

# Comparison of prematurity-related outcomes and complications in very low birth weight (VLBW) neonates fed with mother's own milk versus donor milk: a comparative study

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## ABSTRACT

**Background.** When mother's own milk (MOM) is unavailable or insufficient, donor milk (DM) from a human milk bank serves as an alternative feeding option. Our study sought to investigate and compare the outcomes and complications of very low birth weight (VLBW) preterm infants who receive MOM versus DM.

**Methods.** In this retrospective cohort study conducted between 2018 and 2022, we compared 70 VLBW preterm infants exclusively fed with DM to 70 randomly selected counterparts fed with MOM. Both groups began enteral feeding within 72 hours of birth. Various clinical outcomes were investigated during a three-month follow-up. The clinical outcomes were compared via independent t-tests, Mann-Whitney U, and Fisher's exact test.

**Results.** The mean gestational age of the infants who were included was  $29.6 \pm 1.6$  weeks, 84 (60%) were males, and the average birth weight was  $1217 \pm 151$  grams. Both groups had similar baseline characteristics. The results of the study demonstrated no statistically significant differences between the groups in terms of hospital length of stay ( $37 \pm 16.3$  days in MOM vs  $40.3 \pm 16.9$  days in DM group,  $P = 0.17$ ), growth rate ( $13 \pm 4$  gram/day in MOM vs  $13 \pm 4$  gram/day in DM group,  $P = 0.51$ ), growth velocity ( $9.8 \pm 3.0$  g/kg/d in MOM vs  $9.5 \pm 3.2$  g/kg/d in DM group), infants with in-hospital vomiting (51 cases in MOM vs 59 cases in DM group,  $P = 0.15$ ), vomiting frequency ( $1.3 \pm 1.1$  times in MOM vs  $1.5 \pm 1.0$  times in DM group), incidence of retinopathy of prematurity (ROP) (4 cases in MOM vs 5 cases in DM group,  $P > 0.999$ ) and incidence of bronchopulmonary dysplasia (BPD) (7 cases in MOM vs 6 cases in DM group,  $P > 0.999$ ).

**Conclusion.** Our study findings indicate that the utilization of DM didn't have a substantial negative impact on infants' outcomes nor any complications in comparison with MOM.

**Key words:** mother's own milk, donor milk, very low birth weight, preterm infants.

Very low birth weight (VLBW) infants are defined as newborns with a birth weight below 1500 grams as a result of preterm delivery. It is estimated that the prevalence of this condition is approximately 15-20% of all births, or over 20 million infants annually.

Low- and middle-income nations bear a disproportionate burden on this condition. Prematurity pose long-term complications for these infants, including respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP). The management of premature VLBW infants involves addressing their unique nutritional needs. Premature VLBW infants require specialized feeding strategies and carefully balanced nutrition to support their growth and

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promote organ development while mitigating the risk of these complications.<sup>1-4</sup>

Human milk holds immense significance as the optimal source of nourishment for both term and preterm infants. It contains a wide range of essential nutrients and bioactive components, such as immunoglobulins, enzymes, growth factors, lysozyme, nucleotides, antioxidants, hormones, lactoferrin, and cellular components, which play a crucial role in regulating the immune system and supporting the development of preterm infant. Feeding infants with human milk is associated with a wide range of advantages, contributing to improved short-term and long-term health outcomes.<sup>5,6</sup>

When a mother's own milk (MOM) is unavailable or insufficient, donor milk (DM) from a human milk bank becomes a viable alternative feeding option for premature VLBW infants. Although the pasteurization process of DM may inactivate certain components, such as growth factors, hormones, human milk oligosaccharides, immunological factors, and beneficial microbes, it still provides documented advantages over formula feeding.<sup>5-7</sup>

Multiple studies have consistently shown favorable outcomes when comparing feeding with MOM or DM to formula feeding. However, there is a relative scarcity of studies directly comparing the exclusive use of MOM to DM. Our study has a large sample size to investigate and compare the outcomes and complications of VLBW preterm infants who receive exclusively MOM versus DM. The study's findings empower healthcare professionals to make informed decisions and provide appropriate guidance to parents regarding the optimal feeding choice for their infants.

