Pilot Study on Growth Parameters and Nutritional Biochemical Markers in Very Low Birth Weight Preterm Infants Fed Human Milk Fortified with Either Human Milk Fortifier or Post Discharge Formula

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Background: *Nutrition is an important aspect in the care of very low birth weight (VLBW) preterm infants. Human milk fortified with human milk fortifiers (HMF) is best for enteral feeding of premature infants. HMF is expensive and not easily available in Thailand. Post discharge formula (PDF) has been routinely used to fortify human milk at Queen Sirikit National Institute of Child Health (QSNICH) but there is lack of supportive data regarding efficacy and safety.*

Objective: *To study and compare anthropometrics, biochemical markers and complications in VLBW infants fed human milk fortified with either HMF or PDF.*

Material and Method: *This was a prospective, randomized pilot study conducted in the neonatal unit of QSNICH from 1 March 2010 to 28 February 2011. Very low birth weight neonates, whose mothers had adequate breast milk within 96 hours of birth, were enrolled in the study and received parenteral nutrition and enteral feeding as per protocol. Once the babies were feeding 100 cc/kg/day of human milk, they were randomly divided into two groups: the human milk fortified group (HMF group) and the post discharge formula fortified group (PDF group). Body weight was recorded daily while head circumference and length were recorded weekly. Hematocrit, Blood Urea Nitrogen (BUN), creatinine, electrolytes (including phosphorus and calcium), alkaline phosphatase and albumin were checked at the beginning of the study (feeding 100 cc/kg/day), 3 weeks later and when on full oral breast feeding or reached a weight of 2,000 grams, which ever came first.*

Results: *Thirty-eight infants were enrolled in the study but eventually only 33 remained (18 in HMF group, 15 in PDF group). Both groups had similar baseline demographic data, nutritional management, postnatal morbidities and length of stay. There were no statistically significant differences in growth parameters and serum biochemical markers between the groups. Definite NEC was not different between the groups. Other complications of prematurity including osteopenia of prematurity were similar in both the groups. The cost of breast milk fortification per person in the PDF and HMF group was 605 and 11,655 baht, respectively.*

Conclusion: *Human milk fortifiers are best for fortification of human milk in VLBW babies but using PDF as a fortifier may be considered as an alternative for VLBW infant in resource limited, developing countries. However, it should always be additionally supplemented with multivitamins especially vitamin D, iron, calcium and phosphorus. Complications like feeding intolerances and suspected NEC should be monitored closely. Larger studies focusing on short and long-term outcomes are needed in the future.*

Keywords: *Human milk, Human milk fortifier, Post-discharge formula*

J Med Assoc Thai 2014; 97 (Suppl. 6): S164-S175
Full text. e-Journal: *http://www.jmatonline.com*

Nutritional management is an important aspect in the care of the very low birth weight (VLBW) infant. Both parenteral and enteral nutrition have to be meticulously managed in each baby for optimum growth and development. The American Academy of Pediatrics (AAP) recommends human milk (HM) for enteral feeding of the premature infant[1]. Not only is it easily digested[2,3], when compared with formula, it has been shown to reduce infections such as sepsis, diarrhea, urinary tract infection (UTI), pneumonia and meningitis[4,5]. It has also been shown to decrease the incidence of necrotizing enterocolitis (NEC)[6,7], which is a major morbidity in the VLBW. Along with all of the above, the low birth weight infants fed human milk also

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have higher intelligence quotient (IQ) scores when compared with the formula fed babies[8].

Unfortunately, despite its many advantages for the VLBW, mature human milk does not support optimum growth of these infants. It is unable to provide adequate calories, protein, vitamins and minerals that are essential for this vulnerable group[9,10]. Studies on VLBW neonates fed solely on human milk have shown an increase in the incidence of growth failure and osteopenia of prematurity (OPP)[11-14]. However, studies on infants fed fortified HM showed improved growth and neurodevelopmental outcomes[15-20]. Thus, HM fortification is essential for the optimum growth of these premature infants. Commercially available human milk fortifiers (HMF) come in various forms including dry powder or liquid forms; single or multiple components, and bovine or human.

In Thailand, only the dry bovine multi-component HMF is available from one company. Not only is it very expensive, it has a short shelf life and is frequently unavailable. Hence, in Thailand, VLBW infants fed HM have different feeding protocols in order to provide adequate nutrition. These include fortification of HM with either preterm formula (PTF) or post discharge formula (PDF) during each feed or alternating HM with PTF or PDF. At QSNICH, we have been routinely fortifying HM with PDF in each feed. Our limited database search did not show any studies published in Thailand or anywhere else on this kind of fortification. This routine to research comparative study was conducted to see the short-term outcomes of VLBW infants fed HM fortified with either PDF or HMF.

Objective

The objective of the present study was to compare the anthropometrics, biochemical markers and complications in VLBW infants fed human milk fortified with either HMF or PDF.

Material and Method

This was a prospective randomized study conducted in the neonatal unit of QSNICH from March 2010 to February 2011. All VLBW infants admitted in the unit were eligible for the study. Only those babies whose mothers had adequate BM within 96 hours of birth were enrolled in the present study. Informed consent was obtained from the parents.

