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Early Use of Liquid Human Milk Fortifier in Premature Newborns : Impact on Growth and Hospital Stay

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Abstract

Introduction: *Human milk is the feeding of choice for premature newborns; however, alone it does not meet the high protein, mineral, and energy requirements demanded by the accelerated postnatal growth of this age group. The use of fortifiers — particularly in liquid form — has demonstrated improved growth rates and a reduction in neonatal nutrition-related complications.*

Objective: *To assess the impact of early use of liquid human milk fortifier (LHMF) on somatometry (weight, height, and head circumference) and hospital stay in premature infants with a birth weight below 2,000 g.*

Materials and Methods: *Observational, retrospective, analytical, and longitudinal study using a nested case-control design within a historical cohort. Forty-four premature neonates (< 36 weeks of gestation, weight < 2,000 g) from Dr. José María Rodríguez General Hospital (HGDJMR) were included. Group 1 (n = 22, born in 2024) received exclusive human milk plus LHMF; Group 2 (n = 22, born in 2022) received exclusive unfortified human milk. Follow-up was conducted over four weeks. Descriptive statistics, Student's t-test, relative risk, and Pearson correlation were calculated (IBM SPSS v. 30; significance $p < 0.05$).*

Results: *At four weeks, Group 1 showed greater weight gain (+276.82 g, $p = 0.008$), greater height increase (+1.1 cm, $p = 0.033$), and greater head circumference growth (+0.83 cm, $p = 0.017$). Z-scores for all three variables were closer to 0 in Group 1. NICU stay was 8.64 days shorter and total hospitalization was 13.5 days shorter in Group 1, with statistically significant differences ($p < 0.001$). No cases of necrotizing enterocolitis were recorded in either group.*

Conclusions: *Early use of LHMF significantly improves somatic growth and reduces hospital stay in premature infants, representing a relevant clinical and economic benefit for neonatal intensive care units.*

Keywords : human milk, preterm infant, liquid human milk fortifier, neonatal growth, hospital stay, NICU.

Introduction

In our daily practice within the Neonatal Intensive Care Unit (NICU), one of the most persistent and challenging goals is achieving postnatal growth in premature infants at a rate comparable to what they would have experienced in utero. Human milk undoubtedly represents the first and best feeding option for these small patients; its immunological, bioactive, and neurodevelopmental benefits are widely recognized by the international scientific community [1, 2]. However, as the days in the unit go by, it becomes inevitable to observe that many of these infants — especially those with a birth weight below 1,500 g — do not meet expected growth targets when fed exclusively on unmodified breast milk [1].

This is not a failure on the part of the mother or of human milk itself; it is simply a well-documented physiological consequence. A growing premature infant requires between 3.5 and 4.5 g/kg/day of protein and between 110 and 135 kcal/kg/day of energy [3, 4] — values that standard human milk cannot provide at the feeding volumes these neonates tolerate. Additionally, calcium, phosphorus, iron, and fat-soluble vitamins are frequently found at concentrations insufficient to support the mineral accretion required by a rapidly developing skeleton [4, 5].

Human milk fortifiers were developed precisely as a response to this nutritional gap. The American Academy of Pediatrics establishes that multinutrient fortification should be considered the standard of care for premature infants weighing less than 1,500 g, given its association with better neurodevelopmental outcomes, lower infection rates, and a reduction in gastrointestinal complications [6]. However, the choice between powder and liquid format is not trivial: since 2002, FAO/WHO experts have highlighted the risk of microbial contamination — particularly by Salmonella enterica and Enterobacter sakazakii — associated with powdered products, recommending liquid ready-to-use formulations as a safer alternative [7].

Prior studies have documented that liquid human milk fortifier (LHMF) is not only safe and well tolerated, but may also yield better growth rates in weight, height, and head circumference compared with the powder format [8, 9]. Nevertheless, evidence from neonatal units in Mexico — where clinical conditions, patient characteristics, and available resources differ significantly from the settings described in the Anglo-Saxon literature — remains scarce. The present study was born from that concern: we wanted to know what happened with our own patients when LHMF was introduced early, and whether the benefits reported elsewhere could be replicated in our NICU.

The primary objective was to evaluate the impact of early LHMF use on somatometry — weight, height, and head circumference — and on hospital stay in premature newborns with a birth weight below 1,800 g cared for at Dr. José María Rodríguez General Hospital (HGDJMR), a unit belonging to the IMSS Bienestar program.

Materials and Methods

We designed an observational, retrospective, analytical, and longitudinal study with a nested case-control scheme within a historical cohort. The decision to use this design was driven by ethical and practical reasons: since LHMF was systematically implemented in our unit starting in 2024, it was not possible to prospectively randomize patients. We therefore used the records of an equivalent cohort of patients treated in 2022 — before the product was available — as a historical comparison group.

