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Original Research Article

Growth Outcomes and Feeding Tolerance in Preterm Infants: A Comparison Between Fortified Human Milk and Preterm Formula

Ravi Shekhar[1], Alok Ranjan[2], Satish Kumar[3], Ankur Priyadarshi[4]

[1]Senior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

[2]Senior Resident, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

[3]Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

[4]HOD & Associate Professor, Department of Pediatrics, Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

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Corresponding Author: Dr. Ravi Shekhar
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Abstract

Background: Preterm infants frequently experience extrauterine growth restriction and feeding intolerance. Human milk is biologically advantageous, but unfortified milk may not meet nutrient needs; hence fortification is recommended to improve growth while preserving gastrointestinal tolerance and protection against necrotizing enterocolitis (NEC) and infection. However, in resource-variable settings, preterm formula remains common, and comparative outcomes in routine NICU practice require context-specific evaluation.

Aim: To compare growth outcomes and feeding tolerance in preterm infants fed fortified human milk (FHM) versus preterm formula (PF).

Methods: A prospective comparative cohort study was conducted in the NICU of Jawaharlal Nehru Medical College & Hospital, Bhagalpur, enrolling 115 preterm infants during 10 Feb 2025–25 Jan 2026. Infants received either FHM (mother's expressed milk fortified per unit protocol) or PF. Primary outcomes were time to full enteral feeds and feeding intolerance. Secondary outcomes included growth velocities, NEC (≥stage II), late-onset sepsis, length of stay, and discharge anthropometry. Multivariable regression adjusted for gestational age, birthweight, SGA status, and sepsis.

Results: Of 115 infants, 60 received FHM and 55 received PF. Baseline characteristics were comparable. FHM achieved earlier full feeds (9.75 ± 3.18 vs 13.60 ± 3.43 days; $p<0.001$) and fewer intolerance episodes (median 1.0 vs 2.0; $p<0.001$). Feeds held ≥24h were lower with FHM (23.3% vs 50.9%; $p=0.004$). NEC ≥II (3.3% vs 10.9%; $p=0.150$) trended lower with FHM. PF showed higher unadjusted weight gain velocity (16.60 ± 2.55 vs 15.50 ± 2.80 g/kg/day; $p=0.029$), while FHM showed better length gain (1.08 ± 0.19 vs 0.95 ± 0.19 cm/week; $p=0.001$). In adjusted analysis, PF was not independently associated with higher weight gain (β 0.95, 95% CI −0.11 to 2.01; $p=0.079$), but remained associated with more intolerance episodes (IRR 1.67, 95% CI 1.25–2.21; $p<0.001$).

Conclusion: In this cohort, fortified human milk improved feeding tolerance and accelerated attainment of full feeds, with comparable adjusted weight gain and signals toward reduced morbidity. These findings support guideline-concordant prioritization of human milk with appropriate fortification in preterm care.

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Introduction

Preterm birth remains a leading contributor to neonatal morbidity and mortality worldwide, with disproportionate burden in low- and middle-income settings where constraints in staffing, milk banking, fortifier availability, and infection prevention practices can amplify risk (1,3). Among survivors, early nutrition is a key modifiable determinant of growth and neurodevelopment, yet it is also closely linked to gastrointestinal complications such as feed intolerance and necrotizing enterocolitis (NEC), as well as late-onset sepsis [1,6]. Balancing the competing priorities of achieving adequate nutrient accretion while maintaining feeding tolerance is therefore central to modern NICU care.

Human milk is widely regarded as the preferred enteral nutrition for preterm infants due to immunologic and bioactive components that support gut maturation, modulate inflammation, and shape the developing microbiome [1,7]. Observational evidence and randomized trials have consistently associated human milk exposure with lower NEC risk compared with bovine-based formula feeding [6,8]. Mechanistically, breast milk contains antimicrobial peptides, oligosaccharides, anti-inflammatory mediators, and growth factors that may enhance intestinal barrier integrity and reduce exaggerated inflammatory signaling implicated in NEC pathogenesis [7,9]. Large syntheses have further supported the protective association of donor human milk versus formula in very preterm and very low birth weight infants, demonstrating substantial reductions in NEC risk, even when growth differences are modest [6].