Excluded from the present study were all infants with major congenital anomalies, syndromes, intrauterine infections, definite NEC before randomization, anatomical and severe functional GI tract anomalies, IVH grade >III, severe BPD, chronic diuretic use and mothers who had contraindications for breast feeding.

Parenteral nutrition was started on the first day of life in all the babies. This included protein (10% Amiparen) at 1-1.5 g/kg/day and increased by 1 g/kg/day to a maximum of 3.5-4 g/kg/day. Glucose infusion with 5-10% dextrose was started at 6 mg/kg/min and adjusted to keep blood sugar at 80-120 mg/dL. Lipid emulsion (20% Intralipid) at 0.5-1 g/kg/day was started on the 2nd day of life and increased by 0.5 g/kg/day unless serum triglyceride (TG) levels increased to greater than 150 mg/dL. If the TG levels went above 200 mg/d the lipids were temporarily stopped. The maximum intralipid was 3.5 g/kg/d infused slowly over 24 hours. Parenteral lipids and proteins were gradually weaned off in decrements of 0.5 g/kg/day once the enteral intake was increased.

All babies were started on trophic feeding (<20 cc/kg/day) with human milk once they were considered clinically stable. Feeding was advanced by increments of 15-30 cc/day at the attending neonatologist's discretion. When enteral feeding reached 100 cc/kg/day, the infants were stratified by block randomization into two groups; the PDF fortified group (PDF group) or HMF fortified group (HMF group). Each group was further subdivided into three subgroups by birth weight (<1,000, 1,000-1,249 and 1,250-1,500 grams). The maximum milk intake was 160-200 cc/kg/day. If the mothers were unable to provide HM, the babies were given preterm formula. Infants who received preterm formula more than 20% of the total milk intake were also excluded from the study.

The fortification of BM was prepared by the lactation ward nurses who were specifically assigned to this task. The initial fortification was to 22 cal/oz (2 sachet of HMF/100 cc BM or 1 tsp PDF/130 ml BM) for 2-4 days and then it was increased to 24 cal/oz (4 sachet of HMF/100 cc BM or 1 tsp PDF/70 ml BM)[21]. If the weight gain was less than 10 gm/kg/day or received <120 kcal/kg/day, the feeds were increased to a concentration of 27 cal/oz (0.4 cc MCT oil/30 ml HMF or 1 tsp PDF/40 ml BM) or 30 cal/oz (0.8 cc MCT oil/30 ml HMF or 1 tsp PDF/40 ml BM + 0.4 cc MCT oil). The fortification of milk was performed once daily under aseptic conditions and eight feeds were stocked for each baby. Refrigerated fortified milk that had not been used within 24 hours or unrefrigerated fortified milk that had not been used within 4 hours was discarded[22].

Infants were fed either via orogastric (OG) bolus or 1-1½ hour OG drip with the syringe in an

upright position. Gastric residuals were checked before each feed. If they were >50% of the feed volume, bilious or fecal in nature, the baby would be made nil per os (NPO) and appropriate tests were performed according to the clinical presentation. A complete septic work-up, when indicated, included complete blood count (CBC), urine analysis (UA), stool for occult blood, blood culture, c-reactive protein (CRP) and radiographs were performed. Abdominal radiographs were interpreted by the radiologists who were blinded to the study groups. If the radiographs were normal, the baby would restart with oral feeding, but at half the previously tolerated volumes. If definite NEC was diagnosed according to the modified Bell's criteria, the baby was treated by the standard hospital NEC protocol.

Every infant was supplemented with 2 mg/kg/day of iron after the first two weeks of life and vitamin D supplementation of 400 IU/day. If the infant was suspected to have OOP (serum alkaline phosphatase >450 U/L and serum phosphorus <4.5 mg/dl), vitamin D was increased to 800-1,000 IU/day and additional calcium and phosphate were administered to the baby. The attending neonatologist made adjustments according to the biochemical markers. After the first 2 months of the study, all infants in the PDF group received additional supplements of calcium and phosphorus once full feeding had been achieved. The doses were customized to each baby according to their daily requirements.

Body weight was recorded daily while head circumference and length were recorded weekly. Hematocrit, BUN, creatinine, electrolytes (including phosphorus and calcium), alkaline phosphatase and albumin were checked at the beginning of the present study (feeding 100 cc/kg/day), 3 weeks later and when the neonate was on full oral breast feeds or when a weight of 2,000 grams was attained, which ever came first. Other tests were performed as per routine unit protocol and/or at the discretion of the attending neonatologist.