All premature neonates with a gestational age below 36 weeks and a birth weight under 2,000 g, born at HGDJMR and admitted to the NICU, Intermediate Neonatal Care Unit (INCU), or Growth and Development ward during the study periods were included. Neonates with major congenital malformations, inborn errors of metabolism, or those transferred from another unit with incomplete prior stay documentation were excluded. The final sample comprised 44 patients: 22 in Group 1 (LHMF + human milk, 2024 cohort) and 22 in Group 2 (exclusive unfortified human milk, 2022 cohort).

In both groups, enteral feeding was initiated according to the attending physician's guidelines. In Group 1, once the premature infant reached an enteral volume of 100 mL/kg/day, LHMF was added to each feeding (mean day of initiation: day 9.22 of hospitalization). The mother's own milk was used; when production was insufficient, donated human milk from the hospital's Human Milk Bank was provided. Each patient was followed for four consecutive weeks of hospitalization. Weight, height, and head circumference measurements were performed weekly by trained Nutrition and Nursing staff.

Statistical analysis was performed using IBM SPSS Statistics version 30. Measures of central tendency and dispersion were calculated for quantitative variables. Baseline comparability between groups was assessed using Student's t-test for independent samples. Differences in somatometric increments and days of hospital stay were also analyzed with the same test. Relative risk (RR) and Pearson correlation were calculated to explore associations. A p-value < 0.05 was defined as statistically significant. Weight, height, and head circumference Z-scores were obtained based on the Fenton 2013 postnatal growth reference tables for premature infants.

Results

Baseline Characteristics of the Sample

The total sample consisted of 44 patients: 24 males (54.5%) and 20 females (45.5%), distributed in identical proportions between both groups (12 males and 10 females per group). Gestational age ranged from 29 to 36 weeks, with a global mean of 32.364 ± 0.612 weeks, with no significant difference between groups (Student's t-test, p = 1.00). Birth weight across the full sample ranged from 985 to 2,075 g. Mean height and head circumference values per group, along with 95% confidence intervals, are presented in Table 1. Student's t-test found no statistically significant difference in any baseline variable between the two groups (p = 1.00 for all variables), confirming the comparability of both cohorts.

Table 1: Baseline characteristics of both groups at birth

Variable	Group 1 (n = 22)	Group 2 (n = 22)	p-value
Gestational age (weeks)	29–36	29–36	1.00
Mean ± SD (weeks)	32.364 ± 0.612	32.012 ± 0.712	1.00
Sex (M/F)	12 / 10	12 / 10	1.00
Weight (g)	1,500 ± 154 (1,246–1,654)	1,550 ± 250 (1,300–1,700)	1.00
Height (cm)	40.697 ± 0.804 (40.104–41.781)	40.977 ± 0.704 (40.172–41.880)	1.00
Head circumference (cm)	28.9 ± 0.508 (28.275–29.56)	28.8 ± 0.208 (28.075–29.38)	1.00

Week-by-Week Somatometric Evolution

When analyzing the growth trajectory over the four weeks of follow-up, we identified a clinically significant pattern. During the first week, both groups showed the expected physiological weight loss, virtually identical in magnitude (Group 1: −96.4 g; Group 2: −95.72 g; a difference of merely 0.63 g). This finding reinforces the baseline homogeneity of the sample and rules out the possibility that any subsequent differences could be attributed to differing starting conditions.

From the second week onward — when LHMF began to be systematically incorporated into Group 1's feedings — differences between the two groups became progressively more apparent. In week 2, weight gain was 142.95 g in Group 1 versus 93.18 g in Group 2. By week 3, that gap had widened further: 188.18 g vs. 91.81 g. At the end of week 4, Group 1 recorded a weekly increment of 205.9 g — more than double that of Group 2 (93.18 g). The mean final weight of Group 1 was 1,979.09 g compared with 1,702.27 g in Group 2, representing a between-group difference of +276.82 g at the end of the four-week period ($p = 0.008$). Height and head circumference followed a similar trend (Table 2).

The Z-scores at the end of follow-up clearly summarize the clinical relevance of these findings: in Group 1, the weight Z-score was −1.81 compared with −2.54 in Group 2; height Z-score −1.40 vs. −1.91; and head circumference Z-score −0.77 vs. −1.41. These values indicate that premature infants who received LHMF were considerably closer to the expected growth standards for their corrected gestational age at the end of follow-up.

Table 2: Weekly somatometric evolution and final comparative values

Week	Week G1 Increment (g)	G2 Increment (g)	Difference	p-value
Week 1 (Weight)	−96.4	−95.72	+0.63 g	n.s.
Week 2 (Weight)	142.95	93.18	+49.77 g	< 0.001
Week 3 (Weight)	188.18	91.81	+96.37 g	< 0.001
Week 4 (Weight)	205.9	93.18	+112.72 g	< 0.001
Final weight (4 wk)	1,979.09 g	1,702.27 g	+276.82 g	0.008
Final height (4 wk)	Reference	Reference	+1.1 cm	0.033
Final head circ. (4 wk)	Reference	Reference	+0.83 cm	0.017

NICU and Total Hospital Stay

One of the findings that struck us most when reviewing the data was the difference in hospital stay. Infants in Group 1 spent an average of 10.86 days in the NICU, while those in Group 2 required 19.5 days in the same unit — a difference of 8.64 days that proved statistically significant ($p < 0.001$). When considering total hospital stay, Group 1 remained admitted an average of 26.54 days compared with 40.04 days in Group 2, representing 13.5 fewer hospitalization days in favor of the LHMF group ($p < 0.001$). No patient in either group developed necrotizing enterocolitis (NEC) during the follow-up period (Table 3). Additionally, 100% of premature infants in Group 1 recovered their birth weight, compared with 60% in Group 2.