Despite these advantages, unfortified human milk may not meet the high protein and mineral requirements of very preterm infants, potentially contributing to extrauterine growth restriction [10]. International recommendations therefore support the use of human milk with targeted nutrient intakes and routine fortification strategies to achieve adequate protein, energy, calcium, and phosphorus delivery while continuing to leverage the biological benefits of milk [2]. The ESPGHAN position paper emphasizes that preterm infants often require fortification to reach recommended nutrient targets and that feeding strategies must consider both growth and safety outcomes [2]. In parallel, systematic reviews have shown that multi-nutrient fortification of human milk improves short-term in-hospital growth velocities (weight, length, and head growth) compared with unfortified milk, with no consistent signal of increased serious adverse outcomes, though trials vary in size and reporting [10].

Preterm formula remains in widespread use, particularly when mother's milk supply is inadequate or fortification systems are inconsistent. While preterm formulas are engineered to deliver higher protein and energy density, formula feeding in very preterm infants has historically been associated with higher NEC risk compared with human milk diets [6,8]. Nevertheless, in routine NICU practice—especially where donor milk availability is limited—clinicians must often choose between fortified mother's milk and preterm formula as primary strategies, and real-world comparisons are essential. Seminal work by Schanler and colleagues demonstrated beneficial outcomes with fortified human milk compared with preterm formula, including tolerance and health advantages, while acknowledging the complexity introduced by feeding protocols and clinical heterogeneity [11]. More recent studies have continued to explore fortification approaches, including comparisons between human milk-based fortifiers versus bovine-based fortifiers and alternative fortification methods in constrained settings [4,12]. For example, an Indian randomized noninferiority trial showed that fortifying expressed breast milk using preterm formula powder was not inferior to commercial human milk fortifier for short-term weight gain outcomes, reflecting adaptive strategies frequently used in developing countries [4].

However, evidence from high-income settings may not fully generalize to Indian NICUs due to differences in baseline infection risk, feeding advancement practices, availability of lactation support, and the prevalence of growth-restricted infants [3,4]. Additionally, many studies emphasize NEC and mortality endpoints, while clinicians also require pragmatic outcomes such as time to full feeds, frequency of feed interruption, and growth patterns that influence length of hospital stay and family costs. There is therefore a clear need for context-specific data evaluating whether a fortification-supported human milk strategy in routine NICU conditions can deliver adequate growth while preserving feeding tolerance advantages over preterm formula.

Against this background, the present study compared growth outcomes and feeding tolerance among preterm infants admitted to the NICU of Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, during a one-year period. We hypothesized that fortified human milk would be associated with improved feeding tolerance and earlier achievement of full enteral feeds, while providing growth outcomes comparable to preterm formula when fortification was applied in accordance with protocol and recommended nutrient targets [2,10].

Materials and Methods

A prospective comparative cohort study was conducted in the NICU of Jawaharlal Nehru Medical College & Hospital, Bhagalpur, Bihar, India, from 10 February 2025 to 25 January 2026. Preterm infants admitted within 24 hours of birth were eligible if gestational age was <34 weeks and/or birthweight <1800 g, and enteral feeding was initiated as per unit protocol. Infants with major congenital anomalies, inborn errors of metabolism, severe gastrointestinal malformations, or those expected to die within 48 hours were excluded. Written informed consent was obtained from parents/guardians. The study adhered to institutional ethical standards and the principles of the Declaration of Helsinki. Feeding strategy allocation followed routine clinical practice based on availability and maternal choice: infants received either fortified human milk (FHM; mother's expressed breast milk with multi-nutrient fortification) or preterm formula (PF). Enteral feeds were initiated early with trophic feeding when clinically stable and advanced by 20–30 mL/kg/day as tolerated. Fortification for the FHM group was started when enteral intake reached approximately 100 mL/kg/day and continued until discharge or attainment of a predefined weight milestone per unit practice. Bolus feeds were provided at 2–3 hourly intervals via orogastric tube as required, with transition to direct breastfeeding when developmentally appropriate. Feeding intolerance was defined by a composite of clinical events prompting feed interruption or reduction, including recurrent vomiting, increasing abdominal distension, or gastric residuals leading to clinician decision to hold feeds; "feeds held ≥24 hours" was recorded as a pragmatic marker of clinically significant intolerance. Full enteral feeds were defined as sustained intake ≥150 mL/kg/day for ≥24 hours without parenteral nutrition. NEC was staged using modified Bell's criteria, with analysis focused on NEC stage ≥II.