Skin to skin contact was encouraged and all mothers were taught how to express breast milk manually and via breast pump. If there was lactation failure (<350 cc BM/day after expressing 8-10 times per day), then the mother would be prescribed a galactogue (domperidone 10-20 mg, 3 times per day) to help increase

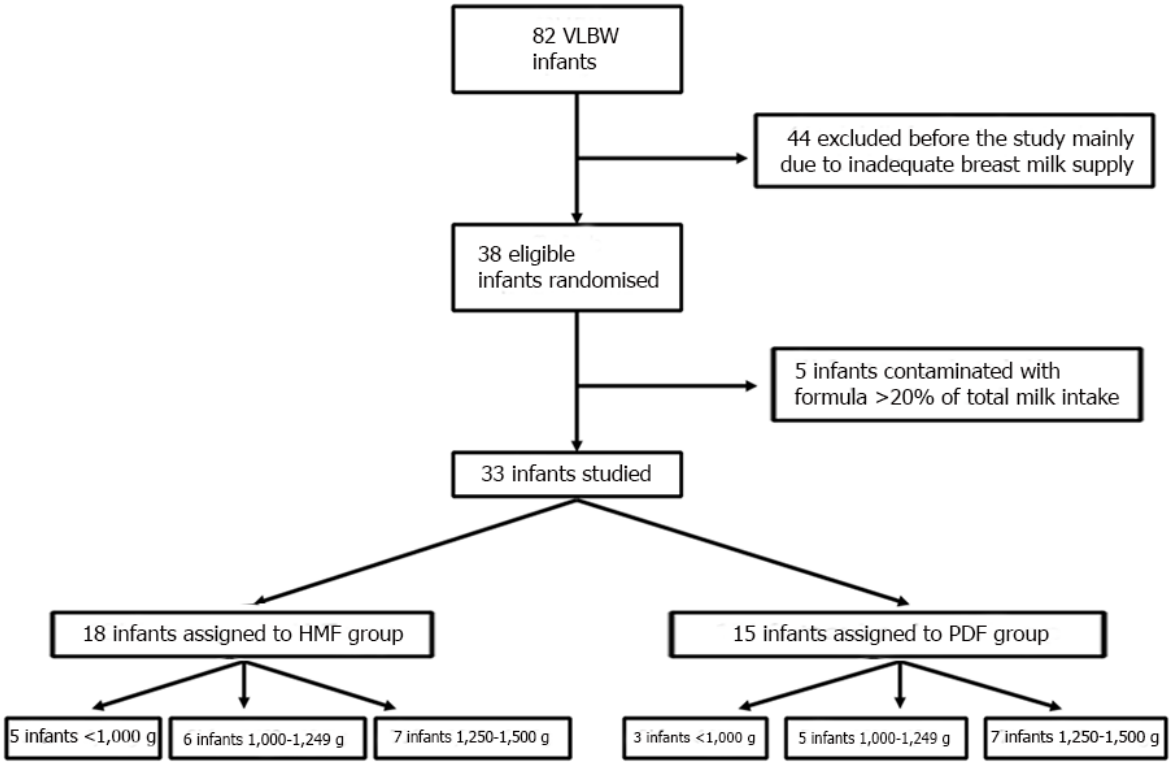

Fig. 1 Diagram.

Table 1. Demonstrates nutrients in human milk which is fortified with HMF 1 pk/25 mL (A), PDF 24 Cal/fl oz (B) and PDF 27 Cal/fl oz (C)[21]

Nutrient per 100 ml	A	B	C
Energy, Cal: (cal/oz)	80.3 (24.09)	83 (24.90)	93 (27.9)
Protein, g:	2.50	1.45	1.73
% of total calories	12	7	7.4
Fat, g:	4.87	4.7	5.27
% of total calories	55	51.2	51
Linoleic Acid, mg:	507.0	486	567
Carbohydrate, g:	7.00	8.69	9.77
% of total calories	35	42.1	42
Calcium, mg	114.7	44	56
Phosphorus, mg	62.7	24	31
Magnesium, mg	4.1	4.9	5.9
Iron, mg	1.56	0.32	0.53
Zinc, mg	1.06	0.31	0.45
Iodine, mcg	-	13	15
Sodium, mg (mEq)	40.7 (1.77)	23	26
Potassium, mg (mEq)	85.7 (2.19)	74	90
Chloride, mg (mEq)	67.7 (1.91)	53	61
Vitamin A, IU:	1,137.7	294	344
Vitamin D, IU:	152	13	21
Vitamin E, IU:	5.66	1	1.4
Vitamin K, mcg:	4.6	2	3.3
Renal solute load, mOsm	22.18	13.6	16.3

Table 2. Excluded cases

Causes	Case (%)
Inadequate breast milk supply	27 (61.36)
Contraindication for breast milk	1 (2.27)
Death before the beginning of study	3 (6.82)
IVH grade III, IV	3 (6.82)
Microcephaly	1 (2.27)
Ileal perforation, before the beginning of study	1 (2.27)
NEC stage III	2 (4.55)
Still on ventilator at full feeding	6 (13.64)

breast milk production[23].

Statistics

Since the authors could not find any previous studies comparing HMF with PDF fortification, sample size was calculated based on a previous study[24] comparing fortified with unfortified human milk feeding. Based on the desired power of 80%, the total sample size was 50. SPSS version 16.0 was use to calculate statistical values. The data were presented as percentages, means ($\pm$SD) or medians (IQR) as appropriate. Comparison between the groups of categorical variables was done using χ^2 or Fisher's exact test while student t-test was used for continuous variables. The non-parametric data was analyzed using the Mann-Whitney U test. A *p*-value of <0.05 was considered statistically significant.

