

# Availability of donor milk improves enteral feeding but has limited effect on body growth of infants with very-low birthweight: Data from a historic cohort study

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## Abstract

Compare with preterm formula, donor human milk (DM) is associated with a lower risk of mortality and morbidity in preterm infants. It is thus deemed superior to preterm formula as the sole diet or supplement to own mother's milk (OMM) for preterm infants, especially for those with very low birthweight (VLBW). This historic cohort study investigated the relationship between DM availability, and enteral feeding, body growth of VLBW infants by comparing two cohorts before and after the establishment of a human milk bank. A sub-analysis was also conducted between small-for-gestational-age (SGA) and non-SGA infants in our cohorts. Our results showed that DM availability was associated with earlier initiation and faster advancement of enteral feeding, earlier attainment of full enteral feeding, and a higher proportion of OMM in enteral feeding. DM availability was also associated with earlier regain of birthweight, but not with better body growth. SGA and non-SGA infants responded differently to DM availability with only the non-SGA group showing improved enteral feeding associated with DM availability. The poor growth of VLBW infants with fortified DM warrants further investigations on better fortification strategies to further improve body growth. Studies are also needed on long-term effects of DM feeding on the development of VLBW infants.

## KEYWORDS

body growth, donor milk, enteral feeding, enteral nutrition, human milk bank, preterm infant nutrition, very low birthweight infants

## 1 | INTRODUCTION

For infants born with very-low birthweight (VLBW < 1500 g), accounting for 15% of all preterm births (Corpeleijn et al., 2016), it is pivotal to acquire sufficient nutrients and energy via the enteral route in a timely

fashion while avoiding feeding-associated adverse sequelae (Dutta et al., 2015). The preferred progression of enteral feeding (EF), as early initiation of enteral nutrition (Walsh et al., 2020), fast EF advancement, and early attainment of full EF, is associated with better developmental outcomes, such as early regaining of birthweight and better neurological

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outcomes in the short and long term, without an increase in the incidence of feeding intolerance, necrotising enterocolitis (NEC) or sepsis (Maas et al., 2013; Walsh et al., 2020). However, there is substantial variation in the practice regarding optimal enteral feeding strategies for VLBW preterm infants, in various clinics.

The type of milk feed can affect the EF progress, developmental outcomes, and incidence of morbidities in VLBW infants. Own mother's milk (OMM) not only provides essential nutrients and energy for infants but is also associated with a low risk of mortality and morbidities, such as late-onset sepsis (LOS), severe retinopathy of prematurity (ROP), and NEC (Bode, 2018; Dritsakou et al., 2016; Miller et al., 2018; The Neovita Study Group, 2016). Studies have also shown an association between OMM and better childhood neurodevelopment (Isaacs et al., 2010), and lower risk of adolescent metabolic syndrome, relative to preterm infant formula (PF) (Lucas, 2005). Thus, OMM is the feed of choice for VLBW infants whenever possible (Dutta et al., 2015). However, lactation is often delayed after preterm delivery, leaving the amount of OMM insufficient during the first few days after delivery. PF has been used to supplement OMM or as a sole diet when OMM is insufficient or unavailable. However, PF is associated with an increased risk of NEC and other morbidities, as shown in both infants (Cristofalo et al., 2013) and animal models (Sangild et al., 2006). Human donor milk (DM) is inferior to OMM in terms of levels of multiple nutrients and suffers from necessary treatments, such as pasteurisation and homogenisation, which potentially reduce its bioactivity (Colaizy, 2015; Meier et al., 2017). However, relative to PF, DM is associated with a lower incidence of NEC (Quigley et al., 2018) and feeding intolerance (Boyd et al., 2007). This makes DM the recommended enteral feed over PF as a supplement to OMM or sole diet by multiple guidelines (Bertino, 2013).

With the beneficial effect of DM on gut-related morbidities, such as NEC, it is hypothesised that the introduction of DM could improve the feeding process and body growth of VLBW infants. To test this hypothesis, two cohorts before and after the establishment of a donor milk bank at our department in December 2015 were compared. This study assesses the association between DM availability and the EF process, including the levels of OMM in enteral feeding and body growth in hospitalised VLBW infants.

## 2 | METHODS

### 2.1 | Ethics

This single-centre, retrospective cohort study was conducted at the Baoan Women's and Children's Hospital, Shenzhen, China, and was approved by the local ethical review committees at the School of Public Health, Sun Yat-sen University, and the study hospital.

### 2.2 | Study population and data collection

Infants born at 22<sup>+0</sup> to 36<sup>+6</sup> weeks of gestation at the study hospital from January 2013 to September 2014 (Cohort I) and from

### Key points

- Compared with the infants before the introduction of donor human milk (DM), very low birthweight infants after that had improved enteral feeding process, shown as earlier enteral feeding introduction, faster advancement, and earlier attainment of full enteral feeding.
- DM availability affects body growth to a limited extent, which calls for a better fortification strategy for DM-fed infants.
- The setup of a human donor milk bank increased the use of own mother's milk for enteral feeding.

