Association between Early Feeding Patterns and Neonatal Outcomes in Very-preterm Infants: A Retrospective Cohort Study

Wesam Alyahya [a, b], PhD, Judith Simpson [c], MD, Ada L. Garcia [a], PhD, Helen Mactier [d], MD, David Young [e], PhD, Christine A. Edwards [a,] PhD.

Affiliations:

[a] Human Nutrition, School of Medicine, Dentistry and Nursing, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK.

[b] Department of Clinical Nutrition, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.

[c] Neonatal Unit, Royal Hospital for Children, Glasgow, UK.

[d] Neonatal Unit, Princess Royal Maternity, Glasgow, UK

[e] Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK.

Short title: Donor milk versus formula for preterm infants.

Corresponding Author:

Dr Wesam Alyahya

Department of Clinical Nutrition

College of Applied Medical Sciences

Imam Abdulrahman Bin Faisal University

2835 King Faisal Road

Dammam 31441, P.O. Box 2435

Kingdom of Saudi Arabia

Tel: +966 13 3331397

Email: waalyahya@iau.edu.sa

Number of Tables: 4

Number of Figures: 2**.**

Word count: 2580.

Key words

Donor human milk- Milk bank – Human milk – breast feeding – premature infants

ABSTRACT

Objective: Mother's own milk (MOM) is the optimal feed for premature infants but may not be sufficiently available. Alternative feeding includes donor human milk (DONOR), with or without fortification and preterm formula. This study evaluated the association between early feeding with exclusively/predominantly MOM (MAINLY-MOM) versus MOM supplemented with fortified-DONOR (MOM+DONOR) or preterm formula (MOM+FORMULA), and in-hospital growth and neonatal morbidities.

Methods: This is a multicentre (n=13 units) cohort study of infants < 32 weeks' gestation. Data captured at the point of care were extracted from the UK National Neonatal Research Database. Study groups where defined based on feeding pattern within the first two weeks using predefined cut-offs. Primary outcome is in-hospital growth rate.

Results: Data from 1272 infants were analysed. Infants fell into two groups: extremely (EPT) and very-preterm infants (VPT), born <28 weeks and 28 - <32 weeks of gestation, respectively.

Only 11/365 EPT received formula supplements, precluding useful comparison of MOM+DONOR and MOM+FORMULA. There was no difference in median (25^{th} -75^{th} centile) growth-velocity over the first 30 days of life between MAINLY-MOM (n= 248) and MOM+DONOR (N = 106) groups: 10 (8 – 13) vs. 10 (7 – 13) g/kg/d.

For VPT infants, there was similarly no difference in growth velocities between MAINLY-MOM (n=407), MOM+DONOR (N= 196) and MOM+FORMULA (N=304): 11 (8 – 14) vs. 11 (8 – 14) vs. 11 (8 – 14) g/kg/day. Head growth was not different (p value=0.670. Cox-regression analysis showed no difference in time to discharge between feeding types nor any difference in major neonatal morbidities.

In both EPT and VPT infants, growth-velocity from the time of regaining birth weight to discharge was significantly lower in MAINLY-MOM compared to MOM-DONOR group (EPT: 12.5 (11 – 14.2) vs. 14 (12.3 – 15.9) p=0.45, VPT 13.5 (11 – 15.7) vs. 14.5 (12.6– 16.8) p=0.015).

Conclusion:

Early feeding with fortified DONOR to supplement MOM in comparison to formula was not associated with any differences in short term growth, length of stay and neonatal morbidities. However, early feeding with mainly maternal milk compared to maternal milk supplemented with donor human milk was associated with significantly lower overall weight gain.

INTRODUCTION

Mother's own milk (MOM) is the optimal feed for all infants, particularly preterm-infants whom it confers many benefits including a reduction in necrotising enterocolitis (NEC) risk when compared with formula [1]. MOM is associated with improved neurological outcomes including better cognitive scores [2] and higher developmental scores compared with formula feeding, independent

of social and educational confounders [3, 4]. Higher doses of MOM in the first 10 days were associated with a significantly lower risk of NEC, sepsis and/or death [Hazard ratio: 0.31, confidence interval (CI):0.18-0.54,p<0.001] compared with formula [5].

Preterm-infants should receive MOM as first choice, with consideration of donor human milk (DONOR) as an alternative if MOM is unavailable or insufficient [6]. The use of DONOR to supplement MOM in preterm-infants has become common practice [7, 8] but data regarding the impact of DONOR upon outcomes in contemporary neonatal care are limited. Fortification of human milk with specialised multi-nutrient human milk fortifier (HMF) is commonly practised in neonatal units [8]. A recent meta-analysis [1] compared feeding preterm-infants with formula versus DONOR. It concluded that in-hospital growth indices were higher in formula fed infants but at the expense of increased NEC risk (risk ratio 1.87,95% CI 1.23-2.85). The mean difference in body weight was 2.51 grams/kg/day (95% CI 1.93-3.08), in length 1.21 cm/week (95% CI 0.77-1.65), and in head growth 0.85 mm/week (95% CI 0.47-1.23). Moreover, out of the twelve included trials, only five recent studies practised DONOR fortification. Whether fortified DONOR improves growth and other outcomes is not clear. Furthermore, enteral feeding practices vary between centres suggesting that outcomes may vary in differing clinical contexts.

