should be adjusted [4].

Individualized fortification (IF) aims to tailor nutrient supplementation to the infant's needs and milk composition. Two main approaches are recognized:

Adjustable fortification (AF) tailors protein supplementation according to metabolic indicators like blood urea nitrogen (BUN) levels [11]. AF has been associated with improved growth and potentially better neurodevelopmental outcomes compared to SF [11]. BUN can be calculated from urea concentration, depending on the unit:

- BUN[mg/dl]=2.8*urea [mmol/l]
- BUN[mg/dl]=urea [mg/dl]/2.14
- BUN[mmol/l]=0.357*urea [mg/dl]

If BUN is < 10mg/dl, protein intake should be increased; if BUN is > 16 mg/dl, protein intake should be decreased [4]

Targeted fortification (TF) involves frequent analysis of breast milk's macronutrient content, allowing for accurate supplementation to achieve ESPGHAN nutrient recommendations [11]. Targeted fortification (TF) has demonstrated improvements in growth quality—such as fat-free mass, length, and head circumference—and is generally well tolerated; however, the requirement for specialized equipment and labor limits its wider adoption [11]. TF has been shown to enhance growth quality such as fat-free mass, length, and head circumference and is generally well tolerated; however, its need for specialized equipment and labor restricts its broader use [11]. Milk analyzers, however, are costly and demand regular, precise calibration, which limits their widespread adoption [4]. Meta-analyses generally support that both AF and TF yield better growth outcomes than SF, although direct comparisons between AF and TF have produced inconsistent results [11].

Benefits of Fortifying Human Milk

Using HMF instead of unfortified human milk in preterm infants primarily helps prevent nutrient deficiencies. A meta-analysis by Campbell-Yeo et al. showed the greatest weight gain outcomes when breast milk or donor milk was fortified with HMF [13].

Protein deficiency, which typically becomes apparent between 8 and 12 weeks of life, results from a decline in protein content in maternal milk. In research conducted by Hemmati and Ghassemzadeh, protein supplementation of up to 4–5 g/kg/day in infants

<1500 g significantly improved anthropometric parameters without adverse effects [12]. Due to insufficient calcium and phosphorus in maternal milk, HMF addition helps prevent poor bone mineralization, rickets, and fractures typically seen around 4–5 months of age. Other metabolic complications that can be prevented include hyponatremia (usually occurring in weeks 4–5 of life) and zinc deficiency (between 2–6 months). Iron and vitamin D are extra supplemented to preterm infants to prevent deficiency. Vitamin A deficiency in human or donor milk may increase the risk of retinopathy of prematurity due to the high demand of premature infants [14]. Therefore, supplementing with HMF may prevent deficiency, but there is no clear research on the appropriate amount.

Safety and Tolerance

Both bovine- and human-based fortifiers are generally well tolerated; however, human milk-based HMFs are considered safer in terms of reducing the risk of necrotizing enterocolitis (NEC) [15]. Numerous studies confirm good gastrointestinal tolerance and no significant effects on electrolyte metabolism (e.g., calcium, phosphorus) in preterm infants [12,16].

Summary

Major scientific organizations like ESPGHAN, WHO, and AAP recommend human milk fortifiers as essential elements of nutritional care for preterm infants. They combine the natural benefits of human milk with the necessary nutrient enrichment required for optimal growth and development in preterm neonates. Although individualized fortification approaches have benefits compared to standard methods, each comes with its own limitations. Emerging techniques offer promising alternatives but require further comprehensive validation. Future research should prioritize clinical trials evaluating safety, effectiveness, and long-term outcomes to advance nutritional care in neonatal intensive care units (NICUs).. Additionally, more large-scale randomized controlled trials are necessary to better define guidelines regarding the timing, duration, and type of fortification used.

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Author's contribution:

Research concept and design – Alicja Stryczek-Schlusche, Oliwia Gugała, Kamil Nowak, Hanna Paszkiewicz.

Data collection and/or compilation – Oliwia Gugała, Patryk Kowalczyk, Bartłomiej, Trzciński, Igor Winogrodzki, Aleksandra Gęsińska, Aleksandra Magdalena Furczyńska.

Data analysis and interpretation – Alicja Stryczek-Schlusche, Oliwia Gugała, Filip Bracichowicz, Kamil Nowak.

Writing – Alicja Stryczek-Schlusche, Hanna Paszkiewicz, Patryk Kowalczyk, Igor Winogrodzki, Bartłomiej Trzciński.

Critical review of the article – Oliwia Gugała, Aleksandra Gęsińska, Aleksandra Magdalena Furczyńska, Filip Bracichowicz.

Supervision, project administration – Alicja Stryczek-Schlusche,

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