January 2017 to December 2019 (Cohort II) were eligible. The data in Cohort I were collected in a previous study (de Waard et al., 2018). Cohort II covered preterm births from 2017, when our donor milk bank became fully functional, to 2019. Inclusion criteria are birth with VLBW ( $\leq 1,500$  g), admission to the neonatal intensive care unit (NICU) within 24 h after birth, and hospitalisation for more than 2 weeks. Exclusion criteria included major congenital anomalies, death during the observation period, exclusive feeding with OMM during the observation period, and incomplete neonatal information. As in our previous study (de Waard et al., 2018), the observation period for both cohorts was set from birth or admission to the NICU to the postconceptional age (PCA) of 37 weeks or discharge on allowing condition or on parental request, whichever came first. Anonymised relevant maternal and neonatal information of the included infants were extracted from the electronic medical record system of the study hospital, including demographics at birth (gestational age [GA], anthropometrics, sex, delivery mode, use of antenatal corticosteroids, Apgar score at 5 min after birth), nutrition regimens (types and feeding levels of enteral nutrition weekly or daily in Cohort I or II, respectively), neonatal use of antibiotics, NEC, and anthropometric data (bodyweight, weekly in Cohort I or daily in Cohort II). Body growth was evaluated using the Fenton growth chart (Fenton & Kim, 2013) as a growth reference. Small for gestational age (SGA) was defined as the 10th percentile for bodyweight at birth. Extremely low birthweight (ELBW) was defined as birthweight  $< 1000$  g.

### 2.3 | Human milk bank

In December 2015, a human milk bank was established aiming to provide DM for hospitalised infants at the Department of Neonatology, including the NICU, with a 1-year transition period (2016). The final establishment and daily running after the transition period complied with the Operation Guidance of Chinese Human Milk Banking (Group of Human Milk Bank of Committee on Child Health of Chinese Medical Doctor Association, 2017). A short description of

the operation of the human milk bank, including the collection, serological and bacteriological assessment, pasteurisation, storage, and distribution of the donor human milk (DM), is provided in [Supplementary Online Information](#).

## 2.4 | Nutrition policy

In both cohorts, OMM was the primary feed and was used whenever possible. PF or DM was used as a supplement or sole feed when OMM was insufficient or unavailable in Cohorts I and II, respectively. Among the included cases, only three infants in Cohort I received a small amount of human milk donated by other mothers in the same ward. In Cohort II PF is used as a supplement to OMM, OMM + DM, or DM, only when the parents do not accept DM, or the infants have protein allergies requiring deep hydrolysed or amino acid-based PF.

In both cohorts, enteral nutrition was started as soon as possible upon allowing clinical condition, that is, no gastrointestinal malformation, severe asphyxia, or use of vasoactive drugs. Bolus feedings were given at 3-h intervals. A standardised feeding regimen was applied to both cohorts. After a successful introduction, EF was maintained at 10–15 ml/kg/d for a few days, then the EF advancement was started with a daily increment of 10–15 ml/kg/d for infants with birthweight < 1000 g, then further to 15–20 ml/kg/d upon positive signs of tolerance. For infants with birthweight  $\geq$  1000 g, the daily increment of EF was 20–30 ml/kg/d. Fortification of DM and/or OMM started when the volume of EF reached 80–100 ml/kg/d using human milk fortifier starting with around 0.74 kcal/(ml OMM or DM), and further increased to around 0.82 kcal/(ml OMM or DM) within 2–4 days.

## 2.5 | Feeding and body growth outcomes

The primary outcome was the time from the EF initiation to full EF of 120 ml/kg/d (TFEF120). Other outcomes included the time (from birth) to the initiation of EF (TIEF, d), the advancement rate of EF (ml/kg/d), the time (from birth) to the regaining of birthweight (TRBW, d), bodyweight Z-scores at the end of the observation period,  $\Delta$ bodyweight Z-scores, growth velocity (GV, g/kg/d) and feeding proportion of OMM in all EF. The advancement rate of EF (ml/kg/d) was defined as the daily increment of the adjusted feeding volume (ml/kg) from 20 ml/kg/d EF to full EF. Bodyweight Z-scores at the end of the observation period were calculated based on the Fenton growth chart ([https://apps.cpeg-gcep.net/premZ\\_cpeg/](https://apps.cpeg-gcep.net/premZ_cpeg/)), and  $\Delta$ bodyweight Z-scores were defined as the difference between the Z-scores at the beginning and the end of the observation period. GV was calculated using an exponential model, by Patel et al. (2005), using bodyweights at birth and at the end of the observation with the equation  $GV(g/kg/d) = [1000 \times \ln(\text{weight day } n / \text{weight day } 1)] / (\text{day } n - \text{day } 1)$ .

The volumes of OMM and PF were divided by those of all enteral feeds throughout the observation period as the proportions of OMM and PF, respectively. The proportions of OMM were divided into three levels, namely: no OMM (0%), low OMM (<50%), and high OMM (50%–<100%). Meanwhile, the proportions of PF were divided into four levels, namely: no PF (0%), low PF (<50%), high PF (50%–<100%) and exclusive PF (100%).

## 2.6 | Statistical analysis

Maternal and neonatal characteristic variables and outcomes were compared between Cohorts I and II using Student's t-test for normally distributed continuous variables, Wilcoxon rank-sum test for continuous nonparametric variables,  $\chi^2$  test for categorical variables, and Fisher exact test for categorical variables with expected frequency under five. All bodyweights were rounded to a hundred g before the analysis for identity protection and after being used for the calculation of bodyweight Z-scores, as in our previous publication (de Waard et al., 2018).

