Early versus Delayed Fortification of Human Milk in Preterm Infants: A Systematic Review

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Keywords

Human milk fortifier · Human milk · Expressed breast milk · Premature infant · Preterm infant feeding

Abstract

Expressed breast milk (EBM) is commonly supplemented with commercially prepared human milk fortifier to meet the additional nutritional needs of preterm infants. The optimal milk intake at which to introduce fortification is unknown. The objective of this systematic review was to compare the effect of early fortification (EF) versus that of delayed introduction of human milk fortifier (DF) on short-term outcomes including growth, feeding intolerance, length of hospital stay, and maturity at discharge in very-low-birth-weight infants. The search was carried out until March 2019 using 5 electronic databases (PubMed, Ovid Medline, Web of Science, Ovid Embase, and the Cochrane Library). The search was supplemented with a search of the clinical trial registry and reference lists. Eligible studies involved randomized controlled trials that had been designed to compare EF against DF using multi-nutrient fortifier for infants of a birth weight of <1,500 g who were fed exclusively or predominantly EBM. Four authors independently screened the stud-

ies for eligibility. A total of 1,972 articles were screened; 2 studies met the inclusion criteria and were included with a total number of participants of 171. The definition of EF and DF was not consistent between the 2 studies. There was no significant impact of EF versus DF on all outcomes. In conclusion, current data are limited and do not provide evidence on the optimal time to start fortification. The definition of EF and DF needs to be agreed upon and further larger randomized controlled trials are required.

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Introduction

The third trimester of pregnancy is a period of nutrient accretion and growth. Preterm infants have missed some or all of that period, and therefore their nutritional requirement is much higher than that of term infants. They accumulate significant nutrient deficiency in early postnatal life, which may result in growth restriction (weight below the 10th centile for postmenstrual age [PMA]). Poor growth is a very common problem in the preterm infant population, with poor postnatal growth found in 99% of extremely low-birth-weight infants [1], and can be

associated with a higher risk for short-term morbidities [2–4]. Postnatal growth restriction has been associated with poorer neurodevelopmental outcomes and may continue to affect ex-preterm infants during later childhood and adulthood [5–7]. Expressed breast milk (EBM) confers numerous advantages for preterm infants, especially those born with a very low birth weight [8]. However, when fed as the only source of nutrition, EBM does not meet the preterm infant's increased nutritional requirements [9, 10]. The protein requirement of growing preterm infants is between 3.5 and 4.5 g/kg/day [11]. Feeding with 150 mL/kg/day of unfortified EBM (often considered full enteral feeding) provides only about 1.8 g/kg/day of protein. Providing optimal early nutrition to preterm infants is challenging, but it can be facilitated by the use of multi-nutrient human milk fortifier (HMF). The addition of an HMF to EBM is recommended but there is no consensus on the timing at which HMF can safely be introduced and practice vary greatly. Fortification alters both the nutrient density and osmolality of EBM, which may affect intestinal peristalsis and feed tolerance, and increase the risk of necrotizing enterocolitis (NEC) [12]. Historically, this has been used as a justification for delaying the introduction of HMF. There is some evidence that these adverse outcomes may be more common with the use of bovine-based HMF, but the data are limited [13–15]. However, any risk needs to be balanced against the early introduction of HMF to avoid postnatal growth failure, which itself may have adverse neurodevelopmental consequences [16]. The aim of this systematic review was to compare in-hospital outcomes of early versus delayed introduction of multi-nutrient human milk fortifier. Outcomes of interest were short-term growth, feeding intolerance, length of hospital stay and PMA at discharge.