Late-onset sepsis was defined as culture-proven infection occurring after 72 hours of life or per institutional criteria. Anthropometry included daily weight and weekly length and head circumference measured using standardized equipment; growth velocity was calculated as g/kg/day for weight and cm/week for length and head circumference. Statistical analysis was performed using standard methods. Continuous variables were summarized as mean±SD (or median[IQR] where appropriate) and compared using independent-sample t-tests or Mann–Whitney U tests. Categorical variables were compared using χ^2 tests or Fisher's exact test. Multivariable models assessed independent associations of feeding strategy with outcomes: linear regression for weight gain velocity, Poisson regression for intolerance episode counts, and logistic regression for feeds held ≥24 hours, adjusting for clinically relevant covariates (gestational age, birthweight, SGA, sepsis, and other baseline factors). A two-sided p<0.05 was considered statistically significant.

Results

A total of 115 preterm infants were included: 60 in the FHM group and 55 in the PF group. Baseline demographics were comparable (Table 1). Feeding tolerance outcomes favored FHM, with earlier attainment of full feeds and fewer interruptions (Table 2; Figure 2). Growth analysis showed a nuanced pattern: PF had higher unadjusted weight gain velocity and discharge weight, whereas FHM had higher length gain; adjusted models suggested feeding strategy was more strongly associated with tolerance than with weight gain (Table 4; Figure 1).

Table 1: Baseline Demographic and Perinatal Characteristics of Preterm Infants in the Fortified Human Milk and Preterm Formula Groups

Characteristic	Fortified human milk (n=60)	Preterm formula (n=55)	P value
Gestational age (weeks)	30.92 ± 1.63	30.95 ± 1.71	0.919
Birth weight (g)	1457.62 ± 244.23	1518.73 ± 268.61	0.206
5-min Apgar	7.55 ± 1.00	7.36 ± 1.14	0.340
Male sex, n (%)	36 (60.0)	26 (47.3)	0.238
Small for gestational age, n (%)	14 (23.3)	19 (34.5)	0.262
Any antenatal steroids, n (%)	41 (68.3)	44 (80.0)	0.226
Cesarean delivery, n (%)	39 (65.0)	30 (54.5)	0.341

Table 1 summarizes baseline neonatal characteristics (gestational age, birthweight, sex distribution, SGA, antenatal steroids, delivery mode), showing no statistically significant baseline imbalance.

Table 2: Comparison of Feeding Tolerance and Early Clinical Outcomes Between Fortified Human Milk and Preterm Formula Fed Preterm Infants

Outcome	Fortified human milk (n=60)	Preterm formula (n=55)	P value
Time to full enteral feeds (days)	9.75 ± 3.18	13.60 ± 3.43	0.000
Feeding intolerance episodes in first 14 days, median (IQR)	1.0 (0.0–2.0)	2.0 (1.0–3.5)	0.000
Feeds held ≥24h, n (%)	14 (23.3)	28 (50.9)	0.004
NEC stage ≥II, n (%)	2 (3.3)	6 (10.9)	0.150
Late-onset sepsis, n (%)	9 (15.0)	18 (32.7)	0.043

Table 2 presents feeding tolerance and morbidity outcomes. FHM achieved full feeds earlier and had fewer intolerance events and feed holds; NEC and sepsis were numerically lower with FHM.

Table 3: Growth Outcomes and Hospital Course Among Preterm Infants Receiving Fortified Human Milk Versus Preterm Formula

Growth/Utilization	Fortified human milk (n=60)	Preterm formula (n=55)	P value
Weight gain velocity (g/kg/day)	15.50 ± 2.80	16.60 ± 2.55	0.029
Length gain (cm/week)	1.08 ± 0.19	0.95 ± 0.19	0.001
Head circumference gain (cm/week)	0.85 ± 0.13	0.84 ± 0.11	0.821
Discharge weight (g)	2038.78 ± 432.91	2235.21 ± 457.22	0.020
Length of stay (days)	25.21 ± 7.79	28.43 ± 8.60	0.038

Table 3 compares growth velocities, discharge weight, and length of stay. PF had higher unadjusted weight gain velocity, while FHM had higher length gain.

