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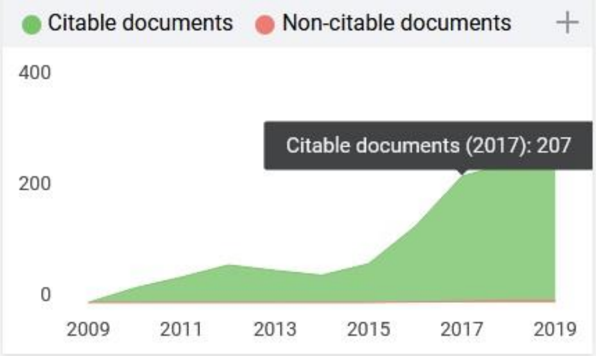

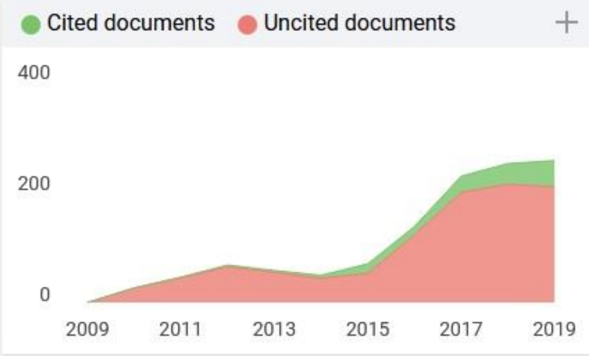

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GAIN VELOCITY AND IGA SECRETORY FECAL BETWEEN PRETERM BABY RECEIVED HUMAN MILK AND HUMAN MILK FORTIFIED

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ABSTRACT

Preterm baby suffered from metabolic stress and hypogammaglobulinemia after birth. Extrauterine growth restriction (EUGR) is a common problem and related to neurodevelopmental outcome. The Independent risk factor of EUGR is necrotizing enterocolitis (NEC). Concentration secretory IgA (sIgA) as main immunity system decreased by age. Human milk fortification may resolve EUGR and organ immaturity of preterm baby.

Objective : Analyzed difference gain velocity and sIgA fecal between preterm baby received human milk and human milk fortified.

Methods : Prospective analytic observational study between December 2015-July 2016 at Soetomo Hospital Surabaya. Inclusion criteria consisted of gestational age ≤ 34 weeks and birth weight 1000 till less than 2000 g. Multiple congenital anomaly and enteral nutrition avoidance as exclusion criteria. Indication human milk fortification were stable period, no suckling reflex and gain weight velocity (GWV) <10 g/kg/d. Preterm baby was recruited and followed in 14 days. Chi-square, Mann-whitney and t-test independent sample used to analyzed discrepancies GWV, gain length velocity (GLV), gain head circumference velocity (GHC) and sIgA fecal.

Results : Human milk fortification (22(12,86-51,76) g/kg/day) showed significance difference to GWV than human milk (14,28(-12,86-(+32,86)) g/kg/day) group (p=0,020). GLV(p=0,257), GHC (p=0,215) and sIgA fecal (p=0,418) revealed no difference. Side effects (feeding intolerance and NEC) not found during observation.

Conclusions : Human milk fortification showed higher GWV than human milk group. Follow up still needed to evaluate anthropometric parameter.

1.Introduction

Prematurity infants have growth problems at 36 weeks postmenstrual age (91%) and mature (30%) (Fanaroff *et al.*, 2007; Leppänen *et al.*, 2014). Growth disorders cause neurodevelopmental disorders, cognitive function, and quality of life of prematurity infants, one of the disturbances in gastrointestinal organs (Cooke *et al.*, 2003). In prematurity infants, there is Immunoglobulin A (the main body's immune system in the gastrointestinal tract) and breast milk is the main source of IgA but its levels decline with the age of prematurity infants (Araújo and Gonçalves, 2005). Growth rates of weight gain were lower in 171 underweight infants who received breast milk > 75% (Colaizy, 2012). Therefore, it needs optimal nutritional support in prematurity infants to fit the intrauterine growth rate based on postconceptional age guidelines (American Academy of Nutrition Committee on Nutrition, 1977).