The main objective of this cohort analysis was to compare in-hospital outcomes of early feeding (first 14 days of life) with mainly MOM, MOM supplemented with fortified DONOR or formula in very preterm-infants (VPT) admitted to one of Scottish neonatal units using National Neonatal Research Database (NNRD).

MATERIALS and METHODS

Study design and subjects

This was a multicentre (n=13 units) retrospective cohort study of infants born before 32 completed weeks of gestation and admitted to a neonatal unit in Scotland. Data were collected for 1663 infants

between January-2014 and July-2017 inclusive, which represented 88 % of the VPT Scottish population (1891 VPT infant born between 2014-2017).

Donor milk in Scotland is provided to all neonatal units from a single national human milk bank. The milk bank adheres to the operational standards laid out in the NICE Clinical Guideline 'Donor milk banks: service operation' (CG93), in particular each donor milk sample comes from a single donor rather than from pooled donors. Enteral feeding practice in all Scottish neonatal units is broadly similar (**Error! Reference source not found.**), as is the use of parenteral nutrition, which also adheres to NICE guidance.

Data were sourced from the National Neonatal Research Database (NNRD). NNRD receives data at the point of care from all neonatal units in the UK. The patient information platform used was Badgernet ®software with data entered by clinical staff.

Ethics

NNRD has permission to store and use patient data [Research Ethics Committee approval (REC) Reference: 16/LO/1093 and Confidentiality Advisory Group approval (CAG)] Reference: ECC 8-05(f) 2010. Specific REC approval was additionally obtained for this study by North of Scotland REC (Reference:17/NS/0052) and NHS Health Research Authority approval on 12 July 2017, along with management permission from each trust.

Inclusion and data management

Data extracted from NNRD were extensively reviewed and cleaned before extracting study variables for analysis. Study variables recorded for the study are described in **Error! Reference source not found.**. Completeness of data recording was high for most variables with missing values not exceeding 5-10% in the majority of episodic and daily variables, respectively. Total daily milk volume intake was poorly documented (data missing for 49% of care days) and could not be used in the analysis. Therefore, age in days rather than ml/kg/day was used to describe the time of fortification initiation. In the case of mixed feeding, information on relative volumes of each milk was not

available (not a standard Badgernet item). Therefore, definition of study groups was based on the number of feeding days. To define the study groups, the pattern of feeding for the entire stay was explored. During the first weeks of life most infants received high amounts of MOM, while DONOR and/or formula were used mainly as a supplement to MOM. Groups were thus defined according to feeding patterns within the first 14 days of life 'the critical phase'. Three study groups were defined as explained in Fig. **1**; exclusively/predominantly MOM fed groups (MAINLY-MOM), DONOR supplementing MOM group (MOM+DONOR) and formula to supplement MOM group (MOM+FORMULA). The HMF used in this cohort was bovine-based.

From a total eligible study population of 1663, 391 infants were excluded for; not been fed enterally for the entire hospital stay (n=70), incomplete records of their hospital stay for more than five days (n=143), fed exclusively with formula (n=46) as the study focuses on supplementing MOM with DONOR or formula. Infants with complex feeding pattern in the first 14 days of life (n=132) were also excluded. Further description of the excluded infants is available in **Error! Reference source not found.**. Thus, 1,272 infants were included in the final analysis (Fig. 2). Infants fell into two groups: extremely (EPT) and VPT, born <28 weeks and 28- <32 weeks, respectively.

Outcomes

The primary study outcome was in-hospital growth measured as weight gain and head circumference change. Weight gain was measured over at two hospitalisation periods: from birth to day 30 of life and from the time birth weight was regained until discharge. Growth-velocity was calculated using the exponential model. Growth velocity=[1000×LN(WTn÷WT1)]÷Dn-D1. Where GV= growth velocity expressed in grams per kilograms per day), W = weight in grams, D = day, 1 = beginning of time interval and n = end of time interval in days, LN= natural log. Head circumference growth was measured by calculating the change between admission and discharge (cm/week). Measurement of birth head circumference was considered only if it was recorded in the database within the first seven days of life. Likewise, discharge measurement was considered only if it was

recorded in the database within the last seven days of stay. Length is not routinely recorded in the database and was not assessed in this study.

Secondary outcomes were 1) NEC defined as confirmed NEC if any of the following was reported in the database: NEC as the cause of death, post-mortem confirmation of NEC, surgical resection for NEC or transferred for management of NEC. 2) Late onset sepsis culture-proven sepsis, defined as a positive blood culture at the age of 5 days or later [10]. 3) ROP defined as positive screening outcome (ROP diagnosis), If laser surgery was done for ROP, it was noted separately (ROP surgery). 4) Bronchopulmonary dysplasia (BPD) was defined by respiratory support (supplemental oxygen or any form of assisted ventilation) at the age of 36 weeks PMA. Statistical analysis

Data were analysed using IBM-SPSS (V-25). Nonparametric data were transformed using log-10 and used in regression models. Multiple imputation (automatic method using linear regression) was done for variables which contained more than 10% missing data. The imputed variables were birth head circumference (25%), mother's ethnicity (34%), smoking during pregnancy (13%).