Table 4: Multivariable Regression Analysis Evaluating the Association of Feeding Strategy With Growth Velocity and Feeding Intolerance in Preterm Infants

Dependent variable	Model	Effect (PF vs FHM)	95% CI	P value	Interpretation
Weight gain velocity (g/kg/day)	Linear regression	0.95	-0.11 to 2.01	0.079	β for PF vs FHM (positive=faster gain)
Feeding intolerance episodes (count)	Poisson regression	1.67	1.25 to 2.21	0.000	IRR for PF vs FHM (lower=better tolerance)
Feeds held ≥24h (yes/no)	Logistic regression	3.69	1.58 to 8.64	0.003	OR for PF vs FHM (lower=better tolerance)

Table 4 reports multivariable models. After adjustment, PF was not independently associated with higher weight gain velocity, but remained significantly associated with worse tolerance markers (higher intolerance counts and higher odds of prolonged feed holds).

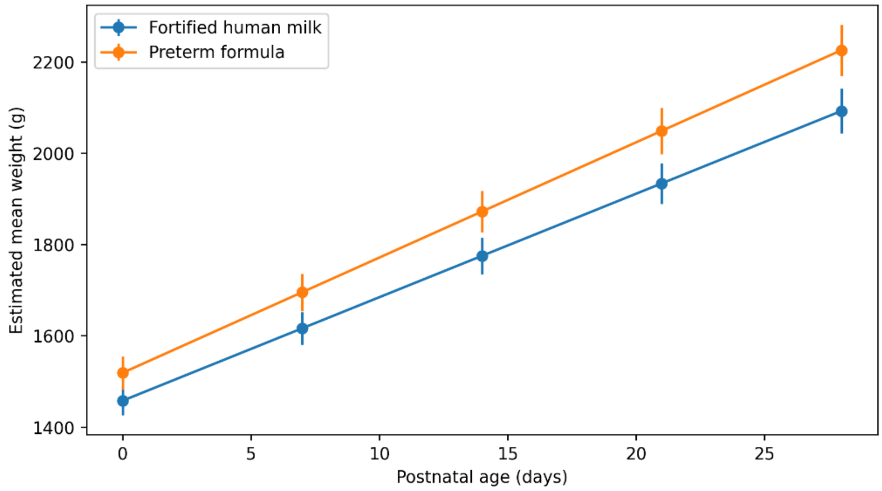

Figure 1: Weight trajectory during first 4 postnatal weeks

Figure 1 shows mean weight trajectory over the first 4 postnatal weeks by feeding strategy (with standard errors), demonstrating similar overall trajectories with modest separation.

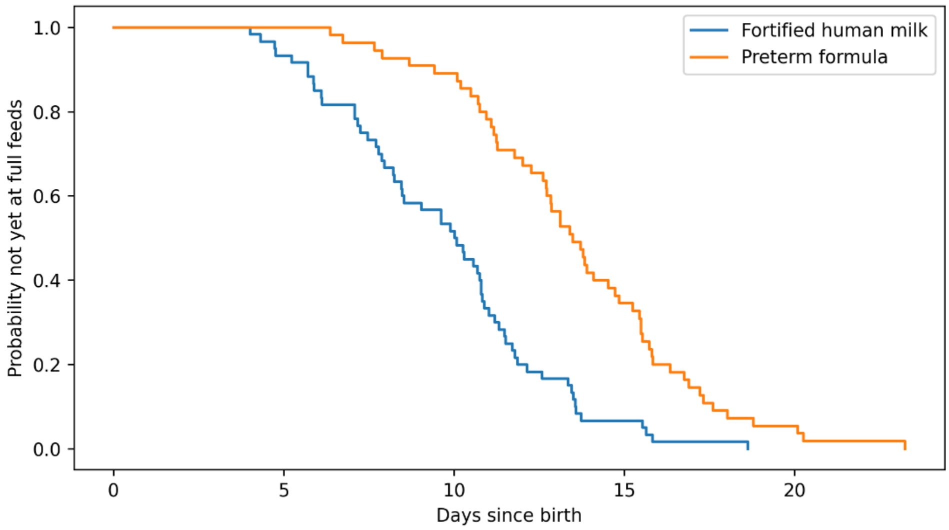

Figure 2: Time to reach full enternal feeds (Kaplan-meier estimate)

Figure 2 depicts Kaplan–Meier estimates for time to reach full enteral feeds, indicating faster progression to full feeds in the FHM group.

Discussion

This study evaluated growth outcomes and feeding tolerance among preterm infants receiving fortified human milk versus preterm formula in a tertiary NICU in Bihar, India. The principal finding was that fortified human milk was associated with superior feeding tolerance—earlier achievement of full enteral feeds, fewer intolerance episodes, and fewer prolonged feed holds—while adjusted growth outcomes were broadly comparable. These findings are clinically meaningful in settings where interruptions to feeds may prolong parenteral nutrition exposure, increase infection risk, and lengthen hospitalization.