The technique of giving fortification to proper infant breastmilk is still continuously studied, as it found in the Gross study that the standard fortification for infants less than 24 kcal/oz was not able to meet the growth rate (Gross, 1987). Meanwhile, standard fortification according to Schutzman of 22 kcal/oz is recommended in prematurity infants with a birth weight of 1000-2000 grams. In 2 cases of underweight infants at Dr. Soetomo General Hospital Surabaya with fortification standard 22 kcal / oz (gestational age 31-33 weeks and birth weight 1400-1500 gram) showed that short-term growth rate (body weight 21.21 g /kg/day, 1 cm/week body length and head circumference 1.75 cm/week) whereas in 4 underweight babies with standard fortification 24 kcal/oz often showed sepsis with feeding intolerance. Adjustable fortification is an invasive technique that shows the growth rate of body length is not significantly different, and the constraint of its implementation is the availability of protein supplementation. (Arslanoglu *et al*., 2006). Tailored fortification is believed to be an appropriate fortification technique but it is expensive and the procedure is complicated (Reali *et al*., 2010).

Accordance with the Republic of Indonesia Government Regulation No. 33 the Year 2012 on exclusive breastfeeding and Regulation of the Republic of Indonesia Health Minister No.39 Year 2013 on infant formula and other infant products, strict evaluation and monitoring of infant formula usage, both from government and related institutions. In this study, observation and analysis of short-term growth rate and immune system of underweight infants receiving breast milk and breast milk were fortified with HMF by anthropometric method and examination of secretory IgA, IgE levels. This study aims to find a proper milking fortification technique and safe to overcome extrauterine growth restriction events and reduce the incidence of infection in infants less months. Thus, researchers observed and analyzed prematurity infants as indicated by breastfeeding fortification with HMF.

2. Materials and methods

This design of this study is a prospective analytic observational design. The study was conducted in the nursery Dr. Soetomo General Hospital Surabaya, which it begins December 2015 - July 2016. Samples were taken by consecutive sampling with a sample of 17 babies. The population of the samples was breastfed infants and breastmilk fortified with HMF (ASI + HMF) with inclusion criteria: Pregnancy age ≤ 34 weeks of gestational, birth weight 1000-2000 grams, subjects whose parents had signed an informed consent at the start of the study.

3.Results and discussions

The collection of research subjects was conducted from December 2015 to July 2016 and obtained 17 infants underwent indication of breastfeeding fortification (gestational age ≤34 weeks, birth weight 1000-2000 grams) and with the approval of the Neonatology Division staff Dr. Soetomo General Hospital Surabaya. Other considerations include poor feeding ability, no history of feeding intolerance, not being treated with oxygen supplementation, not in sepsis. Infants less than matched according to the above criteria will receive HMF fortified milk for 14 days and evaluated anthropometric and secretory IgA parameters before and after the study and monitored adverse effects of feeding intolerance and necrotizing enterocolitis (NEC).

The characteristics of mothers at the research subjects showed no significant differences in age, nutritional status, history of parity, history of preeclampsia / eclampsia, risk of delivery and history of specific illness during pregnancy in Table 1 ($p>0.05$). Characteristics in socio-economic status of both groups showed no significant difference ($p>0.05$) in the education of the father and mother, father's work and mother, income and status home ownership in Table 2. Characteristics of study subjects in terms of sex, type of labor, Apgar score 1 min, Apgar score 5 min gestational age, birth weight (z-score), z-score, premature rupture of membranes, amniotic fluid, history of corticosteroid administration before delivery, neonatal jaundice, seizures, sepsis, oxygen source and type of breastmilk did not get significant difference (p>0.05) in Table 3. Characteristics of the subjects before breastfeeding fortification did not show significant differences (p>0.05) between breastfed and breast-fed groups were fortified with HMF in terms of body weight, z-score, body length (cm), z-score, head circumference (cm), z-score head, fecal concentration of secretory IgA, chronological age, average enteral volume (ml / day) and (ml / kg / day) in Table 4.

Table 1. Characteristics of research subject mothers

Characteristics	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Age (years)	28,82±5,90	28,82±5,71	1,000[3]
Nutritional Status (kg/m^2)			
Malnutrition	2	2	0,714[2]
Normal	13	14	
Overweight	2	1	
History of parity			
Gravida 1	9	7	0,571[2]
Gravida 2	5	6	
Gravida 3	2	4	
>Gravida 3	1	0	
pre-eclampsia/eclampsia history	6	5	1,000[1]
Risk of Labor			
High	10	12	0,721[1]
Low	7	6	
history of specific illness during pregnancy	1	1	1,000[1]

Description: The value of p is significant when the value <0,05. Chi-square test[1], Mann-Whitney[2] test and independent sample[3] test

Table 2. Characteristics of socioeconomic status of parents

Characteristic	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Father's education			
Didn't School	0	1	0,736[2]
Elementary School	1	0	
Junior High School	3	3	
Senior High School	10	10	
Bachelor (S1/S2/S3)	3	3	
Mother's Education			
Elementary School	3	1	0,740[2]
Junior High School	2	3	