Methods

Search

Published literature was searched up to March 28, 2019 using five databases. The reference lists of the most relevant papers and reviews were searched manually. The clinical trial registration websites (clinicaltrials.gov) and Current Controlled Trials (isrctn.com) were searched for ongoing or completed trials. Abstracts were considered for inclusion only if they contained the necessary information. The search strategy was based on MeSH terms/subject headings and separate keywords. The MeSH terms were the following: fortified food, human milk, premature infant, growth and development, mortality, low birth weight, breast milk, and diet supplementation. The keywords were human milk, breast milk, and fortification. Boolean terms (AND, OR) were used to connect

the search words. The study designs included were randomized or quasi-randomized controlled trials in the English language and there was no date restriction. Details of the systematic review protocol and search strategy are available in online supplementary material (Tables a and b; for all online suppl. material, see www.karger.com/doi/10.1159/000501279).

Inclusion Criteria

A study was eligible if it was a randomized or quasi-randomized controlled trial and the participants were both of very low birth weight (<1,500 g) and fed exclusively or predominantly with EBM (either mother's own milk [MOM] or pasteurized donor human milk). We only included studies designed to evaluate early fortification (i.e., added at small enteral volume) versus delayed fortification (i.e., added at larger enteral volume). At least one of our primary outcomes had to be measured. A study was excluded if it did not meet these criteria or included babies with congenital anomalies.

Outcomes

The primary outcomes of this systematic review were short-term growth parameters (length, head growth, and weight gain), feeding intolerance (defined as clinical signs only and/or cessation of feeding), length of hospital stay (number of days that the baby remained in the neonatal unit), and PMA (i.e., gestational age plus chronological age) at discharge. Secondary outcomes were NEC and sepsis.

Study Selection and Data Extraction

To avoid bias in the study selection, the first reviewer (W.A.) screened all titles. Three other reviewers (C.E., A.L.G., and J.S.) screened all the titles again independently to make the final decision and ensure no study was missed. After that, W.A. reviewed the abstracts of all potentially relevant studies and obtained their full text. W.A. assessed full texts against the predetermined inclusion and exclusion criteria with the help of an inclusion checklist form (Appendix, form 1). Excluded studies were double-checked by two reviewers, C.E. and A.L.G. W.A. extracted the data from the studies meeting the inclusion criteria using data extraction sheet (Appendix, form 2). The following data items were extracted: publication year, authors, study settings, country where the study was carried out, design, participants, nutrition intervention, and outcomes of interest. Data were entered into Microsoft Excel.

Individual Study Risk of Bias and Quality Assessment

Three reviewers (W.A., C.E., and A.G.) independently assessed the risk of bias and the overall quality of each study. Criteria suggested by the Cochrane Collaboration tool were applied. Judgment for potential bias in each study methodology was classified as being of low, high or unclear risk according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting [17]. The quality of each individual study was assessed using a scoring tool that we developed. The criteria for quality assessment considered the following aspects: the number of centres involved in the study, sample size, description of the intervention, reporting outcomes definition and method of measurement, study groups' homogeneity, and consideration of confounding factors. Details of our systematic review protocol are available in the supplementary material.

Fig. 1. PRISMA flowchart.

Results

Searches

Database searches returned 5,442 articles, and an additional 25 articles were found through a manual search. After duplicates were removed, the titles of 1,972 articles were screened for relevance, resulting in the exclusion of 1,805 articles. The remaining 167 articles were then assessed by reference to their full texts. After applying our eligibility criteria, 165 records were excluded, and 2 studies [18, 19] were included in this review (Fig. 1).

Description of the Included Studies

The studies' characteristics are summarized in Table 1. The initial sample size was 100 in the trial by Shah et al. [18] and 80 in the trial by Alizadeh et al. [19]. The studies occurred in two distinct geographical regions. One study was carried out in the USA between 2013 and 2015 [18], while the other was done in Iran between 2012 and 2013 [19]. Both studies were published in 2016. One study was conducted in two NICUs [18] and the other in one NICU [19]. Both studies included only preterm infants. In one study, the eligibility criteria included infants below 1,500 g at birth [18], while the other study allowed low birth weights (<2,000 g) to be included; this study was included in the review because the average birth weight of

the participants was 1,295 g. Both studies excluded infants with congenital anomalies. Infants in the study by Alizadeh et al. who had to be fed formula because of insufficient MOM supply were excluded. The average gestational age in the two studies was 29.1 weeks.