Multivariable analysis was used to assess the associations between DM availability and various outcomes using Cohort I as the reference. Logistic regression was used on the incidence of attaining full EF within the observation period and the levels of OMM. Relevant odds ratio (OR), 95% confidence intervals (CIs), and a *p* value by  $\chi^2$  test were reported. The Cox proportional hazard model was used on TIEF, TFEF120, and TRBW with relevant hazard ratios (HRs), 95% CIs, and *p* values by the Wald test reported. Multivariable linear regression was applied to the advancement rate of EF, the rounded bodyweights, and the bodyweight Z-scores at the end, the  $\Delta$ bodyweight Z-scores, and GV. Relevant regression coefficients ( $\beta$ ), 95% CIs, and *p* values from the F test were reported.

Three models were established to adjust for different confounders. In Model I gestational age (GA, continuous), sex (male/female), ELBW (yes/no), and caesarean delivery (yes/no) were adjusted. Antenatal corticosteroid (ACS) exposure (yes/no), age of mother (continuous), and neonatal antibiotic exposure (yes/no) were further adjusted in Model II. The proportion of OMM in three levels was further adjusted in Model III, based on Model II. The proportions of OMM and PF showed strong collinearity, thus only the OMM proportion in three levels was used for adjustment. As the calculation of Z-scores was adjusted for GA and sex, these two confounders were not included in the linear regression models for bodyweight Z-scores.

Stratified analysis was conducted for the small-for-gestational-age (SGA, *n* = 47) and non-SGA infants (*n* = 275) from both cohorts using Cohort I as a reference. Relevant  $\beta$  coefficients, HRs, ORs, and *p*-values were calculated as described above.

A separate analysis on the proportion of OMM in four levels was conducted with the VLBW infants exclusively on OMM re-included in both cohorts (3 and 201 in the Cohorts I and II, respectively) using ordinal multilevel logistic regression with

confounder adjustment identical to the Models I and II described above.

All statistical tests were two-sided, with a significance threshold of 0.05. All data management and statistical analyses were performed in R (R Core Team, 2020) interfaced with R Studio (RStudio Team, 2020). Cox modelling was conducted using the package *survival* (version 3.2-3) (Terry et al., 2000; Therneau, 2020).