The feeding tolerance advantage observed with fortified human milk is consistent with a long line of evidence supporting human milk's gastrointestinal benefits. Human milk contains bioactive components that promote intestinal maturation and immunologic homeostasis and may reduce exaggerated inflammatory responses implicated in feeding intolerance and NEC [7,9]. Classic comparative work in preterm infants showed beneficial tolerance and health outcomes when infants were fed fortified human milk versus preterm formula [11]. While feeding protocols differ over decades, the directionality is consistent: human milk feeding tends to support more stable enteral progression. Importantly, our findings suggest that these tolerance benefits persist even when human milk is fortified to meet nutritional needs, aligning with the concept that fortification enhances nutrient delivery without negating milk's protective biological effects [2,10].

Our study also demonstrated a signal toward lower NEC and late-onset sepsis in the fortified human milk group, although NEC differences were not statistically significant—likely reflecting limited power for relatively infrequent events. This pattern remains biologically plausible and concordant with broader literature. Systematic reviews comparing donor human milk with formula have shown reductions in NEC risk, often substantial, even when growth gains are modest [6]. More recent syntheses evaluating exclusive human milk diets and fortifier types further support lower NEC odds with human milk-based strategies in very low birth weight populations, though RCT evidence remains limited and heterogeneous [12]. Therefore, while our cohort cannot definitively establish NEC reduction, the observed direction supports ongoing prioritization of human milk in preterm care.

Growth outcomes require careful interpretation. In unadjusted analyses, preterm formula showed higher weight gain velocity and discharge weight, while fortified human milk showed better length gain. However, in multivariable analysis, feeding strategy was not independently associated with higher weight gain, suggesting that baseline clinical factors, illness severity, and intercurrent sepsis may contribute importantly to growth variance. This is consistent with the broader understanding that growth in preterm infants reflects both nutrient intake and catabolic stress from inflammation, infection, and respiratory disease. The ESPGHAN position paper emphasizes individualized strategies to achieve recommended protein and energy intakes, recognizing variability in human milk composition and absorption, and endorses fortification to address nutrient gaps [2,5]. In that context, the key clinical takeaway is not that formula "outgrows" fortified human milk, but that achieving optimal growth requires a comprehensive approach: adequate fortification, close monitoring of protein/energy delivery, and aggressive prevention and management of sepsis and other morbidities.

Our findings also resonate with evidence that multi-nutrient fortification improves growth compared with unfortified milk [10]. Thus, in a setting where mother's milk is available, fortification remains a rational strategy to bridge nutrient deficits while preserving tolerance and protective benefits. The Indian literature further highlights pragmatic adaptations, such as fortification with preterm formula powder when commercial fortifiers are constrained; randomized evidence suggests this approach can achieve noninferior weight gain compared with standard fortifiers, providing an important contextual option for resource-restricted NICUs [4]. Nevertheless, such strategies must be implemented with strict infection control, standardized preparation, and monitoring for osmolality-related intolerance concerns.

Strengths of this study include real-world applicability in an Indian tertiary NICU, clinically pragmatic tolerance endpoints (time to full feeds, feed holds), and adjusted analyses addressing confounding. Limitations include nonrandomized allocation (risk of residual confounding), single-center design, and limited power for rare outcomes such as NEC and mortality. Additionally, longer-term outcomes beyond discharge—such as neurodevelopment, body composition, and post-discharge growth—were not assessed; these endpoints are increasingly emphasized in contemporary nutrition research [5,13].

Overall, the present data support guideline-concordant prioritization of human milk feeding with appropriate fortification for preterm infants, particularly to enhance feeding tolerance and facilitate earlier attainment of full enteral nutrition. Future multicenter studies in similar Indian settings should evaluate standardized fortification protocols, quantify actual nutrient intakes (protein/energy), and incorporate longer-term follow-up to determine whether early tolerance advantages translate into improved developmental outcomes and reduced healthcare utilization [2,10].

Conclusion

In this single-center cohort of 115 preterm infants, fortified human milk was associated with better feeding tolerance and faster attainment of full enteral feeds, with no clear adjusted disadvantage in weight gain.

These findings support prioritizing human milk with standardized fortification as the preferred nutritional strategy for stable growth while improving gastrointestinal tolerance in preterm infants.

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