There was inconsistency in the definitions of early fortification (EF) and later or delayed fortification (DF) between the two studies. In the study by Shah et al., EF started at 20 mL/kg/day and DF started at 100 mL/kg/day. This study did not report the postnatal age at which fortification was initiated. In the study by Alizadeh et al., EF was reported as "first feeding" and DF was commenced at 75 mL/kg/day. First feeding was described as starting on the "first day," as trophic feeding at a rate specific to birth weight and maturity level. They reported that the mean postnatal age at introduction of fortification in the EF group was 3.7 days.

Infants were fed exclusively with human milk in both studies. In the study by Shah et al., infants were fed both MOM and donated human milk. Infants in the DF group received a higher proportion of donated human milk than those in the EF group (67 vs. 54%) but it was not reported if this was statistically significant. In the study by Alizadeh et al., infants were only fed MOM. In both studies, the fortifier used was of bovine origin and the method used for fortification was the addition of a standard amount for all babies rather than an individualized approach. Both trials

Table 1. Characteristics of the included studies

	Shah et al. [17]	Alizadeh et al. [18]
<i>Methods</i>		
Settings/study period	Two NICUs in USA/2013–2015	One NICU in Iran/2012–2013
Objective	To compare human milk fortification at two different feeding volumes on time to reach full feeding and feeding intolerance	Compare early versus delayed fortification on growth, feeding intolerance, sepsis, and NEC
<i>Participants</i>		
Inclusion criteria	Preterm, birth weight <1,500 g	Preterm, birth weight <2,000 g
Exclusion criteria	Died or expected to die before 72 h of life, major congenital or chromosomal abnormality, no MOM or refused DHM	Major congenital anomalies, transferred to another hospital, did not attend the neonatal clinic follow-up, had to be fed with formula due to insufficient MOM
Randomized/analyzed, <i>n</i>	100/99	80/72
Gestational age	Median (25th, 75th centile) = 27.8 (26, 30) ¹	Mean ± standard deviation = 30.4±1.9 ¹
Birth weight	Median (25th, 75th centile) = 990 (810, 1,225) ¹	Mean ± standard deviation = 1,295±379 ¹
<i>Nutrition management</i>		
Day EN started	3 (2.5, 4)	One
EN advancement rate	10–20 mL/kg/day	10–20 mL/kg/day
Milk of feeding	MOM or DHM	MOM
<i>Intervention description</i>		
Definition of EF	20 mL/kg/day	First feeding
Definition of DF	100 mL/kg/day	75 mL/kg/day
Age at fortification	No data	EF: 3.7±2.76 DF: 9.48±5.31
Fortifier name	Enfamil HMF liquid	Aptamil FMS
Fortifier type	Bovine origin Acidified liquid HMF	Bovine origin Powder
Fortifier dose	5 mL added to 25 mL of EBM	4.4 g added to 100 mL of EBM
Duration of fortification	No data on criteria to stop fortification	Until weight reaches 3 kg
Fortified EBM energy density	24 kcal/oz.	24 kcal/oz.
Fortification method	Standard	Standard

NICU, neonatal intensive care unit; MOM, mother's own milk; DHM, donated human milk; HMF, human milk fortifier; EBM, expressed breast milk; NEC, necrotizing enterocolitis. ¹ Average value is calculated for the two study groups.

aimed to increase EBM caloric density to 24 kcal/oz. Fortification was continued until the weight reached 3,000 g in the study by Alizadeh et al., but the study by Shah et al. did not report a criterion for discontinuing fortification.