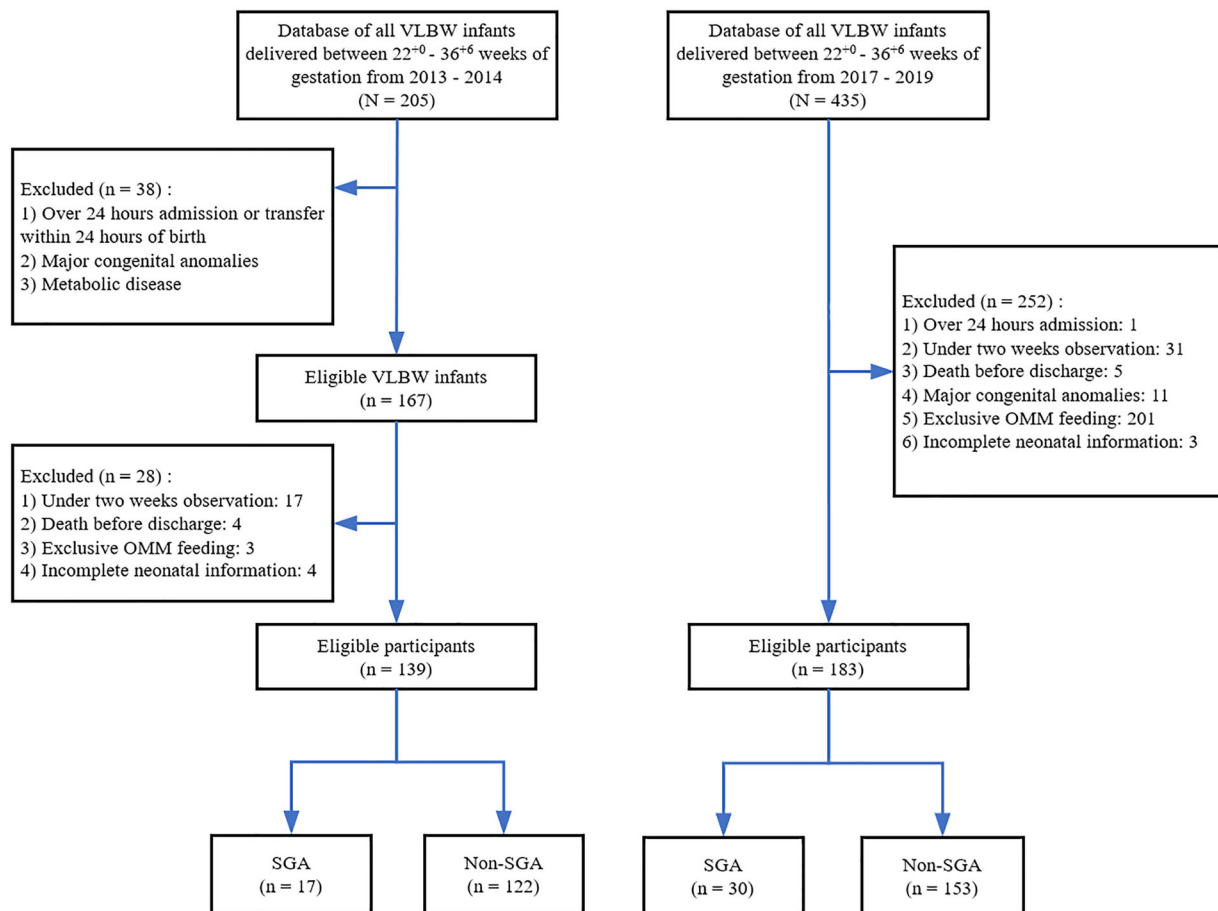
### 3 | RESULTS

In total, 205 and 435 VLBW preterm infants were eligible from 2013 to 2014 and from 2017 to 2019, respectively. In Cohort I 139 infants were included and 183 were in Cohort II (Figure 1). The characteristics of the infants in the entire study population and in both cohorts are shown in Table 1. Compared with Cohort I, Cohort II had a higher proportion of infants born via caesarean section (60.7% vs. 41.7%), a higher proportion of ELBW infants (32.8% vs. 7.2%) and poorer neonatal condition at birth, shown as lower bodyweight Z-scores and higher incidence of Apgar score at 5 min <8 (22.1% vs. 8.8%,  $p < 0.01$ ). In addition, a higher proportion of infants in Cohort II had

exposure to antenatal corticosteroids (ACS, 83.1% vs. 54.0%,  $p < 0.001$ ) and a lower proportion had neonatal antibiotics (90.7% vs. 98.6%,  $p < 0.01$ ), compared with Cohort I. Enteral feeding variables and growth data in both cohorts during the observation period are listed in Table 2. Relative to those in Cohort I, higher levels of OMM and lower levels of PF (both  $p < 0.001$ ) were observed in Cohort II. Only two and three NEC cases were found in Cohorts I and II, respectively.

The results of the multivariable analyses are presented in Table 3. Within the observation period, DM availability was associated with earlier EF introduction (i.e., shorter TIEF, HR: 1.46, 95% CIs: 1.10–1.93,  $p < 0.01$ ), faster advancement ( $\beta$ : 2.77, 95% CIs: 1.12–4.41,  $p < 0.001$ ), and earlier attainment of full EF (i.e., shorter TFEF120, median 20 d vs. 21 d, HR: 1.70, 95% CIs: 1.11–2.60,  $p = 0.01$ ) after adjustment in Model III that included the levels of OMM.

DM availability was associated with shorter TRBW (median 8 d vs. 11 d, HR: 2.04, 95% CIs: 1.34–3.11,  $p < 0.001$ ) after adjustment in Model III. At the end of the observation period the bodyweight Z-scores were negatively associated with DM availability in Model I ( $\beta$ : -0.21, 95% CIs: -0.39 to -0.04,  $p = 0.02$ ), while the  $\Delta$ bodyweight Z-scores were negatively associated with DM availability before the



**FIGURE 1** Flowchart identifying the study population. OMM, own mother's milk; SGA, small for gestational age; VLBW, very-low birthweight

**TABLE 1** Maternal and neonatal characteristics of the whole population: Cohorts I and II

	Whole population (n = 322)	Cohort I (n = 139)	Cohort I (n = 183)	p (between cohorts)
Male, yes, n (%)	174 (54.0)	90 (64.7)	84 (45.9)	<0.001 <sup>a</sup>
GA, weeks, mean ± SD	29.1 ± 2.3	29.5 ± 1.9	28.9 ± 2.5	0.01 <sup>b</sup>
SGA at birth, yes, n (%)	47 (14.6)	17 (12.2)	30 (16.4)	0.29 <sup>a</sup>
Singleton, yes, n (%)	233 (72.4)	104 (74.8)	129 (70.5)	0.39 <sup>a</sup>
Caesarean delivery, yes, n (%)	169 (52.5)	58 (41.7)	111 (60.7)	<0.001 <sup>a</sup>
5-min Apgar score < 8, n (%), (n = 136 vs. n = 181) <sup>e</sup>	52 (16.4)	12 (8.8)	40 (22.1)	<0.01 <sup>a</sup>
Bodyweight at birth, g, median (IQR)	1200 (1000–1300)	1300 (1100–1400)	1200 (900–1300)	<0.001
Bodyweight Z score at birth, mean ± SD	−0.3 ± 0.8	−0.2 ± 0.8	−0.4 ± 0.8	0.05 <sup>b</sup>
ELBW, yes, n (%)	70 (21.7)	10 (7.2)	60 (32.8)	<0.001 <sup>a</sup>
Body length at birth, cm, mean ± SD, (n = 139 vs. n = 177) <sup>e</sup>	37.8 ± 3.1	39.0 ± 2.1	37.0 ± 3.5	<0.001 <sup>b</sup>
L-Z score at birth, mean ± SD, (n = 139 vs. n = 176) <sup>e</sup>	−0.2 ± 1.1	0.1 ± 1.0	−0.4 ± 1.1	<0.001 <sup>b</sup>
Head-circumference at birth, cm, mean ± SD, (n = 139 vs. n = 177) <sup>e</sup>	26.9 ± 2.1	27.1 ± 1.5	26.7 ± 2.5	0.06 <sup>b</sup>
H-Z score at birth, mean ± SD, (n = 139 vs. n = 176) <sup>e</sup>	0.0 ± 1.2	−0.1 ± 1.1	0.0 ± 1.3	0.51 <sup>b</sup>
Antibiotics use, yes, n (%)	303 (94.1)	137 (98.6)	166 (90.7)	<0.01 <sup>a</sup>
Non-intubated respiratory support, yes, n (%)	287 (89.1)	119 (85.6)	168 (91.8)	0.08 <sup>a</sup>
NEC, yes, n (%)	5 (1.6)	2 (1.4)	3 (1.6)	1.00 <sup>d</sup>
Age-Mother, mean ± SD	29.5 ± 5.3	27.4 ± 4.6	31.0 ± 5.2	<0.001 <sup>b</sup>
Primipara, yes, n (%)	158 (49.1)	66 (47.5)	92 (50.3)	0.62 <sup>a</sup>
Abortion history, yes, n (%)	137 (42.5)	53 (38.1)	84 (45.9)	0.16 <sup>a</sup>
ACS exposure, yes, n (%)	227 (70.5)	75 (54.0)	152 (83.1)	<0.001 <sup>a</sup>

Abbreviations: ACS, antenatal corticosteroids; ELBW, extremely low birth weight; GA, gestational age; IQR, interquartile range; NEC, necrotising enterocolitis; PCA, postconceptional age; SD, standard deviation; SGA, small for gestational age.