## Methods

### Study design

Our retrospective cohort study aims to compare the impact of feeding with MOM and DM on the growth rate and clinical outcomes of preterm

(born before 37 weeks of gestation) VLBW infants. We conducted a comparison between two groups of 70 VLBW preterm infants each, born in the Akbarabadi Children's Hospital Newborn Intensive Care Unit (NICU) between 2018 and 2022. One group was exclusively fed DM, while the other group, selected randomly, received MOM while enteral feeding for both groups commenced within 72 hours of birth. The exclusion criteria encompassed multiple births and infants with enteral feeding abnormalities that would hinder the use of MOM or DM after three days of birth, and infants who received a combination of MOM and DM (or did not exclusively receive MOM and DM). Additionally, infants with specific medical conditions or birth defects, and small for gestational age (SGA) infants, were also excluded.

### Feeding protocol

The recruited infants were initially provided with parenteral nutrition. After three days, enteral feeding was initiated. The enteral feeding volume was gradually increased over time, aiming to reach a target of 20 mL per kilogram per day. The DM utilized in this study was obtained from a human milk bank and underwent pasteurization. The same fortifier was utilized in both groups. Once the milk volume reached 50 mL/kg/d, human milk fortifiers (HMF) were added to the milk in both groups. The fortification process followed the manufacturers' recommendation, with 1 sachet added to 25 mL of milk.

### Data collection and outcome measures

The primary outcomes of interest in this study include the rate of growth (calculated from birth to discharge), growth velocity, in-hospital vomiting occurrences, the frequency of vomiting, incidences of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP). They were investigated through a three-month follow-up. In this study, we defined NEC as stage II or stage III according to Bell's classification.<sup>8</sup>

The growth velocity (g/kg/d) was determined using the exponential model (EM) approach, computed as  $[1000 \times \ln(\text{discharge weight/birth weight})] / \text{length of hospital stay}$ , where  $\ln$  represents the natural logarithm, and weights are measured in grams, with the length of hospital stay expressed in days.<sup>9</sup> In our study the occurrence of vomiting in infants, the frequency of vomiting during entire hospitalization was collected from medical records. As per routine, a 24-hour period of NPO (nothing by mouth) was implemented for infants who experienced vomiting before resuming feeding. The perinatal extension component of the Score for Neonatal Acute Physiology with Perinatal Extension II (SNAPPE-II) is utilized to assess the clinical severity of newborns in the NICU. This component incorporates three key elements: birth weight, size relative to gestational age, and the Apgar score at 5 minutes.<sup>10</sup>

### Ethics approval

The study complies with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committees of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.FMD.REC.1401.244).

### Statistical analysis

The statistical analysis was conducted using SPSS version 26. The normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed data, independent t-tests were used for between-group comparisons, while the Mann-Whitney U test was utilized for non-normally distributed variables. Categorical variables were analyzed using Fisher's exact test. For all tests, statistical significance was set at  $p \leq 0.05$ .

### Results

#### Clinical characteristics

The mean gestational age was  $29.6 \pm 1.6$  weeks, and 84 (60%) infants were male. The average birth weight of the infants was  $1217 \pm 151$  grams. 120 (85.7%) infants were delivered via cesarean section. Their mean Apgar scores at 1 and 5 minutes were  $6 \pm 1$  and  $8 \pm 1$  respectively. Umbilical cord arterial blood gas (ABG) revealed a mean base deficit of  $4.0 \pm 2.3$ . Additionally, 104 (74.3%) required invasive ventilation in the early days of their lives and the overall mean duration of oxygen therapy was found to be  $11.33 \pm 8.8$  days. The mean SNAPPE-II score was  $2.1 \pm 5.4$ . Table I, provides a summary of the baseline

**Table I.** Baseline characteristics of the infants.

	MOM group (n=70)	DM group (n=70)	P value
Gestational age, week	29.7±1.5	29.6±1.8	0.72
Male, n (%)	45 (63.8%)	39 (56.3%)	0.39
Birth weight, gram	1218±166	1217±137	0.73
Cesarean delivery, n (%)	58 (82.6%)	62 (88.7%)	0.47
Received surfactant, n (%)	53 (75.8%)	49 (70%)	0.57
Apgar score—1 min	6±2	6±1	0.70
Apgar score—5 min	8±1	8±1	0.10
Base deficit, mEq/L	4.1±2.3	3.8±2.3	0.37
Invasive ventilation, n (%)	53 (75.8%)	51 (72.8%)	0.84
Total O <sub>2</sub> therapy duration, d	11.2±8.7	11.5±9.1	0.94
SNAPPE-II	2.1±5.3	2.1±5.7	0.87

Values are presented as means  $\pm$  SDs (*P* value from independent t test or Mann-Whitney U), or frequencies (n) and percentages (%) (*P* value from Fisher's exact test). DM: donor human milk; MOM: mother's own milk. O<sub>2</sub>: Oxygen.

characteristics of the infants in each group. The results indicate that there were no statistically significant differences between the two groups regarding their baseline characteristics.