The definition of NEC, feeding intolerance, and sepsis outcomes varied between the two studies. In the study by Shah et al., feeding intolerance was defined as symptoms or signs leading to feeding cessation, whereas in the study by Alizadeh et al., it was defined as signs of feeding intolerance only. NEC was defined in the study by Shah et al. using Bell's criteria (stage II or more), but the other study used a list of clinical, laboratory and radiological diagnostic criteria. In the study by Shah et al., sepsis was defined by clinical signs of sepsis proven by blood culture, where-

as the other study defined it by clinical signs only. Definitions for all reported outcomes are listed in the online supplementary file (Table e).

Individual Studies' Risks of Bias and Quality Assessments

There was a low risk of selection bias in the study by Shah et al. In the study by Alizadeh et al., the risk of selection bias was unclear, as no details were provided on the tool used to perform block randomization, and the allocation was concealed. There was a high risk of performance bias in the trial by Shah et al., as the blinding of infants' caregivers and the research investigator was not possible due to the fortification of EBM occurring at the bedside. In the trial by Aliza-

Table 2. Risk of bias assessment

Domain	Shah et al. [17]		Alizadeh et al. [18]	
	review authors' judgement	support for judgement	review authors' judgement	support for judgement
<i>Selection bias</i>				
Random sequence generation	Low risk	Use of blocked stratified randomization approach by computerized software	Unclear risk	Block randomization method, no details how
Allocation concealment	Low risk	The research coordinator and principal investigator performed the enrolment and assignment of infants after randomization	Unclear risk	Double blinded, no details how
<i>Performance bias</i>				
Blinding of participants and personnel (all outcomes)	High risk	Infants' caregiver and research investigators were not blinded; Fortification (intervention) occurred at bedside, blinding was not possible	Unclear risk	It was not reported if the caregiver and researcher were blinded
<i>Detection bias</i>				
Blinding of outcome assessment	Unclear risk	Was not clearly reported if the outcomes measurers were blinded	Unclear risk	It is unclear if the outcome measurer was blinded at the time of outcome measurement
<i>Attrition bias</i>				
Incomplete outcome data	Low risk	99% of the participant were analysed	Low risk	90% of the participant were analysed
<i>Reporting bias</i>				
Selective reporting	Low risk	Outcomes were reported	Low risk	Outcomes were reported

deh et al., the risk of performance bias was unclear, as no details were provided. The risk of detection bias was unclear in both studies. There was a low risk of attrition bias in both studies, as most of the participants remained in the study until the intervention ended (90% in the study by Alizadeh et al. and 99% in the study by Shah et al.). No selective reporting was observed in either trial (Table 2). Shah's study was evaluated to be of high quality, while the other study was evaluated to be of moderate quality (Table 3).

Effect of EF versus DF on Outcomes

Most of the primary and secondary outcomes were measured in both studies with the exception of length of hospital stay, which was reported by only one study (Shah's study). Neither study reported PMA at discharge. The primary outcome in the study by Shah et al. was days to reach full feeding, while in-hospital growth was the primary outcome in Alizadeh's study. Due to the small number of included studies, meta-analysis was not performed. Data on all primary outcomes except length of stay were available for 171 infants in the two trials. Length-of-stay data were available for 99 infants in the trial by Shah et al. Neither study reported differences between groups including NEC or sepsis (Table 4).

Discussion and Conclusion

The main finding of this systematic review is that there is insufficient evidence to evaluate the effects of EF against DF of human milk in very-low-birth-weight infants. Despite screening a large number of international studies using a robust search strategy, we found little evidence on the benefits of EF versus DF. The number of studies was small, and the definitions of EF and DF varied. In one of the included trials, by Shah et al., the primary outcome was days to achieve full feeding volume. They showed that the median days to achieve full feeding and the number of events of feeding intolerance were similar in the EF and DF groups. Some published studies that did not meet our inclusion criteria showed some benefits of EF. One observational study compared EF (80 mL/kg/day) with DF (160 mL/kg/day) in late preterm infants and found that infants in the EF group regained their birth weight faster and had fewer events of feeding intolerance [19]. A clinical trial by Sullivan et al. [20] (which was not designed to compare EF with DF) showed that fortification with human-milk-based fortifier was tolerated at 40 mL/kg/day. An observational study by Tillman et al. [21] showed that EF (from the first feeding) improved bone mineralization (lower alkaline phosphatase).