<sup>a</sup> $\chi^2$  test.

<sup>b</sup>Student's t-test.

<sup>c</sup>Wilcoxon rank-sum test.

<sup>d</sup>Fisher exact test.

<sup>e</sup>Data are unavailable for the cases in 5-min Apgar score, body length, and head circumference at birth.

proportion of OMM was adjusted in Model III, and no association was found for GV. A significant improvement in the OMM levels was associated with DM availability (OR: 135.07; 95% CIs: 70.28–275.14,  $p < 0.001$ ).

The characteristics of the SGA and non-SGA subgroups are listed in Table S1. Different associations were observed between the two subgroups (Table 4). No significant association was found in the SGA group, except for TRBW, before the OMM proportion was adjusted in Model III. In the non-SGA group DM availability was associated with improved EF process, shown as shorter TIEF (HR: 1.56, 95% CIs: 1.16–2.11,  $p < 0.01$ ) and TFEF120 (HR: 1.76, 95% CIs: 1.09–2.85,  $p = 0.02$ ), and faster EF advancement ( $\beta$ : 2.21, 95% CIs: 0.38–4.04,  $p = 0.02$ ). Earlier regain of birth weight and lower bodyweight Z-scores at the end, but not  $\Delta$ bodyweight Z-scores, were associated with DM availability in Model III.

## 4 | DISCUSSION

The establishment of donor milk banks is now recognised as an approach to provide DM in a systematic and well-managed fashion, triggering many establishing plans around the world, despite the high operational cost (Committee on Nutrition et al., 2017; Daili et al., 2020). This warrants investigations on the effects of DM on various aspects related to growth and development of preterm infants. The current study did not aim to assess the effects of DM and PF per se, but rather the difference before and after the complete introduction of DM at our department. This study showed that DM availability was independently associated with improved EF progress and increased use of OMM for VLBW infants.

A report on earlier initiation of breastfeeding, showing that earlier initiation by even one day can reduce infant mortality,

**TABLE 2** Enteral feeding progress and body growth of the whole population: Cohorts I and II

	Whole population (n = 322)	Cohort I (n = 139)	Cohort II (n = 183)	p (between cohorts)
TIEF, d, median (IQR)	2.0 (1.0 – 3.0)	2.0 (2.0–3.0)	2.0 (1.0–3.0)	<0.001 <sup>a</sup>
Advancement rate of enteral feeding, ml/kg/d, mean ± SD, (n = 119 vs. n = 165) <sup>e</sup>	8.8 ± 4.3	7.4 ± 3.5	9.9 ± 4.5	<0.001 <sup>b</sup>
Attainment of full enteral feeding, yes, n (%)	284 (88.2)	119 (85.6)	165 (90.2)	0.21 <sup>c</sup>
TFEF120, d, median (IQR)	21.0 (14.0–29.0)	21.0 (14.5–31.0)	20.0 (14.0–28.0)	0.22 <sup>a</sup>
Regaining birthweight, yes, n (%)	321 (99.7)	138 (99.3)	183 (100.0)	0.43 <sup>d</sup>
TRBW, d, median (IQR)	9.0 (6.0–12.0)	11.0 (8.0–14.0)	8.0 (3.0–11.0)	<0.001 <sup>a</sup>
Bodyweight at the end, g, median (IQR)	2000 (1800–2200)	2100 (1900–2300)	2000 (1800–2100)	<0.001 <sup>a</sup>
Bodyweight Z score at the end, mean ± SD	−1.8 ± 0.8	−1.5 ± 0.8	−1.9 ± 0.7	<0.001 <sup>b</sup>
ΔBodyweight Z score, mean ± SD	−1.4 ± 0.6	−1.3 ± 0.6	−1.5 ± 0.6	<0.01 <sup>b</sup>
GV, g/kg/d, mean ± SD	11.4 ± 3.2	11.3 ± 2.8	11.5 ± 3.4	0.47 <sup>b</sup>
Proportion of OMM, n (%)				<0.001 <sup>c</sup>
No OMM (0)	99 (30.7)	95 (68.3)	4 (2.2)	
Low OMM (< 50%)	70 (21.7)	36 (25.9)	37 (20.2)	
High OMM (50% - < 100%)	153 (47.5)	8 (5.8)	142 (77.6)	
Exclusive OMM (100%), (n = 142 vs. n = 384) <sup>f</sup>	204 (38.8)	3 (2.1)	201 (52.3)	
Proportion of PF, n (%)				<0.001 <sup>c</sup>
No PF (0)	111 (34.5)	0 (0)	111 (60.7)	
Low PF (<50%)	57 (17.7)	6 (4.3)	61 (33.3)	
High PF (50% - <100%)	59 (18.3)	38 (27.3)	11 (6.0)	
Exclusive PF (100%)	95 (29.5)	95 (68.3)	0 (0)	

Abbreviations: GV, growth velocity; IQR, interquartile range; OMM, own mother's milk; PF, preterm formula; SD, standard deviation; TIEF, time to initiation of enteral feeding; TFEF120, time to full enteral feeding of 120 ml/kg/d; TRBW, time to regain birth weight.