Products used in the present study were- Enfamil Human Milk Fortifier (Mead Johnson Nutrition Ltd) as the HMF and-Similac NeoSure Advance Powder (Abbott Laboratories) as the PDF. Their nutrient values are shown in Table 1

Results

Eighty-two VLBW infants were initially recruited into the present study, however, 44 infants were excluded due to various reasons as shown in Table 2. The major cause (61.36%) of exclusion was inadequate milk supply. Thirty-eight infants were randomized for the study, but only 33 were ultimately included as five infants who received more than 20% formula of their total milk intake. There were 18 VLBW infants in the HMF group and 15 in the PDF group as shown in diagram.

Table 3. Demographic data

Characteristics	HMF (n = 18)	PDF (n = 15)	*p*-value
Birth weight, g	1,158.61±232.94	1,206.67±224.99	0.553
Birth weight classified into 3 groups <1,000 g, (median: 892.5, min-max: 635-995)	5 (27.78)	3 (21.4)	0.590
1,000-1,249 g, (median: 1,180, min-max: 1,010-1,240)	6 (33.33)	5 (33.33)	
1,250-1,500 g, (median: 1,395, min-max: 1,266-1,500)	7 (38.89)	7 (46.67)	
Gestational age, weeks	30.00±1.88	30.67±2.32	0.368
Male	11 (61.11)	9 (60.0)	0.948
Mother age ≥30 years	8 (44.40)	7 (46.70)	0.898
[+] Higher parental education	14 (77.77)	10 (66.67)	0.697
Income >10,000 baht/month	16 (88.89)	12 (80.0)	0.332
Cesarean section	11 (61.11)	10 (66.67)	0.741
[++] Perinatal asphyxia	13 (68.42)	11 (78.57)	0.403
Antenatal corticosteroid	15 (78.95)	8 (57.14)	0.126
PDA (confirmed by echocardiography)	11 (57.89)	8 (57.14)	0.665
Medical closure of PDA,	10 (52.63)	7 (50.00)	0.624[b]
Non-invasive ventilator (days) (median: 3, min-max: 0-34)	6.50±9.88	4.67±5.90	0.533
Conventional ventilator (days) (median: 3, min-max: 0-18)	5.00±5.78	2.20±3.49	0.111
[#] HFOV (days) (median: 0, min-max: 0-8)	0.56±1.92	0	0.036**
Regained birth weight (days) (median: 9, min-max: 1-21)	10.00±4.04	8.20±4.78	0.250
Weight at beginning of study, g (median: 1,335, min-max: 770-1,767)	1,270.78±239.13	1,319.13±267.45	0.587
Clinical sepsis before study	17 (94.45%)	14 (93.34%)	0.859

Data are mean ± SD, n (%).[+] higher parental education: college and university level or above; [++] perinatal asphyxia: Apgar score at 1 minute is 7 or below; [#] both the patient on HFOV were in then HMF arm and the indication in both was air leak syndrome; there were 2 SGA babies in the study (HMF 1, PDF 1); All of 3 outborn babies in the study were in PDF group and there was no diagnosis of definite NEC before begin the study period

Table 4. Nutritional data

Nutritional management data	HMF (n = 18)	PDF (n = 15)	*p*-value
Onset of oral feeding, (day) (median: 4, min-max: 1-20)	5.67±4.67	4.80±2.78	0.533
Age at start of study, (day) (median: 14, min-max: 5-29)	16.27±5.92	14.60±4.73	0.382
Complete [#]OGT feeding, (day) (median: 19, min-max: 10-44)	19.83±7.35	21.80±9.46	0.506
Complete breast/bottle feeding, (day) (median: 55, min-max: 22-98)	57.89±18.25	53.07±14.78	0.417
Duration of PN**, (day) (median: 17, min-max: 9-44)	21.94±11.48	22.27±10.84	0.935
Total fluid intake, (cc/kg/day) (median: 144, min-max: 128.59-166.19)	146.72±9.46	144.07±7.60	0.388
Total calories intake, (kcal/kg/day) (median: 107.55, min-max: 70.06-129.88)	112.34±14.69	106.55±15.51	0.280
Total human milk intake, (cc/kg/day) (median: 142.60, min-max: 116.59-166.19)	143.61±11.93	139.27±10.40	0.279
Formula intake, (cc/kg/day) (median: 0, min-max: 0-29.32)	5 (3.11±8.25)	7 (4.80±8.92)	0.576
* Proportion increased to 27 kcal/oz,	9 (50.00)	8 (53.30)	0.849

Data are mean ± SD, n (%). *there was no infant who was fed 30 kcal/oz. concentration, **PN = parenteral nutrition, [#] OGT = orogastric tube

Table 5. Primary outcome: growth parameters

Growth parameters	HMF (n = 18)	PDF (n = 15)	*p*-value
Delta weight, (g/day) (median: 20.45, min-max: 15.04-33.07)	21.20±4.02	21.14±4.96	0.974
Delta length, (cm/wk) (median: 0.84, min-max: 0.32-1.73)	0.90±0.27	0.86±0.34	0.713
Delta OFC*, (cm/wk) (median: 0.94, min-max: 0.26-1.5)	0.86±0.24	0.84±0.28	0.795
Weight at discharge, (g) (median: 2,230, min-max: 1,736-2,892)	2,193.33±195.38	2,259.80±327.14	0.475