Table 3. Quality assessment of the included studies

	Shah et al. [17]		Alizadeh et al. [18]	
	score	rationale	score	rationale
Multi-centre	1	Two centres	0	One centre
Sample size	1	99 infants included	1	72 infants included
Description of intervention	2	EF and DF were clearly defined as mL/kg/day	1	EF was defined as “first feeding,” specific volume was not reported
Baseline characteristics comparable	1	EF and DF groups had similar demographic	1	EF and DF groups had similar demographic
Outcomes defined	1	Yes	1	Yes
Outcomes measurement described	1	Yes	0	Yes
Confounding factors	1	RCT but 13% difference in donated human milk intake between groups; not reported if statistically significant	1	RCT
Score (quality level)	8 (high)		5 (moderate)	

Table 4. Effect of EF versus DF on outcomes

Outcome and study	Unit	Early fortification	Delayed fortification	<i>p</i> value
Weight gain, g/kg/day				
Shah, 4 weeks of life	Median (IQR)	8.7 (6.4, 12.2)	7.7 (5.1, 10.6)	0.08
Shah, 36 weeks PMA	Median (IQR)	18.3 (14.9, 20.7)	16.7 (13.9, 22)	0.3
Alizadeh	<i>z</i> score	−1.24 (−3.74 to 0.84)	−1.23 (−3.92 to 1.16)	0.864
Head growth				
Shah, 4 weeks of life	Mean (SD)	−0.97 (0.91)	−0.95 (1.0)	0.90
Shah, 36 weeks PMA	Mean (SD)	−0.71 (1.08)	−0.65 (1.07)	0.80
Alizadeh	<i>z</i> score	−5.15 (−0.95 to 1.66)	−0.43 (−2.77 to 1.10)	0.787
Length gain				
Shah, 4 weeks of life	Mean (SD)	−1.0 (0.57)	0.97 (0.69)	0.81
Shah, 36 weeks PMA	Mean (SD)	−1.58 (0.93)	1.59 (0.89)	0.93
Alizadeh	<i>z</i> score	−0.14 (−3.74 to 2.26)	−0.44 (−4.11 to 1.82)	0.348
Feeding intolerance				
Shah	<i>n</i> (%)	15 (31)	15 (30)	1
Alizadeh	<i>n</i> (%)	5 (14)	3 (9)	0.771
Length of hospital stay, days				
Shah	Median (IQR)	68 (41, 101)	63 (50, 83)	0.49
Necrotizing enterocolitis				
Shah	<i>n</i> (%)	2 (4)	2 (4)	1
Alizadeh	<i>n</i> (%)	2 (6)	0	0.223
Sepsis				
Shah	<i>n</i> (%)	3 (6)	6 (12)	0.49
Alizadeh	<i>n</i> (%)	2 (6)	1 (3)	0.572

IQR, interquartile range; SD, standard deviation. The number of participants analysed for all outcomes in the study by Shah et al. (EF = 49, DF = 50) and in the study by Alizadeh et al. (EF = 36, DF = 36).

and did not have higher events of feeding intolerance. Nevertheless, proper randomized clinical trials designed to evaluate the effectiveness and safety of EF in high-risk infants are needed to inform feeding practice.