Chi-square tests were used to determine associations between groups and categorical variables. For continuous variables, ANOVA or Kruskal-Wallis tests were used. Where appropriate post hoc tests were done using pairwise comparisons. Results were considered significant with p value <0.05 and are reported unadjusted for multiple comparisons.

Outcome analysis

All analyses were performed separately for the two subgroups, EPT and VPT. For EPT infants the outcomes were compared for MAINLY-MOM and MOM+DONOR only because of the small number of infants in the MOM+FORMULA group (n=11).

In-hospital weight gain velocity was compared using a linear regression model. Covariates (including gestational age, timing of fortification, maternal health during pregnancy, age of first feeding, days on parenteral nutrition, neonatal morbidities including NEC, BPD, sepsis, ROP and neonatal unit) were screened as potential confounders of weight gain velocity. This was done by entering each variable into univariate linear regression analysis. If the variable showed significant association with

weight gain and head growth-velocity, then it was included in the final multivariate model using 'Enter' method.

To investigate the interaction effect between weight gain and overall mortality/morbidity, an illness score was given to indicate the number of adverse events (zero to tow or more events) that infants had experienced during their hospital stay. The illness score indicates any event of mortality and/or morbidity (NEC, ROP, sepsis or BPD). The interaction effect was tested using ANOVA (**Error! Reference source not found.**).

Length of stay before discharge home was compared using Cox regression survival analysis.

RESULTS

Study population characteristics

The number of infants who met the inclusion criteria was 1272. All three feeding groups had comparable clinical characteristics however the degree of maturity and size at birth differed. MOM+FORMULA infants were more mature at birth than infants in both MOM+DONOR and MAINLY-MOM groups. For the cohort as a whole median (25^{th}-75^{th} centile) gestational age was 29 (27-31) weeks, range 23-31 weeks and birth weight were 1240 (980-1536) g, range 400-2490 g. Antenatal factors were similar across the three feeding groups. Caesarean section rate was 70% in MOM+DONOR group compared to 63% in both PREDOM-MOM and MOM+FORMULA groups. This difference was not significant (Table 1).

All clinical characteristics were comparable for MAINLY-MOM and MOM+DONOR but different for MOM+FORMULA except for antibiotic use. Reflective of greater maturity at birth, MOM+FORMULA had less respiratory illness and were more likely to survive (Table 2). Fortification of human milk was started earliest in the MOM+FORMULA group, followed by MOM+DONOR groups, and latest in the MAINLY-MOM group . Feeding pattern of the study groups throughout admission were broadly similar. The general feeding trend over admission period can be described as the following: MOM

feeding was high up to the first month. After that, MOM feeding started to decrease at the same time formula feeding started to increase progressively (**Error! Reference source not found.**).

Outcomes

In-hospital weight gain in EPT infants (N=365)

Analysis for EPT infants was done for only MAINLY-MOM and MOM+DONOR groups as there were just 11 infants in the MOM+FORMULA group. Feeding type in the critical phase predicted statistically different overall weight gain. Analysis of growth-velocity from the time birth weight was regained until discharge according to feed type in the critical phase was adjusted for birth weight and age of receiving fortifier by including the variables in the multivariate model using 'Enter' method. After adjustment, it remained higher in MOM+DONOR group compared with the MAINLY-MOM group (p=0.045). The pattern of growth over the hospitalisation three-time intervals in MAINLY-MOM and MOM+DONOR groups was generally similar although higher in MOM+DONOR than MAINLY-MOM from day 31 to 60. Growth-velocity from birth to day 30 was not different between MAINLY-MOM and MOM+DONOR groups (Table 3).

In-hospital weight gain in VPT infants (N=907)

In VPT infants, growth-velocity from when birth weight was regained until discharge analysis was adjusted for birth weight, age of receiving fortifier, length of hospital stay and receiving corticosteroids (Table 3). The adjusted analysis showed higher growth-velocity in MOM+DONOR group than in MAINLY-MOM group (p=0.015).

In comparison with MOM+FORMULA groups, growth-velocity was not different from either MAINLY-MOM (p=0.338) and MOM+DONOR (p=0.273) groups. Comparison between MAINLY-MOM and MOM+FORMULA was adjusted for birth weight, age of receiving fortifier, length of hospital stay and receiving corticosteroids. Growth-velocity from birth to day 30 was not different between MAINLY-MOM, MOM+DONOR and MOM+FORMULA groups.

The analysis of interaction effect between the feeding group and weight gain velocities was not affected by the change in infant illness (P>0.05,**Error! Reference source not found.**). Illustration of mortality/morbidity score in the study sample is shown in and stratified by the level of prematurity.

Head growth

Although MOM+DONOR feeding predicted significantly higher overall growth-velocity than MAINLY-MOM, this was not reflected in higher head growth in either EPT or VPT infants (p=0.670). Head growth in MOM+FORMULA group did not differ significantly in compared to other groups in of VPT infants (P=0.670)

Time to discharge home

Since the discharge destination is not home for all infants as some may move to other hospitals or die, survival analysis was done for only those infants who were discharged home which was the majority. In EPT infants (97% of infants are discharged home), survival analysis showed that time to discharge home was not different between infants in MAINLY-MOM groups and infants in the MOM+DONOR group [Odds ratio OR (95% CI) 0.924 (0.655-1.303), p=0.652]. Similarly, in VPT infants (100 % of infants are discharged home), feeding type did not have an effect [MOM+DONOR and MAINLY-MOM group OR (95% CI) = 0.937 (0.777-1.130, P=0.496) After adjusting for day HMF received, birth weight, gestational age, and neonatal unit, there was no difference in the time to discharge home between infants in MOM+FORMULA compared to both MAINLY-MOM and MOM+DONOR (p value of MAINLY-MOM versus MOM+FORMULA=0.066, MOM+DONOR versus MOM+FORMULA=0.118).