Data are mean ± SD, n (%)

Table 6. Biochemical protein markers

Biochemistry lab	Time*	HMF (n = 18)	PDF (n = 15)	*p*-value
BUN**, (mg/dl)	1	8.10±3.42	8.32±5.6	0.891
	2	4.98±2.74	54.87±2.39	0.909
	3	4.61±2.91	3.89±1.16	0.367
Creatinine, (mg/dl)	1	0.54±0.14	0.54±0.11	0.897
	2	0.35±0.07	0.37±0.08	0.443
	3	0.29±0.05	0.31±0.06	0.377
Serum albumin, (g/dl)	1	3.28±0.49	3.40±0.39	0.452
	2	3.44±0.33	3.22±0.46	0.129
	3	3.37±0.25	3.28±0.22	0.323

Data are mean ± SD, n (%); * Time: 1 = start of randomization, 2 = 3 weeks after the start of study, 3 = on full breast feeding or at 2 kgs whichever came first; ** Blood urea nitrogen

Table 7. Biochemistry serum bone markers

Biochemistry lab	Time	HMF (n = 18)	PDF (n = 15)	*p*-value
Alkaline phosphatase, (U/L)	1	311.72±115.20	281.53±68.79	0.360
	2	428.67±158.29	378.29±113.83	0.323
	3	347.35±167.56	343.62±68.44	0.940
Serum total calcium, (mmol/L)	1	2.48±0.15	2.40±0.20	0.245
	2	2.45±0.14	2.47±0.19	0.728
	3	2.49±0.15	2.39±0.18	0.111
Serum phosphate, (mg/dl)	1	5.65±1.17	5.52±0.98	0.730
	2	6.37±1.15	5.56±0.99	0.044*
	3	6.26±1.12	6.68±0.93	0.276

Data are mean ± SD, n (%)

As can be seen from Table 3, the mean birth weights were similar in both groups: 1,158.61±232.94 grams in the HMF group and 1,206±224.99 grams in the PDF group ($p = 0.553$). The 3 weight subgroups were also similar. The mean gestational ages in the HMF and in the PDF groups were 30.00±1.88 weeks and 30.67±2.32 weeks respectively ($p = 0.368$). The maternal age, parental education status and incomes were also similar in both the groups. Even though the maternal antenatal steroid use seemed higher (78.95%) in the HMF group compared with the PDF group (57.14%), it was statistically insignificant ($p = 0.126$). Other data, including the rate of PDA, medical closure for PDA, mean non-invasive and conventional ventilator days,

Table 8. Urine biochemical bone markers

Biochemistry lab	Time	HMF (n = 18)	PDF (n = 15)	*p*-value
Urine Ca/Cr, mean ± SD				
(median: 9.46, min-max: 0.28-85.95)	1	24.83±26.83	20.01±24.03	0.594
(median: 7.22, min-max: 0.24-265.87)	2	8.79±8.53	43.05±77.44	0.123
(median: 9.50, min-max: 0.41-70.66)	3	19.45±21.02	11.95±12.36	0.263
Urine PO_4/Cr, mean±SD				
(median: 2.58, min-max: 0-162.01)	1	24.62±43.23	8.04±10.42	0.132
(median: 4.95, min-max: 0-279.4)	2	21.33±34.87	51.37±95.35	0.279
(median: 11.80, min-max: 0.094-233.03)	3	19.23±30.47	49.44±63.15	0.094
% TRP, mean ± SD				
(median: 99.16, min-max: 15.86-100)	1	89.55±20.67	97.47±3.419	0.127
(median: 98.92, min-max: 44.1-100)	2	96.31±6.12	0.28±17.56	0.238
(median: 98.32, min-max: 58.35-99.98)	3	97.09±4.90	92.07±11.01	0.103

Data are mean ± SD, Ca = calcium, PO_4 = phosphate, Cr = Creatinine, % TRP = percent tubular reabsorption of phosphate
Note: 2 infants in the PDF and 1 in the HMF received short term diuretics

Table 9. GI and non-GI morbidities and complications

Morbidity or complication	HMF (n = 18)	PDF (n = 15)	*p*-value
Gastrointestinal			
NPO during study period, (day) (median: 0, min-max: 0-13)	1.94±3.70	3.90±4.33	0.172
TPN induced cholestatic jaundice	1 (5.6)	1 (6.7)	1.000
Suspected NEC	1 (5.6)	6 (40.0)	0.030*
Definite NEC	2 (11.1)	0 (0)	0.489[b]
Episodes of rectal bleeding	0.28±0.96	0.33±0.49	0.066
Episodes of feeding intolerance	0.94±0.99	1.80±1.52	0.063
Non-gastrointestinal			
BPD	7 (38.90)	5 (33.33)	0.741
IVH	4 (22.23)	0 (0)	0.070
ROP	3 (16.67)	1 (6.67)	0.369
Suspected osteopenia of prematurity	6 (33.33)	6 (40.00)	0.692
Episodes of suspected clinical sepsis	0.28±0.57	0.53±0.83	0.307
Episodes of culture positive sepsis	0.06±0.24**	0.00±0.00	0.370
EUGR	18 (100)	13 (86.67)	0.199
Subcutaneous fat necrosis	0 (0)	2 (13.33)	0.199