Senior High School Bachelor (S1/S2/S3)	9 3	10 3	
Father's Job Working Not Working **Mother's Job** Working Not Working	 17 0 4 13	 16 1 13 12	 1,000[1] 1,000[1]
Income Insufficient Sufficient More than enough	 10 7	 7 10	 0,494[2]
Home Ownership Status One's Own Family Owner Someone else	5 9 3	5 9 3	1,000[2]

Description: The value of p is significant when the value <0,05. Chi-square[1] Test and Mann-Whitney[2] Test

Table 3. Characteristic of Research Subject

Characteristic	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Sex (n) Male Female	 8 9	 8 9	 1,000[1]
Type of Parity Normal *Cesarean section*	 7 10	 7 10	 1,000[2]
Apgar score 1 minute	6(1-8)	6(1-8)	0,722[2]
Apgar score 5 minute	8(3-9)	8(3-9)	0,750[2]
Gestational Age (week)	32(30-34)	31(30-34)	0,110[2]
Aterm	17	17	-
Birth Weight (g) **Birth Weight to Age (z-score)**	1700 (1000-1900) -0,73±0,82	1650 (1000-1950) -0,26±0,80	0,986[2] 0,101[3]
Birth Length (cm) **Birth Length (z-score)**	41,58±2,92 -0,72±1,25	41,58±3,04 -0,32±1,07	1,000[3] 0,329[3]
Birth Head Circumference(cm) **Birth Head Circumference (z-score)**	29(25-32) -0,36(-2.02-(+0,59))	29(22-31) -0,59(-1,90-(+1,25))	0,169[2] 0,581[2]
Prematurity of Rupture Membrane	4	10	0,080[1]
Amniotic fluid Clear Murky	 16 1	 15 2	 1,000[1]

History of antenatal corticosteroid administration	6	9	0,491[1]
Icterus Neonatal	16	16	1,000[1]
Seizure	0	1	1,000[1]
Sepsis	6	6	1,000[1]
Oxygen			
Room	2	0	0,220[1]
CPAP	15	15	
Ventilator	0	1	
Type of breastfed			
Week 1	3	2	0,949[2]
Week 2	11	13	
Week 3/4	3	2	

Description: P value means when value <0,05. Chi-square[1] test, Mann-whitney[2] test and t-test independent sample[3]

Table 4. Characteristic of Subject before Breastfeeding Fortification

Characteristic	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Weight (g)	1590 (1070-1950)	1620 (1160-1770)	0,629[1]
Weight to Age (z-score)	-1,52±0,65	-1,32±0,56	0,379[2]
Length (cm)	42,53±2,70	43,09±2,50	0,322[2]
Length to Age (z-score)	-1,20±1,29	-0,51±1,02	0,930[2]
Head Circumference (cm)	29,26±2,05	29,32±1,86	0,931[2]
Head Circumference to Age (z-score)	-1,17±0,87	-0,86±1,12	0,381[2]
IgA secretory fecal (µg/ml)	1312,90(194,43-2304,60)	1299,65(63,18-1373,62)	0,082[1]
Age of Chronology (day)	11,41±3,43	11,41±3,54	1,000[2]
Enteral Volume (ml/day)	192(180-300)	216(180-300)	0,133[1]
Enteral Volume (ml/kg/day)	130±21,50	140,94±22.7	0,151[2]

Description: The value of p is significant when the value <0,05.Mann-Whitney[1] test and independent t-test sample [2]

Weight (gram) and age-weighted (z-score) parameters showed significantly different changes (p<0.05) and in the breastmilk group 192.65±170.78 grams and the breastfeeding group was fortified with HMF 355. 88±162.30 grams. In the parameter of body length (cm), head circumference (cm) and the secretory IgA did not show significantly different changes (p>0.05) in Table 5. The breastfed group of fortified HMF had a faster growth rate of body weight of 22 (12.86-51.76) g / kg / day than the breastfeeding group 14.28 (-12.86 - (+ 32.86) g / kg / day (p = 0,020). While growth rate of body length and head circumference did not show significant difference (p>0.05) presented in Table 6. The mean age-to-weight (z-score) score was higher in the HMF-fortified breastfeeding group than in the breast milk group. Mean age-weighted values did not show significant differences at birth, before fortification and day 7 (p>0.05). However, the mean value of body weight according to age at day 14 showed significant difference (p<0.05) in Figure 1.