Secondary outcomes are presented descriptively due to the small number of cases (Table 4). There were no apparent differences between groups for any of the morbidities.

DISCUSSION

Evidence of the in-hospital outcomes of preterm-infants fed with fortified DONOR in comparison with preterm formula within contemporary neonatal practice is limited. The main finding of this study was that early feeding with fortified DONOR in comparison with formula to supplement MOM resulted in comparable weight gain at one month and from regaining birth weight until discharge with no difference in major morbidities. Earlier studies using unfortified DONOR either as sole diet or as a supplement to MOM showed DONOR to be associated with slower weight gain compared to formula [12-15]. Among more recent studies the conclusions are mixed; two observed that feeding with fortified DONOR results in growth rates similar to those associated with formula [16, 17], whereas two RCTs and two observational studies found that fortified DONOR was associated with slower weight gain than formula feeding [18-21]. The trial by Schanler et al. measured primarily NEC and infection-related outcomes and in the study of Cristofalo et al., the sample size was calculated based on days of parenteral nutrition, with neither considering growth as the primary outcome. It is possible that some of the reason for not seeing difference in growth rates is that slow growth may initiate nutritional intervention such as adding HMF or increasing it is concentration. More Interventional studies that are powered to detect changes in growth rates are needed.

Infants in the MAINLY-MOM group had significantly lower growth rates compared with MOM+DONOR group from the time birth weight was regained until discharge. It is possible that the change in feeding pattern throughout admission might have contributed to this difference. DONOR is mainly used to initiate and establish feeding and is usually switched to fortified MOM or formula after two weeks. More infants in the MOM+DONOR group were then switched to formula than infants in MAINLY-MOM group where they remained on MOM. Formula is protein and caloric dense compared with MOM and is associated with higher growth rates [1].

The average growth rates showed in this study are lower than that reported in the literature. For example, a clinical trial done by O'Connor et al comparing fortified DONOR with preterm formula as

a supplement to MOM in very low birth weight infants showed mean weight gain of 23.9 versus 25.5 g/kg/day [22] whereas in this study it was 14.7 versus 14.5 g/kg/day from the time weight gain was regained until discharge. Potential reasons for this difference could be the variation in feeding practices as shown in an international survey [8] and the difference in study design. Growth is not the only measure which should be used to assess the benefits of feeding regimens. The optimal growth rate associated with improved neurodevelopment outcomes without causing metabolic harm is not well established. Head circumference has been used as an indicator of brain growth as it correlates well with brain size and weight [23]. In our study head growth was not different between study groups. This concurs with the Cochrane review that compared DONOR with formula [1]; three recent RCT of fortified DONOR versus formula showed no different advantage on head growth (z-score=1.04, p=0.30). An observational study found head growth was significantly higher in fortified DONOR group than formula group (mean difference in head circumference z-score=0.41, p=0.03) [15].

Optimal weight gain in premature infants is also not clearly defined [24, 25]. A growth rate higher than 18 g/k/d was associated with improved mental and psychomotor developmental indices [26] and avoidance of growth failure has an important impact on in-hospital outcomes such as bronchopulmonary dysplasia [27]. Larger RCTs designed to measure growth as primary outcomes are required to confirm the effect of fortified DONOR.

In our cohort for EPT infants, all secondary outcomes were similar between MAINLY-MOM and MOM+DONOR groups including NEC. A recent trial found that DONOR feeding did have a protective effect against NEC compared with formula [28]; the lack of benefit in our study could be explained by small study numbers.

Study groups definition was based on early feeding exposure to different types of milk; it should be noted that feeding may change throughout hospital stay, depending on clinical condition, availability of MOM and growth status. This study showed variability in fortification practices such as time of

initiation and duration of use. Fortifier was started five days later in the less mature infants (MAINLY-MOM feeding) compared with the more mature ones (MOM+FORMULA feeding). The optimal time to start fortification of human milk is not known [29]. Further research is needed to identify the best time to introduce HMF in VPT infants.

There are several strengths in this study. The sample size was larger than most RCT and observational studies, and infants came from multiple neonatal units across Scotland. The described cohort is highly representative of the very-preterm population born in Scotland. Data for this study were collected over three and half consecutive years at point of care. Data captured at point of care are likely to be more accurate than retrospectively collected data. Overall data completeness was high and was 100% for important data such as birth weight and gestational age. The database contained many data items which allowed potential confounders to be accounted for. Clinical characteristics between groups were comparable. The main limitation in this study was the large proportion of missing data on total enteral milk volume, which meant days of feeding had to be substituted and this may have influenced the comparison data analysis. Another limitation is the lack of the information on the percentage of specific each type of milk type in the case of mixed feeding. The study sample could have been maximised in this study if feeding data in the database were in a form that allowed quantification of milk volumes in the mixed feeding infants. Nearly one quarter of the cohort were excluded from the study for this reason. However, the excluded infants were not clustered by birth year nor were smaller than the included infants. Nutritional intakes expressed as calories and protein per day were not possible to describe due to lack of relevant data entries in the database. Recording the precise total daily enteral intake amounts in an electronic database can be difficult to achieve in the busy neonatal environment. Daily total fluid needs can also change based on the hemodynamic status of the infant. However, this finding should inform the NNRD on optimisation of the data quality for enteral intake. Interpretation of these results maybe limited as calculating energy and nutrients intake was not possible due to the nature of the available data.