Table 3: Hospital stay, final Z-scores, and complications

Variable	Group 1	Group 2	p-value
Days in NICU	10.86	19.5	< 0.001
Total hospital stay (days)	26.54	40.04	< 0.001
Weight Z-score	−1.81	−2.54	< 0.001
Height Z-score	−1.40	−1.91	0.010
Head circumference Z-score	−0.77	−1.41	0.003
NEC	0 cases (0%)	0 cases (0%)	n.s.

Discussion

The results of our study confirm and extend what the international literature has been documenting over the past decade: fortification of human milk with a liquid product is not only safe and well tolerated, but produces clinically significant benefits in somatic growth and hospital outcomes for premature newborns. Beyond the numbers, however, what these results tell us is that timely nutritional intervention makes a real difference in the lives of these infants and in the functioning of neonatal units.

The improvement in weight gain observed in Group 1 (+276.82 g between-group difference at week 4, $p = 0.008$) is consistent with the findings of Moya et al. [8], who reported significantly higher growth rates with LHMF compared with the powder format. In our study, the difference between the two groups began to emerge from the second week onward and became progressively more pronounced, suggesting a cumulative and sustained effect of nutritional supplementation. This pattern is consistent with the biological premise that protein and mineral availability are critical determinants of cellular and tissue growth in the premature infant [10, 11].

An aspect we consider particularly relevant is that we detected that the human milk used in our patients had a creamatocrit of between 40 and 67 kcal/100 mL, placing it in the hypocaloric range or at the lower limit of recommended standards [12]. This may partly explain why, even with high feeding volumes (180–220 mL/kg/day), weight gain in Group 2 infants was insufficient. The compositional variability of human milk — well documented by Cooper et al. [3] — justifies individual assessment of the caloric and protein content of each sample, and reinforces the appropriateness of LHMF supplementation regardless of feeding volume.

The reduction in hospital stay is arguably the finding with the greatest impact on resource management in units such as ours. Guest and Moya [9] estimated that the use of LHMF in premature infants in the United States was associated with a one-day reduction in NICU stay compared with the powder format, and with a difference of up to 18 days in cases that developed NEC or sepsis. In our context, the difference was even greater: 8.64 fewer days in the NICU and 13.5 fewer days of total hospitalization, which in operational terms represents significant bed availability for other critically ill patients and a reduction in direct and indirect costs for families and the health system.

The absence of NEC cases in both groups is a reassuring finding, consistent with the safety profile of LHMF demonstrated in prior clinical trials [13]. This result may also be influenced by the predominant use of the mother's own milk — the most robust protective factor against NEC — and by the progressive enteral feeding practices applied in our unit [14].

We acknowledge the limitations of this work. The retrospective design cannot rule out differences in clinical practice between 2022 and 2024 that may have influenced the results beyond the nutritional intervention per se. The sample size, while sufficient to detect the observed differences, is relatively small. Furthermore, we do not have long-term follow-up to assess the impact of LHMF on neurodevelopment, an outcome that the literature identifies as one of the most important in this population [6, 15]. These aspects will be addressed in future studies from our unit.

Conclusions

Early use of liquid human milk fortifier in premature newborns with a birth weight below 2,000 g proved to be a safe, effective, and clinically impactful strategy in our neonatal unit. The main findings of our study are:

Incorporation of LHMF from an enteral volume of 100 mL/kg/day produced significantly greater weight gain (+276.82 g difference at four weeks, $p = 0.008$), as well as superior increments in height (+1.1 cm, $p = 0.033$) and head circumference (+0.83 cm, $p = 0.017$).

Z-scores for all three somatometric variables were considerably closer to 0 in the group receiving LHMF, indicating better alignment with expected growth standards for corrected gestational age.

100% of premature infants in the LHMF group recovered their birth weight, versus 60% in the control group — a difference with clear practical implications.

NICU stay was 8.64 days shorter and total hospitalization was 13.5 days shorter in the LHMF group, with statistically significant differences ($p < 0.001$).

No cases of NEC were recorded in either group, supporting the safety profile of the product.

The variability in human milk caloric content (40–67 kcal/100 mL) detected in our sample underscores the need to individually assess each premature infant and implement targeted and timely fortification.

These results encourage us to continue promoting the use of LHMF as the standard of care in our NICU, and to design prospective studies that will allow us to assess its long-term impact, including neurodevelopment and body composition. Optimal nutrition for the premature infant is not a clinical luxury; it is an ethical and scientific imperative.

Funding and Conflicts of Interest

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