<sup>a</sup>Wilcoxon rank-sum test.

<sup>b</sup>Student's t-test.

<sup>c</sup> $\chi^2$  test.

<sup>d</sup>Fisher exact test.

<sup>e</sup>Data are unavailable in the cases that did not attain full enteral feeding.

<sup>f</sup>Data are calculated separately in the population re-included VLBW infants exclusively on OMM.

suggests the crucial importance of early initiation of EF (The Neovita Study Group, 2016). Earlier initiation of EF is associated with the earlier removal of vascular catheters, thus, potentially lowering the risk of infection (Dutta et al., 2015; Rochow et al., 2012). In the present study, DM availability was associated with earlier initiation of enteral nutrition, which is in line with a previous study, where a 0.5-day earlier start of EF was found in very preterm infants after the introduction of DM (Cañizo Vázquez et al., 2019). A meta-analysis of 20 randomised controlled trials (RCTs) revealed that early trophic feeding did not increase the risk of NEC as it may improve maturation of the gastrointestinal tract by stimulating gastrointestinal motility and hormone secretion (Kwok et al., 2019). However, the same study did not find any effect of early EF on feeding tolerance, nor on the incidence of LOS or short-term growth (Kwok et al., 2019). No information regarding infection was collected in Cohort I, so it is

impossible to evaluate how neonatal infection was affected after the introduction of DM in this study.

After the introduction of DM the EF advancement was faster, even after adjusting for confounders. Correspondingly, the time to reach full EF (TFEF120) was shorter by approximately 1 day, which is in line with previous observational studies (Maas et al., 2013; Morgan et al., 2015). In both cohorts, a high proportion of infants (>80%) reached full EF within the observation period. Unlike our study, a recent RCT showed no difference in TFEF120 between PF-fed and DM-fed VLBW infants (Corpeleijn et al., 2016), warranting a further investigation. Multiple studies, including historic cohort studies and meta-analyses, showed that faster EF advancement and early attainment of full EF did not increase the risk of NEC (Maas et al., 2013; Morgan et al., 2015; Oddie et al., 2017), but could lower the risk of infection (Kwok et al., 2019) and parenteral nutrition-related



**TABLE 3** Association of the availability of DM and neonatal outcomes in three different models

Outcomes	Model I <sup>a</sup>		Model II <sup>b</sup>		Model III <sup>c</sup>	
	$\beta$ /OR/HR (95% CIs)	<i>p</i>	$\beta$ /OR/HR (95% CIs)	<i>p</i>	$\beta$ /OR/HR (95% CIs)	<i>p</i>
TIEF (HR)	1.55 (1.21, 2.00)	<0.001	1.46 (1.10, 1.93)	<0.01	-	-
Advancement rate of enteral feeding ( $\beta$ ), ( <i>n</i> = 119 vs. <i>n</i> = 165) <sup>g</sup>	3.44 (2.41, 4.46)	<0.001	3.07 (1.95, 4.19)	<0.001	2.77 (1.12, 4.41)	<0.001
Attainment of full enteral feeding (OR)	1.57 (0.74, 3.38)	0.24	1.42 (0.63, 3.27)	0.40	1.49 (0.46, 4.91)	0.51
TFEF120 (HR)	1.58 (1.20, 2.07)	0.001	1.51 (1.13, 2.03)	<0.01	1.70 (1.11, 2.60)	0.01
Proportion of OMM (OR), ( <i>n</i> = 142 vs. <i>n</i> = 384) <sup>h</sup>	138.59 (73.90, 276.12)	<0.001	135.07 (70.28, 275.14)	<0.001		
TRBW (HR)	1.67 (1.30, 2.13)	<0.001	1.60 (1.22, 2.09)	<0.001	2.04 (1.34, 3.11)	<0.001
Bodyweight at the end ( $\beta$ )	-0.05 (-0.12, 0.02)	0.17	-0.06 (-0.14, 0.02)	0.12	-0.07 (-0.18, 0.04)	0.22
Bodyweight Z-score at the end ( $\beta$ )	-0.21 (-0.39, -0.04)	0.02 <sup>d</sup>	-0.14 (-0.34, 0.05)	0.14 <sup>e</sup>	-0.27 (-0.55, 0.01)	0.06 <sup>f</sup>
$\Delta$ Bodyweight Z-score ( $\beta$ )	-0.17 (-0.31, -0.03)	0.02 <sup>d</sup>	-0.18 (-0.34, -0.03)	0.02 <sup>e</sup>	-0.06 (-0.28, 0.17)	0.60 <sup>f</sup>
GV ( $\beta$ )	-0.23 (-0.98, 0.52)	0.55	-0.36 (-1.18, 0.47)	0.40	0.01 (-1.19, 1.20)	0.99

Abbreviations: DM, donor milk; ELBW, extremely low birth weight; GV, growth velocity; HR, hazard ratio; PCA, postconceptional age; OMM, own mother's milk; OR, odds ratio; TIEF, time to the initiation of enteral feeding; TFEF120, time to full enteral feeding of 120 ml/kg/d; TRBW, time to regain birth weight; VLBW, very-low birthweight.