CONCLUSION

This study showed that in VPT, feeding with fortified DONOR to supplement MOM in comparison to formula was not associated with any differences in short term growth, length of stay and neonatal morbidities. There was not enough data in the extremely preterm-infants to compare donor milk with formula feeding. Future evaluation of feeding practices should additionally consider other outcomes such as neurodevelopment.

Acknowledgments

This study is part of a PhD study and funded by the Royal Embassy of Saudi Arabia Cultural Bureau. We thank Richard Colquhoun and the Neonatal Data Analysis Unit/ Imperial College of London for their advice in achieving ethical approval. Thanks to Dr Tunny Sebastian for reviewing the statistical analysis.

Statement of Ethics

This study protocol was reviewed and approved by [North of Scotland Research Ethics Committee] approval number 17/NS/0052 and NHS Health Research Authority approval on 12 July 2017, along with management permission from each trust. Written informed consent from the parents was not required for the study presented in this article in accordance with North of Scotland Research Ethics Committee guidelines.

Conflict of Interest Statement

Professor Edwards was chair of an expert group ‘Early bacterial colonisation and potential implications later in life for ILSI Europe’. Other authors have no potential conflicts of interest to disclose.

Funding Sources

This work is part of PhD study and funded by the Royal Embassy of Saudi Arabia Cultural Bureau.

Author Contributions

Prof Edwards, Dr Garcia, Dr Judith Simpson, and Dr Helen Mactier conceptualised and designed the study, reviewed the data analysis, and reviewed and revised the manuscript. Mrs Wesam Alyahya conceptualised and designed the study, obtained ethical approvals, carried out data cleaning, conducted statistical analysis, drafted the initial manuscript, and reviewed and revised the manuscript. Dr David Young reviewed the statistical analysis and the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1. Quigley, M., N.D. Embleton, and W. McGuire, *Formula versus donor breast milk for feeding preterm or low birth weight infants.* Cochrane Database of Systematic Reviews, 2019(7).
2. Angelsen, N., et al., *Breast feeding and cognitive development at age 1 and 5 years.* Archives of Disease in Childhood, 2001. **85**(3): p. 183-188.
3. Ehrenkranz, R.A., et al., *Early nutrition mediates the influence of severity of illness on extremely LBW infants.* Pediatric Research, 2011. **69**(6): p. 522.
4. Curtis, M.D., Rigo, J *Extrauterine growth restriction in very-low-birthweight infants.* Acta paediatrica, 2004. **93**(12): p. 1563-1568.
5. Corpeleijn, W.E., et al., *Intake of Own Mother's Milk during the First Days of Life Is Associated with Decreased Morbidity and Mortality in Very Low Birth Weight Infants during the First 60 Days of Life.* Neonatology, 2012. **102**(4): p. 276-281.
6. AAP committee on nutrition, A.s.o.b., AAP committee on fetus and newborn., *Donor Human Milk for the High-Risk Infant: Preparation, Safety, and Usage Options in the United States.* Pediatrics, 2017. **139**(1): p. e20163440.
7. Alyahya, W., et al., *Donated human milk use and subsequent feeding pattern in neonatal units.* International Breastfeeding Journal, 2019. **14**(1): p. 39.
8. Klingenberg, C., et al., *Enteral feeding practices in very preterm infants: An international survey.* Archives of Disease in Childhood: Fetal and Neonatal Edition, 2012. **97**(1): p. F56-F61.
9. Scotland, N.e.f. *Parenteral Feeding of Preterm and Term infant.* . 2021 [cited 2022 29/07]; Available from: http://www.knowledge.scot.nhs.uk/media/CLT/PcResources/4102026/6e0e1bf5-9c7c-4910-8d76-cae9d251a459.pdf.
10. Weisman, L.E., et al., *Intravenous immune globulin prophylaxis of late-onset sepsis in premature neonates.* Journal of Pediatrics, 1994. **125**(6): p. 922-930.
11. Ehrenkranz, R.A., et al., *Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia.* Pediatrics, 2005. **116**(6): p. 1353-60.