**Clinical outcomes**

The infants who were included in the study were followed up during the study period in order to evaluate the effect of receiving different types of nutrition on various outcomes such as hospital length of stay, growth rates, growth velocity, vomiting and incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD).

The mean hospital length of stay for the MOM group was 37.0±16.3 days, while for the DM group, it was 40.3±16.9 days. There was no statistically significant difference in hospital stay length between the two groups (P= 0.17). The mean daily weight gain, measured as growth rate, was 13.1±3.9 and 12.6±4.0 gram/day in MOM and DM groups, respectively. There was no statistically significant difference observed between the two groups (P=0.51). In the context of in-hospital vomiting episodes, 82.8% (59 cases) of infants in the DM group and 72.8% (51 cases) in the MOM group experienced vomiting. Also, when considering the frequency of vomiting, with a rate of 1.52±0.94 times in the DM group versus 1.33±1.09 times in the MOM group, no statistically significant

differences were observed between the two groups (P=0.15 and P=0.17 respectively). NEC was not developed in any of the cases in study. About the incidence of ROP, 4 (5.7%) infants in the MOM group and 5 (7.1%) infants in the DM group developed ROP grade 2 or 3, suggesting a similar rate of occurrence in both groups (P>0.999). No occurrences of ROP (grade 4 or 5) were observed in either group. Similarly, the incidence of BPD was almost identical in both the MOM and DM groups, with 7 (10%) and 6(8.6%) of cases, respectively (P > 0.999). Table II summarizes the clinical outcome information in each group. There was no mortality observed in either of the groups.

**Discussion**

In this cohort of premature VLBW infants, we evaluated the relationships between the source of human milk (mother or donor) with postnatal growth and prematurity-related outcomes and complications. The results showed that the cohorts were matched for the demographic and baseline characteristics. Our study directly compared clinical outcomes in VLBW infants fed exclusively MOM with those fed exclusively DM in the setting of an exclusively human milk diet (without formula milk), during a three-month follow-up. Our findings indicated that there was no significant difference in the hospital length of stay between the two groups, which is consistent with previously published

**Table II.** Clinical outcomes of the infants.

	MOM group (n=70)	DM group (n=70)	P value
Length of hospital stay, day	37±16.3	40.3±16.9	0.17
Growth rate, gram/day	13.07±3.9	12.63±4	0.51
Growth velocity, gram/kg/day	9.84±3.01	9.47±3.22	0.34
Infants experienced vomiting, n (%)	51 (72.8%)	59 (82.8%)	0.15
Vomiting frequency during entire hospitalization	1.33±1.09	1.52±0.94	0.17
NEC, n (%)	0	0	> 0.999
ROP, n (%)	4 (5.7%)	5 (7.1%)	> 0.999
BPD, n (%)	7 (10%)	6 (8.6%)	> 0.999

Values are presented as means ± SDs, (independent t test or Mann-Whitney U) or as frequencies (n) and percentages (%) (Fisher’s exact test). DM, donor human milk; MOM, mother’s own milk; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.

studies.<sup>7,11</sup> This suggests that feeding with DM does not prolong the hospital stay for VLBW infants.