Data are mean ± SD, n (%); * statistically significant difference (*p*-value <0.05); ** 1 infant in HMF group has positive blood culture and the pathogen was *Klebsiella pneumoniae* (ESBL); GI = gastrointestinal tract; NPO = nothing per oral; NEC = necrotizing enterocolitis; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; ROP = retinopathy of prematurity; EUGR = extrauterine growth restriction (body weight <10 percentile at 36 wk PMA or at discharge)

were not significantly different. Two infants in the HMF group were on HFOV for air leak syndrome. Time to regain birth weight was 10.00±4.04 days in the HMF group and 8.20±4.78 days in the PDF group ($p = 0.25$). The weight at the randomization was also similar between both the groups; 1,270.78±239.13 grams in the HMF group and 1,319.13±267.45 grams in the PDF group ($p = 0.587$).

Table 4 shows the nutritional data of the infants. The mean age at onset of oral feedings was 5.67±4.67 days in the HMF group and 4.80±2.78 days in the PDF group (p = 0.533). The age at the start of the study was 16.27±5.92 days in the HMF group and 14.60±4.73 days in the PDF group ($p = 0.382$). The infants were on full orogastric tube (OGT) feeding and complete breast/bottle feeding by 19.83±7.35 days and

Table 10. Length of stay and GA at discharge

	HMF (n = 18)	PDF (n = 15)	*p*-value
LOS, (day) (median: 58, min-max: 23-100)	60.33±17.80	56.33±16.50	0.511
PMA at discharge, (weeks) (median: 37, min-max: 35.71-42.86)	38.62±1.39	38.71±2.05	0.876

Data are mean ± SD, n (%); LOS = length of stay; PMA = post menstrual age

57.89±18.25 days, respectively, in the HMF group and 21.80±9.46 days and 53.07±14.78 days, respectively, in the PDF group ($p = 0.506$, 0.417). The mean duration of parenteral nutrition was 21.94±11.48 days in the HMF group and 22.27±10.84 days in the PDF group. The mean fluid volume and assumed caloric intake was 146.72±9.46 cc/kg/day and 112.34±14.69 kcal/kg/day, respectively, in the HMF group and 144.07±7.60 cc/kg/day and 106.55±15.51 kcal/kg/day, respectively, in the PDF group ($p = 0.388$, 0.280). The mean total breast milk was 143.61±11.93 cc/kg/day in the HMF group and 139.27±10.40 cc/kg/day in the PDF group ($p = 0.279$).

Primary outcomes

There were no statistically significant differences in the growth parameters and weight at discharge between the two groups (Table 5). The mean delta weight, length and occipitofrontal head circumference were 21.20±4.02 g/day, 0.90±0.27 cm/week, and 0.86±0.24 cm/week, respectively, in the HMF group. The mean delta weight, length and occipitofrontal head circumference were 21.14±4.96 g/day, 0.86±0.34 cm/week, and 0.84±0.28 cm/week, respectively, in the PDF group.

As can be seen from Tables 6-8, the biochemical markers (protein and bone) did not show any statistically significant differences during the 3 time periods for which they were tested. The only exception being the mean phosphorus level, even though within normal limits, which was lower 5.56±0.99 mg/dl in the PDF group 3 weeks after start of fortification when compared with the HMF group 6.37±1.15 mg/dl ($p = 0.044$) (Fig. 1).

Secondary outcomes

Most of the gastrointestinal (GI) complications were not statistically different between the two groups (Table 9). There was a significantly higher percentage of suspected NEC in the PDF group compared with the HMF group (40% vs. 5.6%, $p = 0.03$). However, there were two cases of definite NEC in the HMF group but none in the PDF group. There were no statistically significant differences in the non-GI morbidities or complications including suspected osteopenia of prematurity (OOP), BPD, IVH or ROP.

The postmenstrual age at discharge and total length of hospital stay in the HMF group were 38.62±1.39 weeks and 60.33±17.80 days, respectively compared to 38.71±2.05 weeks and 56.33±16.50 days respectively in the PDF group. This was not statistically significant (Table 10).

The total cost of the nutritional fortification was 11,655 baht per baby in the HMF group and 605 baht per baby in the PDF group for an average duration of 38 and 36 days, respectively.

Discussion

This was a routine to research prospective study. In order to optimize breastfeeding in the preterm infants, we had been routinely fortifying HM with PDF for feeding our premies, as HMF is expensive and not easily available. To our knowledge, this is the first study in Thailand to compare short-term outcomes of HM fortified with either PDF or HMF in feeding preterm infants before discharge from the hospital. Unfortunately, of all the eligible premies, approximately 40% were excluded, mainly due to inadequate breast milk. Extrauterine growth restriction (growth below 10th percentile at 36 weeks post- menstrual age or at discharge) was detected in 100% and 86.67% in the HMF and PDF groups respectively. This is similar to other previously reported studies[24].