12. Davies, D.P., *Adequacy of expressed breast milk for early gwoth of preterm infants.* Archives of Disease in Childhood, 1977. **52**(4): p. 296-301.
13. Lucas, A., et al., *Multicentre trial on feeding low birthweight infants: effects of diet on early growth.* Archives of Disease in Childhood, 1984. **59**(8): p. 722-730.
14. Behrman, R.E., et al., *Growth, metabolic response, and development in very-low-birth-weight infants fed banked human milk or enriched formula. I. Neonatal findings.* The Journal of Pediatrics, 1983. **103**(1): p. 95-104.
15. Cooper, P.A., et al., *Growth and biochemical response of premature infants fed pooled preterm milk or special formula.* Journal Pediatr Gastroenterol Nutr, 1984. **3**(5): p. 749-54.
16. Ginovart, G., et al., *A Fortified Donor Milk Policy is Associated With Improved In-Hospital Head Growth and Weight Gain in Very Low-Birth-Weight Infants.* Advances in Neonatal Care, 2017. **17**(4): p. 250-257.
17. Sisk, P.M., et al., *Necrotizing enterocolitis and growth in preterm infants fed predominantly maternal milk, pasteurized donor milk, or preterm formula: a retrospective study.* American Journal of Perinatology, 2017. **34**(07): p. 676-683.
18. Cristofalo, E.A., et al., *Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants.* The Journal of Pediatrics, 2013. **163**(6): p. 1592-1595. e1.
19. Schanler, R.J., et al., *Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants.* Pediatrics, 2005. **116**(2): p. 400.
20. Verd, S., et al., *Hospital outcomes of extremely low birth weight infants after introduction of donor milk to supplement mother's milk.* Breastfeeding Medicine, 2015. **10**(3): p. 150-155.
21. Madore, L.S., et al., *Effects of donor breastmilk feeding on growth and early neurodevelopmental outcomes in preterm infants: an observational study.* Clinical Therapeutics, 2017. **39**(6): p. 1210-1220.
22. O'Connor, D.L., et al., *Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial.* JAMA, 2016. **316**(18): p. 1897-1905.
23. Bray, P.F., et al., *Occipitofrontal head circumference—an accurate measure of intracranial volume.* The Journal of Pediatrics, 1969. **75**(2): p. 303-305.

24. Corpeleijn, W.E., S.M. Kouwenhoven, and J.B. van Goudoever, *Optimal growth of preterm infants*, in *Nutrition and Growth*. 2013, Karger Publishers. p. 149-155.
25. Thureen, P.J., *The Neonatologist's Dilemma: Catch-up Growth or Beneficial Undernutrition in Very Low Birth Weight Infants—What Are Optimal Growth Rates?* Journal of Pediatric Gastroenterology and Nutrition, 2007. **45**: p. S152-S154.
26. Ehrenkranz, R.A., et al., *Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants.* Pediatrics-English Edition, 2006. **117**(4): p. 1253-1261.
27. Kurzner, S.I., et al., *Growth Failure in Infants With Bronchopulmonary Dysplasia: Nutrition and Elevated Resting Metabolic Expenditure.* Pediatrics, 1988. **81**(3): p. 379-384.
28. Corpeleijn, W.E., et al., *Effect of donor milk on severe infections and mortality in very low-birth-weight infants: the early nutrition study randomized clinical trial.* JAMA Pediatrics, 2016. **170**(7): p. 654-661.
29. Alyahya, W., et al., *Early versus delayed fortification of human milk in preterm infants: a systematic review.* Neonatology, 2020. **117**(1): p. 24-32.

Legends

Tables

Table 1 Maternal and Infant Characteristics
Table 2. Clinical Characteristics and Feeding
Table 3 Weight Gain Comparisons Across Study Groups (g/kg/day)
Table 4 Secondary Outcomes

Figures

Fig. 1 Inclusion Criteria for Study Groups
Fig. 2 Inclusion and Study Groups

Figures' footnotes

Figure 2 Inclusion and Study Groups
Study groups definition based on feeding pattern from birth to day 14 (MAINLY-MOM: infants were fed predominantly/exclusively mother's own milk group, MOM+DONOR: infants were fed mother's own milk supplemented with donor human milk group, MOM+FORMULA: infants were fed mother's own milk supplemented with formula), HMF: Human milk fortifier. This figure is original work.

Table 1 Maternal and Infant Characteristics

	Feeding type in the critical phase			
	MAINLY-MOM (n=655)	**MOM+DONOR (n= 302)**	**MOM+FORMULA (n=315)**	**P value[1]**
Gestational age, weeks	28 (26 - 30)	29 (27 - 30)	30 (30- 31)	<.001
Birth weight, g	1090 (860 - 1390)	1140 (920 - 1360)	1520 (1325 - 1700)	<.001
Birth head circumference, cm	26 (24 - 28)	26.5 (24.7 - 28)	28.6 (27.5 - 29.5)	<.001
Number (%)				
Male	338 (52)	144 (48)	155 (49)	0.497
Antenatal steroids	592 (90)	279 (92)	287 (91)	0.777
Caesarean section	411 (63)	212 (70)	200 (63)	0.057
White ethnicity	585 (89)	272 (90)	281 (89)	0.755
Smoking	127 (19)	61 (20)	71 (23)	0.711
Preeclampsia	57 (9)	27 (9)	23 (7)	0.710
Gestational diabetes	5 (<1)	12 (4)	7 (2)	Too few
Intrauterine growth retardation	68 (10)	40 (13)	24 (8)	0.073

Values expressed as Median (25th-75th centile) unless otherwise noted. [1] P value is based on chi-square for categorical variables and Kruskal-Wallis test for continuous variables. Post hoc comparisons using Mann-Whitney test showed significant differences between PREDOM-MOM and MDHM (p=0.037), MAINLY-MOM and MOM+FORMULA (p <0.002), MOM+DONOR and MOM+FORMULA (p<0.001) for gestational age. For birth weight the differences were between MAINLY-MOM and MF (p <0.001), MOM+DONOR and MOM+FORMULA (p<0.001). For head circumference the differences were between MAINLY-MOM and MOM+FORMULA (p <0.001), MOM+DONOR and MOM+FORMULA (p<0.001).
MAINLY-MOM: Predominantly/exclusively MOM group, MOM+DONOR: donor human milk supplementing mother's own milk group, MOM+FORMULA: formula supplementing mother's own milk group.