The mean length-for-age (z-score) rate was higher in the HMF-fortified breastfeeding group than in the breastmilk group. The mean value of body length according to age did not show significant difference at birth (p>0.05), before fortification and day 7. The mean value of body length according to age at day 14 showed a significant difference (p<0.05) in Figure 2. The mean age of z-score head circumference was higher in the breastfed fortified HMF group than in the breastmilk group. The mean head circumference value according to age did not show significant difference at birth (p>0.05), before fortification, day 7 and day 14 in Figure 3.

The mean of enteral volume in breastmilk group was 178,42±17,85 ml / kg / day and breastfed group was fortified HMF 175,04±13,91 ml / kg / day were given in Table 7 indicating no significant difference. While caloric mean showed significant difference that was in breastfed group of HMF 144,47±10,03 kkal / kg / day and milk group 119,17±14,17 kcal / kg / day (p<0.05) in Table 8. The mean protein values were significantly different in the breastfed group of HMF 5.44±0.49 g / kg / day and breastfed group 3,43±0,42 g / kg / day (p<0.05) presented in Table 9. During the study, side effects of feeding intolerance with systemic symptoms and NEC were not found.

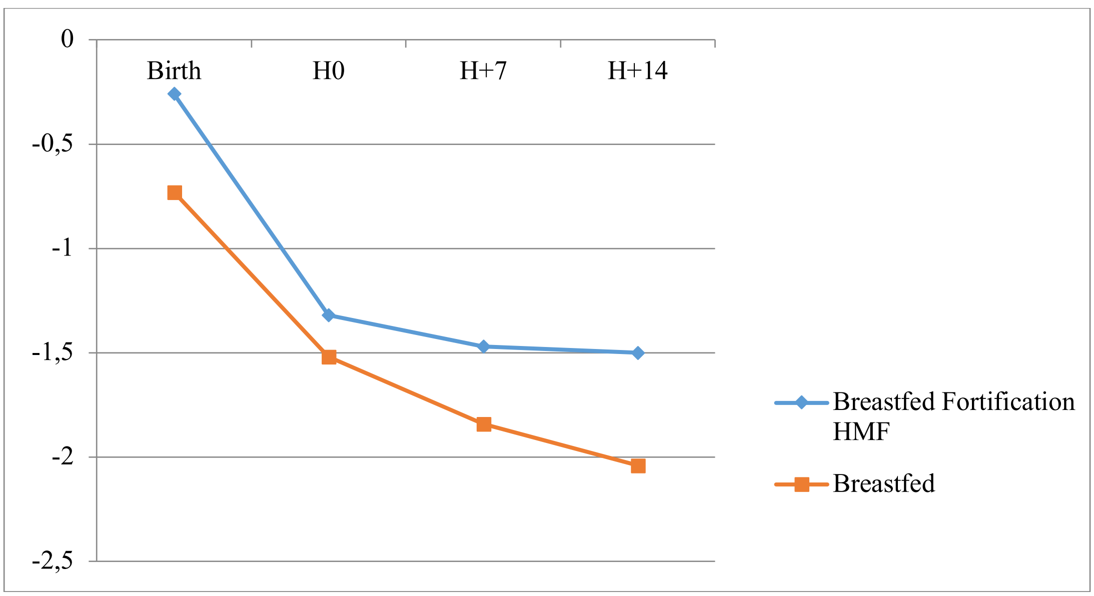

Figure 1. Comparison of mean age-weight (z-score) between breastfeeding and breast milk group was fortified by HMF. Description: blue line is a group of breastfed fortified HMF and red line is a breastmilk group. The p value is significant when the value is <0,05. Mann-Whitney[1] test and independent t-test sample[2].