Approximately half of pediatric mortality occurs during the neonatal stage, with low birth weight (LBW) being recognized as a primary contributing factor to neonatal mortality. Nearly 80% of deaths occur among VLBW infants. This subgroup of preterm and LBW neonates represents a vulnerable population, facing a greater likelihood of encountering physical and mental challenges in contrast to infants born at normal weights.<sup>12,13</sup> Weight gain is crucial to a newborn's growth and overall health. Our study examined the weight gain of VLBW infants who received DM versus those who received MOM. Although the DM group had a slightly lower weight gain than the MOM group, this difference was not statistically significant. These findings align with a study by Sun and colleagues where infants fed raw breast milk and those fed pasteurized human milk showed similar growth patterns.<sup>11</sup> The duration of follow-up in Sun's and our study was relatively long compared to other studies<sup>7,14,15</sup> that reported significantly higher growth rates in infants fed with unpasteurized mothers' own milk. These data suggest that DM-feeding infants may have a slower growth speed in the first 4 weeks of life, but longer follow-up will remove this effect and equalize the growth rate in both groups. In a study conducted by Montjoux-Régis et al. in 2011, three distinct cohorts of infants were compared. These cohorts comprised infants who received less than 20% of their required intake of MOM, infants who received between 20% and less than 80% of their MOM, and infants who received at least 80% of their MOM. The findings revealed that infants who were fed MOM demonstrated greater weight gain in comparison to infants who were fed DM. However, no discernible disparity in linear growth was observed among the three aforementioned groups.<sup>16</sup> In a similar study, Alizadeh et al. recently reported no statistically significant differences in weight gain velocity between DM and MOM groups.<sup>17</sup>

The results demonstrated no significant difference in the incidence of in hospital vomiting among infants. It is important to note that our definition of feeding intolerance focuses on the vomiting of consumed food, while the general well-being of the individual remains satisfactory, and there are no indications of abdominal distention. To manage the situation, we simply need to withhold one or two meals from the patient's diet. Ford et al. employed varying definitions of feeding intolerance in their study. Notably, no statistically significant distinctions were observed regarding the duration required to achieve the ultimate enteral feed volume or the duration of parenteral nutrition across the different definitions. However, it was found that the number of feeds withheld per day and the duration of NPO subsequent to the initiation of feeds were greater in the DM group.<sup>7</sup>

The incidence of complications, including NEC, ROP, and BPD were also examined in our study. We found no incidence of NEC in either the DM or MOM group. This aligns with previous research that showed no significant difference in NEC incidence when comparing unpasteurized and pasteurized human milk.<sup>18,19</sup> Similarly, the incidence of ROP did not differ between the two groups, consistent with other studies that compared unpasteurized and pasteurized human milk.<sup>5</sup> Furthermore, we observed no significant difference in the incidence of BPD between the DM and MOM groups, which is in line with previous studies.<sup>7,15,19,20</sup>

This study demonstrates the non-inferiority of DM compared to MOM in preventing complications such as BPD, NEC, ROP, and feeding intolerance in VLBW infants. While maintaining an adequate supply of MOM can be challenging for mothers of VLBW infants, our findings suggest that DM is a suitable alternative when MOM is unavailable or contraindicated. Previous studies have also indicated the superiority of DM over preterm formula in reducing complications.<sup>19,20</sup>

The strength of our study was the matched baseline characteristics and equal number of cohort groups which provided the statistical power to determine relationships between DM and the outcomes. Another important strength of this study is that the DM group includes infants exclusively fed with donor bank milk throughout their hospitalization period. However, it is also important to consider the limitations. Our study was retrospective in design. As such, we were unable to account for potential confounding variables and other sources of bias. Additionally, randomization was not possible because it is not acceptable to not give MOM when available. We also did not take stool exams to evaluate how source of human milk could be associated with gut microbiota diversity. We did not explore differences in the onset of sepsis, both early and late, between the two groups. Additionally, neurodevelopmental outcomes such as head circumference were not assessed. Lastly, our study did not evaluate the volume of gastric residue in the reported vomiting incidents. Further research is recommended to extend the follow-up period and evaluate the long-term effects of feeding type on later growth.

Our study findings show that DM is an effective alternative to MOM for feeding VLBW newborns. Both DM and MOM showed similar outcomes in terms of hospital length of stay, weight gain, vomiting, and the incidence of complications. Whenever the MOM is unavailable, the education and support for using pasteurized and appropriately fortified DM should be prioritized in the care of preterm infants. Future studies with extended follow-up periods are recommended to assess the effects of feeding type on long-term growth.

## Ethical approval

The study complies with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committees of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.FMD.REC.1401.244).

## Author contribution

The authors contributed to this article as follows: NS and ZV designed the research; MK, AA, HZ, and MS conducted the research; AA and HZ analyzed the data; MK, AA, and HZ wrote the first draft of the manuscript; and all authors read and approved the final manuscript.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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