Table 2. Clinical Characteristics and Feeding

	Feeding type in the critical phase			
	MAINLY-MOM (n=655)	**MOM+DONOR (n= 302)**	**MOM+FORMULA (n=315)**	**P value**
Clinical characteristics, n (%)				
Surfactant given	348 (53) [bc]	134 (44) [bc]	97 (31) [bc]	<0.001
Discharge home	489 (75) [bc]	240 (79) [bc]	274 (87) [bc]	<0.001
Antibiotics	632 (96)	286 (95)	304 (97)	0.375
Diuretics	249 (38) [bc]	112 (37) [bc]	45 (14) [bc]	<0.001
Corticosteroids	120 (18)	57 (19)	8 (3)	Too few
Mechanical ventilation	486 (74) [bc]	193 (64) [bc]	121 (38) [bc]	<0.001
Feeding, Median (25th-75th centile)				
Age feed started, hours	30 (12 – 53) [bc]	29 (12 – 45) [bc]	19 (9 – 35) [bc]	<0.001
Days nil per mouth	2 (1 - 5) [abc]	2 (1-3) [abc]	1 (0 – 2) [abc]	<0.001
Age fortification initiated, d	18 (14 – 24) [ab]	15 (11-21) [a]	13 (9 – 18) [b]	<0.001
Fortification Duration, d	7 (0 – 20) [abc]	5 (0 – 13) [abc]	0 (0 – 3) [abc]	<0.001

P value is based on chi-square test. Superscripts are significantly different for comparisons between groups [a]: MAINly-MOM versus MOM+DONOR, [b]:

Table 3 Weight Gain Comparisons Across Study Groups (g/kg/day) N= 1272

	Feeding type in the critical phase			P values		
	MAINLY-MOM	**MOM+DONOR**	**MOM+FORMULA**	**MAINLY-MOM vs MOM+DONOR**	**MAINLY-MOM vs. MOM+FORMULA**	**MOM+DONOR vs. MOM+FORMULA**
Extremely preterm infants (n=365)	(n= 248)	(n= 106)	(n= 11)			
Birth to 30 days	10 (8 – 13)	10 (7 – 13)	10 (6 – 12)	0.545	Too few	Too few
Day 31 to 60	15 (12 – 18)	17 (14 – 20)	15 (14 – 20)	-	-	-
Day 61 to discharge	12 (10 – 14)	12 (9 – 15)	Discharged by day 60	-	-	-
Regain birth weight to discharge	12.5 (11 – 14.2)	14 (12.3 – 15.9)	14 (12.3 – 16)	*0.045 [a]	Too few	Too few
Very preterm infants (n=907)	(n= 407)	(n= 196)	(n= 304)			
Birth to 30 days	11 (8 – 14)	11 (8 – 14)	11 (8 – 14)	0.341	0.518	0.512
Day 31 to 60	13 (10 – 16)	14 (12 – 17)	12 (9 – 16)	-	-	-
Day 61 to discharge	10 (8 – 13)	11 (9 – 12)	9 (8 -10)/11	-	-	-
Birth to discharge	11 (9 – 13)	12 (10 – 14)	11 (9 – 13)	-	-	-
Regain birth weight to discharge	13.5 (11 – 15.7)	14.5 (12.6– 16.8)	14.7 (11.6– 16.8)	*0.015 [b]	0.338 [b]	0.273

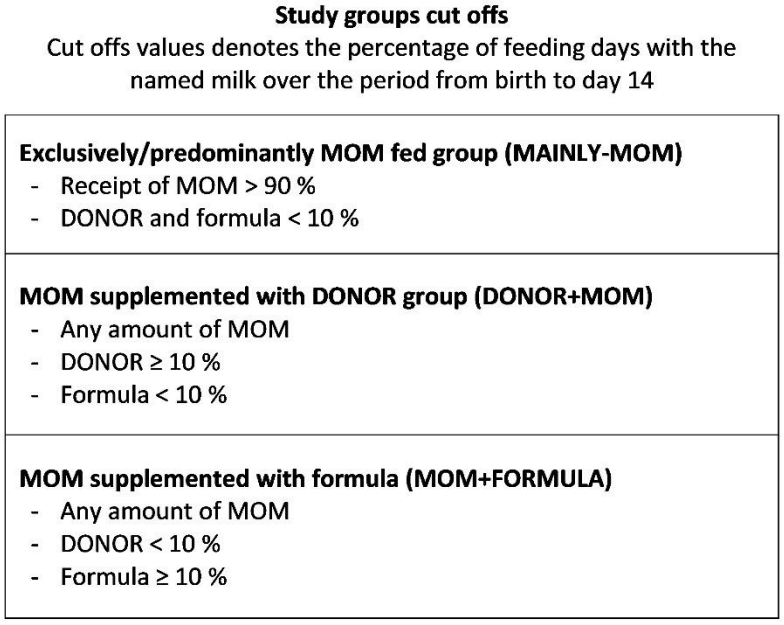
Values expressed as median (25^{th}, 75th centile)/number of infants in the analysis. P value is based on linear regression analysis. [a] adjusted for birth weight and age of receiving fortifier. [b] adjusted for birth weight, age of receiving fortifier and length of hospital stay and corticosteroids use. *: statistically significant at level 0.05.