There were no clinically significant differences in the primary outcomes between the groups. One of the reasons for this, especially in regards to the biochemical bone markers, could be due to the fact that after the first two months of the study, all babies who had been randomized into the in the PDF group were given an additional supplement of calcium and phosphorus, customized to meet their requirements as per the ESPGAN recommendations[25].

There were no statistically significant differences in the secondary outcomes between the groups, except for suspected NEC, which was greater

in the PDF group. However, there was a trend towards a higher number of definite NEC in the HMF group. The overall NEC rate in the current study was 6% which is lower than other studies, some being as high as 10%[26]. The lower occurrence of NEC could be explained by the protective effect of human milk[27].

One of the major concerns in the preterm infants fed human milk without fortification is its effect on bone growth, which could result in osteopenia of prematurity and short stature. There were no differences seen between the groups in the present study with regard to this complication. As stated earlier, all the infants in the PDF group were additionally supplemented with calcium and phosphorus to make up for the low level of these minerals in PDF.

The time to discharge and length of hospital stay were also similar between the groups. One major concern in the developing region is the financial burden incurred from the care of the VLBW infant. Since HMF is very expensive, the cost of the nutritional supplementation was also calculated. The cost of nutritional supplementation in the PDF group was found to be 20 times lower than the HMF group even though the total duration of supplementation was similar.

There were many limitations to the present study. The number of cases recruited was lower than the sample size calculated to show the differences in the weight gain. This was due to the high cost of HMF that eventually led to early termination of the study. However, a total sample size of 32 and 18 cases were required to show the significant difference in length and head circumference respectively. Secondly, the majority of cases included in the study were in the 1,250-1,500 gram weight range. Thus, the present study may not adequately represent the extremely low birth weight group in whom fortification of HM is very important. A third and important limitation of the present study was that measurement of bone mineral content and bone mineral density, assessed by dual-energy absorptiometry (DEXA) and considered as golden standard for detecting and monitoring osteopenia, was not performed. Until recently, it has been more of a research tool, not used widely. Serum calcium, phosphorus and alkaline phosphatase, which were used as bone markers in the present study, are not reliable markers for the detection of mineral status or bone storage. Similarly, urine calcium/phosphorus to urine creatinine ratios, which were also used in the current study, show marked variability in the preterm infants and are not reliable[28]. Tubular reabsorption of phosphorus may be a better guide to the adequacy of the phosphate supplement, >95% indicating inadequate supplementation[28,29]. Finally, only the short-term outcomes were studied.

Conclusion

This routine research pilot study is the first of its kind in Thailand. Human milk fortified with post discharge formula may be considered as an alternative means of fortification in a resource limited country, however, it is also not enough and the additional calcium, phosphorus and vitamin D must be supplemented. Larger studies, including more of the extremely low birth weight infants, who are the most at risk for poor growth and developmental outcomes due to inadequate nutrition, are needed along with the long-term outcomes.

Acknowledgement

The present study was partially funded by grants from the Department of Medical Services, Ministry of Public Health and the Perinatal Society of Thailand.

Potential conflicts of interest

None.

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โครงการนำร่องการศึกษาการเจริญเติบโตและค่าทางชีวะเคมีของภาวะโภชนาการของทารกเกิดก่อนกำหนดน้ำหนักน้อยระหว่างกลุ่มที่ได้นมแม่ที่ผสม human milk fortifier กับกลุ่มที่ได้นมแม่ที่ผสมนมผงดัดแปลงสำหรับทารกเกิดก่อนกำหนดสูตรต่อเนื่อง

มิรา โครานา, ชนินทร์ เจียมสัจจะมงคล

ภูมิหลัง: นมแม่เป็นอาหารที่ดีที่สุดสำหรับทารกแรกเกิด แต่สารอาหารหลายอย่างไม่เพียงพอต่อการเจริญเติบโตของทารกแรกเกิดก่อนกำหนด จึงจำเป็นต้องมีการเติม HMF เสริมแต่ด้วยราคาที่แพงและบางครั้งขาดตลาด จึงมีการนำนมผงสำหรับทารกเกิดก่อนกำหนดมาใช้เติมในนมแม่ การดูแลทางโภชนาการจัดว่ามีความสำคัญอย่างมากต่อการให้การดูแลทารกแรกเกิดน้ำหนักตัวน้อย (VLBW) ที่ผ่านมานมแม่ได้รับการจัดว่าเป็นอาหารที่ให้ทางลำไส้ดีที่สุด แต่อย่างไรก็ตามสารอาหารหลายๆ อย่างไม่เพียงพอต่อการเจริญเติบโตของทารกแรกเกิดก่อนกำหนดน้ำหนักตัวน้อยการเสริมสารอาหารในนมแม่ด้วยการเติม human milk fortifier จึงเป็นสิ่งจำเป็นต่อทารกกลุ่มนี้แต่ยังมีปัญหาราคาที่สูง และบางครั้งผลิตภัณฑ์ขาดตลาด ทางเลือกหนึ่งโดยดัดแปลงใช้นมผงสำหรับทารกเกิดก่อนกำหนดสูตรต่อเนื่องมาผสมนมแม่ แต่ข้อมูลในด้านประสิทธิภาพและความปลอดภัยยังไม่เพียงพอ