Although optimizing nutrition for preterm infants is advantageous in terms of improved short-term growth, there remains a lack of evidence on the longer-term benefits of fortification of EBM. A recently published Cochrane meta-analysis comparing the growth and developmental outcomes of using fortified EBM against unfortified EBM found insufficient data from which to draw any meaningful conclusions [22]. Despite a rigorous search methodology, the authors concluded that there is limited evidence for evaluating the benefits of multi-nutrient fortification of EBM against unfortified EBM.

In summary, current evidence does not provide guidance on the optimal time to start fortification. Further and larger randomized clinical trials comparing the effect of EF versus DF are needed. Future studies should measure core outcomes that are important for both parents and health professionals to allow results to be compared and combined [23].

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Appendix

Form 1: Eligibility checklist			
Criteria		Yes	No
Participants	Were study participants VLBW preterm infants?		
	Did participants have any congenital problems?		
Settings	Were infants fed exclusively or predominantly (>50% of enteral feeding) with EBM (mothers' own milk or donated human milk) during the study period?		
	Did the study take place in neonatal intensive care units or a special care baby unit?		
Study design	Was the study designed to be randomized controlled trials or quasi-randomized controlled trials?		
Interventions or exposures	Was the aim of the study to test early versus delayed fortification of EBM?		
Outcomes measurement	Was any of the following outcomes measured?		
	Primary:		
	Short-term growth parameters [length, head growth, and weight gain]		
	Feeding intolerance		
	Length of hospital stay		
	Post-menstrual age (PMA) at discharge (i.e. gestational age plus chronological age)		
	Secondary:		
Decision to include study	Necrotizing enterocolitis		
	Sepsis		
Reason for exclusion			

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

C.A.E. has been involved in workshops for ILSI Europe. The other authors have indicated they have no potential conflicts of interest to disclose.

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Author Contributions

Mrs. Alyahya conceptualized and designed the systematic review, carried out the searches, screened the studies, assessed the full text, extracted the data, carried out the analysis, and drafted and revised the manuscript.

Prof. Edwards and Dr. Garcia conceptualized and designed the systematic review, screened the studies, supervised the data extraction and analysis and critically reviewed the manuscript.

Dr. Simpson screened the studies and reviewed the analysis and critically reviewed the manuscript.

Dr. Mactier conceptualized and designed the systematic review and critically reviewed the manuscript.

All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Form 2: Data extraction sheet			
Authors, date		Number of centres	
Aim/hypothesis		Location	
Methods			
Study design		Settings	
Study period			
Baseline subjects characteristics			
Number of subjects		Gestational age	wk
Birth weight	g		
Nutrition			
Day PN started		Day EN started	
EN advancement rate	mL/kg/day		
Milk 1: Primary milk for feeding	☐ Mothers' own milk ☐ Donated human milk ☐ Formula		
Milk 2: secondary milk for feeding	☐ Mothers' own milk ☐ Donated human milk ☐ Formula		
Percentage of EBM intake during the study	%		
Fortification			
Fortification method	☐ Standard ☐ Adjustable ☐ Targeted		
HMF name			
HMF type	☐ Powder ☐ Liquid		
HMF dose added to EBM			
HMF origin	☐ Human milk based ☐ Bovine based		
Energy of fortified EBM, kcal/oz			
Nutrition content per 100 mL of fortified EBM			
Method of calculation	☐ Analysed by infrared milk analyser ☐ Assuming EBM content		
Energy	kcal		
Protein	g		
Fat	g		
Osmolality	mosm/L		
Outcomes definition			
Feeding intolerance			
NEC			
Sepsis			
	Intervention group	Control group	p value
Gestational age			
Birth weight			
Age HMF given			
Volume HMF given			
Duration HMF given			
Total energy intake during study			
Total protein intake during study			
Weight gain			
Head growth			
Length gain			
Feeding intolerance, <i>n</i>			
Feeding intolerance, %			
Length of stay, days			
PMA at discharge, weeks			
NEC, <i>n</i>			
NEC, %			
Days of PN			
Sepsis, <i>n</i>			
Sepsis, %			
Day to full feed			

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