449 **Table 4 Secondary Outcomes**

	Feeding type in the critical phase		
	MAINLY-MOM	**MOM+DHM**	**MOM+FORMULA**
Extremely preterm infants	(n= 248)	(n= 106)	(n= 11)
Median (25th-75th centile)			
Length of hospital stay, d	98 (76-113)	90 (71-108)	89 (56-112)
parenteral nutrition, d	16 (10 – 24)	13 (9 – 21)	10 (7 – 15)
PMA at discharge, wk.	38 (33, 41)	38(35 – 41)	38 (33 – 40)
Morbidities, n (%)			
Confirmed NEC	23 (9)	9 (9)	0
Bronchopulmonary dysplasia	41 (17)	13 (12)	1 (9)
Late onset Sepsis	69 (28)	29 (27)	3 (27)
ROP surgery	17 (7)	7 (7)	1 (9)
ROP diagnosis	20 (8)	9 (9)	1 (9)
Very preterm infants	(n= 407)	(n= 196)	(n= 304)
Median (25th-75th centile)			
Length of hospital stay, d	50 (40-67)	52 (40-67)	36 (28-46)
parenteral nutrition, d	9 (6 – 14)	8 (6 – 12)	6 (3 – 8)
PMA at discharge, wk.	36 (35 – 38)	37 (35 – 39)	35 (34 – 37)
Morbidities, n (%)			
Confirmed NEC	6 (2)	3 (2)	2 (1)
Bronchopulmonary dysplasia	18 (4)	8 (4)	4 (1)
Late onset Sepsis	45 (11)	14 (7)	17 (6)
ROP surgery	6 (2)	2 (1)	0
ROP diagnosis	4 (1)	4 (2)	1 (<1)

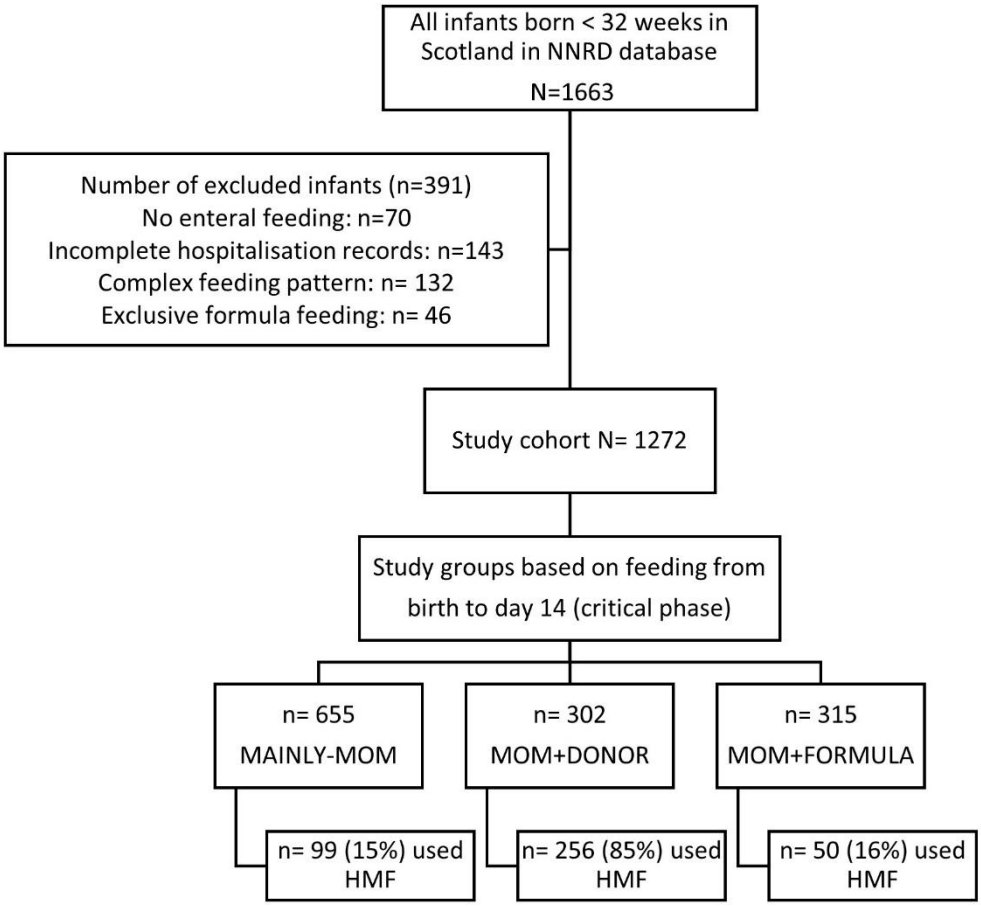
450 NEC: necrotising enterocolitis, ROP: retinopathy of prematurity, BPD: bronchopulmonary dysplasia, PMA:
451 postmenstrual age at discharge.

452 Figure 1



453

454 Figure 2



455