<sup>a</sup>Adjusted for GA, sex, ELBW, and caesarean delivery, unless otherwise specified.

<sup>b</sup>Further adjusted for ACS use, age of mother, and antibiotic use unless otherwise specified.

<sup>c</sup>Further adjusted for the proportion of OMM, unless otherwise specified.

<sup>d</sup>Adjusted for ELBW and caesarean delivery for Z-score.

<sup>e</sup>Adjusted for ELBW, caesarean delivery, ACS use, age of mother, and antibiotic use for Z-score.

<sup>f</sup>Adjusted for ELBW, caesarean delivery, ACS use, age of mother, antibiotic use, and the proportion of OMM for Z-score.

<sup>g</sup>Data are unavailable for cases that did not attain full enteral feeding within the observation period.

<sup>h</sup>Data were calculated separately in the population re-included VLBW infants exclusively on OMM.

morbidities, potentially by reducing the time of catheterisation. In a recent multicentre trial in the UK (Abbott et al., 2017), no difference was found in the incidence of LOS or NEC between the very preterm or VLBW infants receiving EF of 30 ml/kg/d and 18 ml/kg/d (Dorling et al., 2020). This implies the safety of a fast EF advancement for VLBW infants. Specifically, even with DM feeding, the EF advancement rate at our unit is still low, making our TFEF120 rather long (median, 20 d), compared to those in the Western units in our previous report in 2014 (median, 11 d) (de Waard et al., 2018). This could be due to the rather conservative feeding policy at our department mentioned in the Method section (15–20 ml/kg/d), in fear of NEC.

The earlier onset of EF and attainment of full EF are associated with a shorter time to regain birth weight in preterm infants (Hay, 2013). In this study TRBW, shorter by 3 days, was observed in Cohort II. However, no association was observed between DM availability and  $\Delta$ bodyweight Z-scores (after the OMM proportion adjusted) or the adjusted growth velocity (GV, g/kg/d). This indicates that DM availability did not improve body growth, at least in the observation period. Studies have shown slower body weight gain under DM feeding, relative to PF feeding, in the early neonatal period (Boyd et al., 2007; Quigley et al., 2018; Yu et al., 2019). Taken together, these results suggest that DM feeding may not provide sufficient nutrients and energy for body growth, thus, calling for more desirable nutrition or fortification policy.

In this study, the non-SGA infants showed associations similar to the whole population, whereas, no improvement in the EF process was observed in the SGA infants after DM became available, ratifying the difficulty of feeding infants being both VLBW and SGA. The disappearance of the significance of shorter TRBW and lower  $\Delta$ bodyweight Z scores observed in Model III of the SGA and non-SGA infants, respectively, demonstrated the dependence of DM availability on the OMM usage. This underscores the benefits of OMM feeding in both SGA and non-SGA infants. However, the low number of SGA infants limited any reliable inference, and further studies are needed on this specific population.

Studies have shown that DM feeding decreases the incidence of NEC (Cañizo Vázquez et al., 2019). The limited number of NEC cases in this study left no statistical power to assess this effect. The low NEC incidence in our study could be attributed to the high proportion of OMM used in our cohorts, which is supported by another study (Corpeleijn et al., 2012). Another contributing factor could be our rather conservative feeding strategy with a rather low advancement rate (15–20 ml/kg/d).

There is a concern that establishing a human milk bank would inhibit OMM provision. In contrast, a positive association between the levels of OMM feeding and DM availability was observed, independent of maternal and neonatal factors. This is in line with other studies showing that the introduction of DM did not change (Cañizo

TABLE 4 Stratified analysis by SGA on the association of the availability of DM and the neonatal outcomes