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบการเจริญเติบโต ค่าทางชีวะเคมีของภาวะโภชนาการและภาวะแทรกซ้อนที่เกิดขึ้นในทารกเกิดก่อนกำหนดน้ำหนักตัวน้อยระหว่างกลุ่มที่ได้นมแม่ที่ผสม human milk fortifier (กลุ่ม HMF) กับกลุ่มที่ได้นมแม่ที่ผสมนมผงสำหรับทารกเกิดก่อนกำหนดสูตรต่อเนื่อง (กลุ่ม PDF)

วัสดุและวิธีการ: เป็นโครงการนำร่องแบบ prospective randomized study ที่หน่วยทารกแรกเกิดสถาบันสุขภาพเด็กแห่งชาติมหาราชินี โดยทำการศึกษาระหว่างวันที่ 1 มีนาคม พ.ศ. 2553 ถึง วันที่ 28 กุมภาพันธ์ พ.ศ. 2554 โดยทารกแรกเกิด ที่มีน้ำหนักแรกเกิดน้อยที่มารดามีน้ำนมเพียงพอภายใน 96 ชั่วโมง หลังทารกเกิดจะได้รับการเข้าร่วมการศึกษา ทารกทุกรายจะได้รับโภชนาการสารอาหารทางหลอดเลือดและทางลำไส้ตามระเบียบแบบแผน ของหน่วยทารกแรกเกิดเมื่อทารกกินนมปริมาณถึง 100 มิลลิลิตรต่อน้ำหนักตัวหนึ่งกิโลกรัมต่อวัน ทารกจะถูกแบ่งกลุ่มเป็นคือ 2 กลุ่มคือ กลุ่มที่เสริมสารอาหารในนมแม่ด้วยการเติม human milk fortifier (กลุ่ม HMF) กับกลุ่มที่เสริมอาหารในนมแม่ ด้วยการเติมนมผงสำหรับทารกเกิดก่อนกำหนดสูตรต่อเนื่อง (กลุ่ม PDF) ทารกจะได้รับการติดตามการเจริญเติบโต เพราะตรวจเลือดเป็นระยะจนกว่าทารกจะสามารถดูดนมจากเต้าได้หมดหรือน้ำหนักตัวถึง 2 กิโลกรัม ขึ้นกับสิ่งใดมาถึงก่อน

ผลการศึกษา: มีทารกเข้าร่วมการวิจัย 33 ราย โดยแบ่งเป็นกลุ่ม HMF 18 ราย และกลุ่ม PDF 15 ราย โดยทารกทั้ง 2 กลุ่ม มีลักษณะทั่วไป การให้การดูแลทางโภชนาการ ภาวะแทรกซ้อนภายหลังที่พบได้ในทารกเกิดก่อนกำหนด และจำนวนวันนอนโรงพยาบาลไม่แตกต่างกัน ไม่พบความแตกต่างกับทางสถิติในแง่การเจริญเติบโตและค่าทางชีวเคมีในเลือดระหว่างทารกทั้ง 2 กลุ่ม ภาวะ suspected NEC และ feeding intolerance พบได้บ่อยกว่าในกลุ่ม PDF แต่มีเพียงภาวะ suspected NEC ที่มีนัยสำคัญทางสถิติโดยที่ภาวะ Definite NEC ไม่มีความแตกต่างกันในทารกทั้ง 2 กลุ่ม (ภาวะแทรกซ้อนอื่นๆ ของทารกเกิดก่อนกำหนดรวมถึงภาวะ) osteopenia of prematurity คล้ายคลึงกันในทารกทั้ง 2 กลุ่ม ค่าใช้จ่ายในการเสริมโภชนาการในนมแม่เฉลี่ย 605 บาท และ 11,655 บาทต่อคนในทารกกลุ่ม PDF และ HMF ตามลำดับ

สรุป: การให้โภชนาการบำบัดเสริมในนมแม่ ถือเป็นทางเลือกสำหรับการให้อาหารทารกที่น้ำหนักตัวน้อย การใช้ post discharge formula เสริมในนมแม่

อาจเป็นทางเลือกหนึ่งที่ใช้ทดแทน human milk fortifier ได้ในประเทศที่มีทรัพยากรจำกัดและกำลังพัฒนาอย่างไรก็ตาม ควรมีการเติมวิตามินรวม โดยเฉพาะวิตามินดี ธาตุเหล็ก แคลเซียมและฟอสฟอรัสเพิ่มเติมด้วย ควรมีการเฝ้าระวังติดตามปัญหาแทรกซ้อน เช่น feeding intolerance และ suspected NEC และควรมีการศึกษาที่ประชากรมากขึ้นเพิ่มเติมเพื่อดูผลลัพธ์ของการรักษาทั้งระยะสั้นและระยะยาวต่อทารกในอนาคต