Outcomes	SGA (n = 47)			Non-SGA (n = 275)									
	Model I <sup>a</sup>			Model I <sup>a</sup>									
	p	$\beta$ /OR/HR (95% CIs)	$\beta$ /OR/HR (95% CIs)	p	$\beta$ /OR/HR (95% CIs)	$\beta$ /OR/HR (95% CIs)							
TIEF (HR)	0.13	1.80 (0.79, 4.08)	0.16	-	1.61 (1.23, 2.10)	<0.001	1.56 (1.16, 2.11)	<0.001	-				
Advancement rate of enteral feeding ( $\beta$ ) <sup>e</sup>	0.08	2.06 (-0.90, 5.02)	0.17	3.27 (-0.78, 7.32)	0.11	3.42 (2.34, 4.49)	<0.001	2.98 (1.78, 4.17)	<0.001	2.21 (0.38, 4.04)	0.02		
Attainment of full enteral feeding (OR)	0.77	1.88 (0.23, 16.60)	0.55	1.27 (0.11, 16.25)	0.84	1.60 (0.69, 3.81)	0.28	1.51 (0.60, 3.84)	0.38	1.91 (0.45, 7.99)	0.37		
TFF120 (HR)	0.51	1.51 (0.60, 3.77)	0.38	1.80 (0.55, 5.91)	0.34	1.58 (1.19, 2.09)	<0.01	1.53 (1.12, 2.09)	<0.01	1.76 (1.09, 2.85)	0.02		
TRBW (HR)	0.01	2.26 (1.03, 4.96)	0.04	2.21 (0.73, 6.68)	0.16	1.74 (1.35, 2.25)	<0.001	1.68 (1.25, 2.25)	<0.001	1.98 (1.22, 3.23)	<0.01		
Bodyweight at the end ( $\beta$ )	0.12	-0.11 (-0.24, 0.03)	0.12	-0.09 (-0.25, 0.07)	0.26	-0.02 (-0.22, 0.18)	0.85	-0.09 (-0.17, -0.01)	0.02	-0.10 (-0.19, -0.01)	0.02	-0.12 (-0.26, 0.02)	0.10
Bodyweight Z score at the end ( $\beta$ )	0.74 <sup>d</sup>	0.06 (-0.31, 0.43)	0.74 <sup>d</sup>	0.10 (-0.34, 0.54)	0.65 <sup>e</sup>	0.29 (-0.26, 0.85)	0.29 <sup>f</sup>	-0.37 (-0.53, -0.21)	<0.001 <sup>d</sup>	-0.35 (-0.52, -0.17)	<0.001 <sup>e</sup>	-0.38 (-0.66, -0.09)	0.01 <sup>f</sup>
$\Delta$ Bodyweight Z score ( $\beta$ )	0.29 <sup>d</sup>	-0.19 (-0.55, 0.17)	0.29 <sup>d</sup>	-0.18 (-0.58, 0.22)	0.37 <sup>e</sup>	-0.11 (-0.61, 0.39)	0.66 <sup>f</sup>	-0.24 (-0.38, -0.1)	<0.001 <sup>d</sup>	-0.23 (-0.38, -0.07)	<0.001 <sup>e</sup>	-0.19 (-0.43, 0.06)	0.14 <sup>f</sup>
GV ( $\beta$ )	0.30	-1.89 (-5.56, 1.78)	0.30	-3.08 (-7.38, 1.22)	0.16	-2.78 (-7.89, 2.33)	0.28	0.19 (-0.43, 0.82)	0.55	0.24 (-0.46, 0.94)	0.50	0.04 (-1.04, 1.12)	0.94

Abbreviations: CIs, confidence interval; DM, donor milk; GV, growth velocity; HR, hazard ratio; OMM, own mother's milk; OR, odds ratio; TFF120, time to full enteral feeding of 120 mL/kg/d; SGA, small for gestational age; TIEF, time to the initiation of enteral feeding; TRBW, time to regain birth weight.

<sup>a</sup>Adjusted for GA, sex, and caesarean delivery, unless otherwise specified.

<sup>b</sup>Further adjusted for ACS use, age of mother, and antibiotic use, unless otherwise specified.

<sup>c</sup>Further adjusted for the proportion of OMM, unless otherwise specified.

<sup>d</sup>Adjusted for caesarean delivery for Z-score.

<sup>e</sup>Adjusted for caesarean delivery, ACS use, age of mother, and antibiotic use for Z-score.

<sup>f</sup>Adjusted for caesarean delivery, ACS use, age of mother, antibiotic use, and the proportion of OMM for Z-score.

<sup>g</sup>Data were unavailable for cases that did not attain full enteral feeding.



Vázquez et al., 2019) or even increase the breastfeeding rate (Arslanoglu et al., 2013; Bertino, 2013). This could be attributed to the promotion of breastfeeding education after the establishment of a human milk bank (Arslanoglu et al., 2013).

Various confounders of maternal and neonatal conditions and treatments were included in different statistical models in an attempt to properly account for the potential difference between the two cohorts with a two-year time gap. For example, the proportions of ELBW infants and OMM showed significant differences between the two cohorts and were included in Models I and III, respectively, for confounder adjustment. A higher proportion of infants receiving ACS in Cohort II is another factor that was adjusted for. Our previous publication (de Waard et al., 2018), comparing our unit with others in the West, may have brought awareness of the fast advancement of EF being safe among the staff at our unit. It is also possible that there are other possible treatments or interventions were changed in the two cohorts. However, their potential effect resides together with the time difference between the two cohorts, and thus could not be adjusted. In addition, the retrospective and single-centre nature still left the effects of incomplete or inconsistent information about the clinical inventions unaccounted for in our study. Due to no information with respect to feeding intolerance being collected, assessment of feeding intolerance, the functional parameter indicating the tolerance of enteral feed and gut maturation, was not possible.

## 5 | CONCLUSION

Currently, DM is regarded as enteral nutrition of choice over PF for preterm infants. In this study, our analysis showed that the introduction of DM was associated with improved enteral feeding and increased OMM feeding in VLBW infants, but not with body growth, at least during the observation period. This suggests a lack of energy and nutrients under the current nutrition policy with DM. SGA infants responded differently to DM availability than non-SGA infants. This calls for further studies specifically on those who are, potentially, the most vulnerable population. Further investigations are needed on better nutrition or fortification strategies to improve the body growth of DM-fed infants. Finally, it remains important to investigate whether the growth differences during hospitalisation have long-term effects on the development of these infants.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## ETHICS STATEMENT

Ethical approvals were granted by the local ethical review committees at the School of Public Health, Sun Yat-sen University (permit no. 2019-148) and the Bao'an Maternal and Children's Hospital (Permit No. LISCHY2019-10-04-01).

## AUTHOR CONTRIBUTIONS

PZ and P-PJ contributed to the conception of the research. PL, Y-NJ, XL, and P-PJ contributed to the design of the research. LM and YC contributed to the acquisition of the data. TW, PL, and Y-NJ contributed to the analysis of the data. TW, PZ, and P-PJ contributed to the interpretation of the data. TW drafted the manuscript. PZ and P-PJ critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data sets analysed during the current study are available from the corresponding author on reasonable request.

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