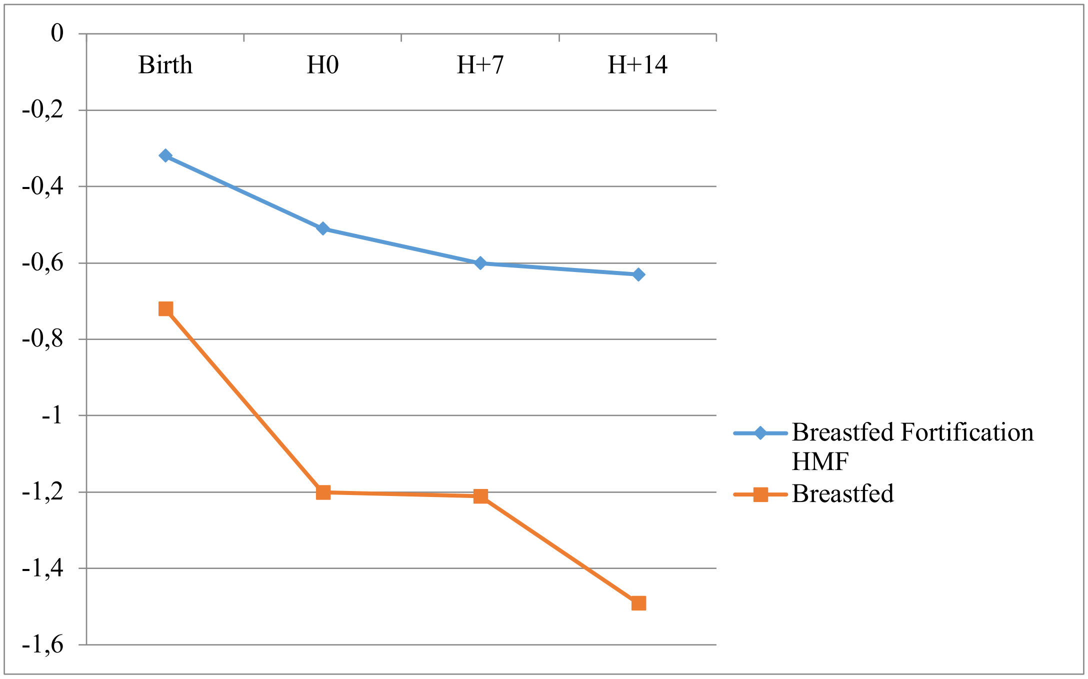

Figure 2. Comparison of mean age-for-age (z-score) scores between Breastfed and breast milk groups was fortified by HMF. Description: blue line is a group of Breastfed fortified HMF and red line is a breastmilk group. The p value is significant when the value is <0,05. Independent t-test test sample.

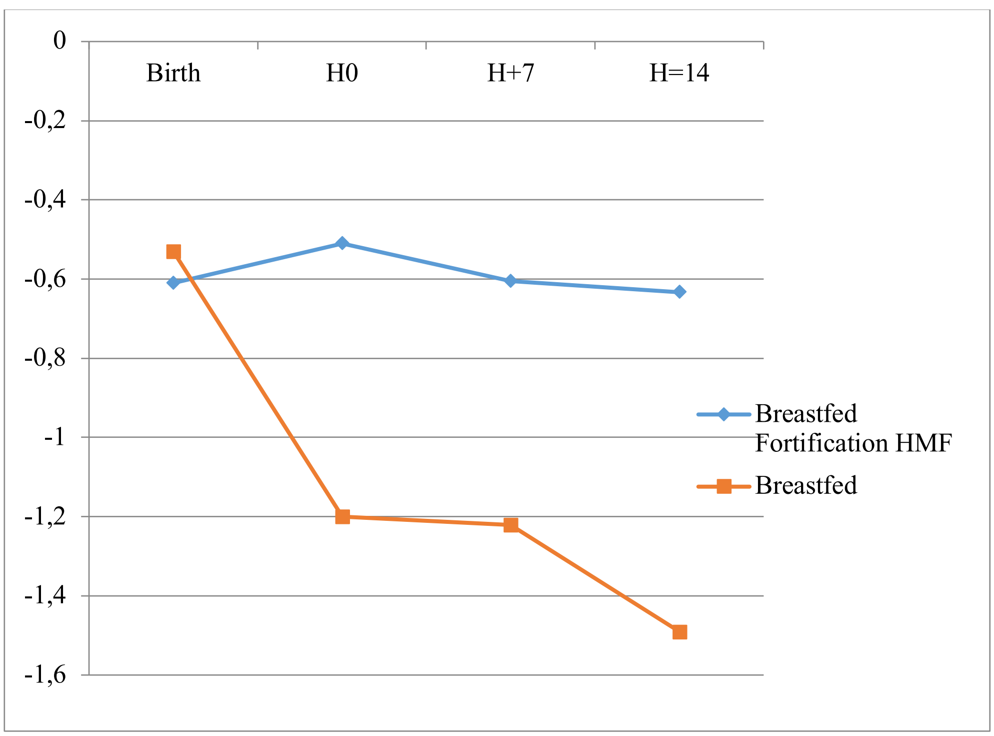

Figure 3. Comparison of mean z-score head circumference between breastmilk and breast milk group was fortified by HMF. Description: blue line is a group of breastmilk fortified HMF and red line is a breastmilk group. The p value is significant when the value is <0,05. Mann-Whitney[1] test and independent t-test sample[2].

The median birth weight of breastfed milk group HMF in this research was 1650 (1000-1950) gram, according to Mukhopadhyay et al., the average birth weight of 1202±202 grams (Mukhopadhyay *et al*., 2007). The Cochrane Review also mentions the indication of breastfeeding fortification as a term infant with a mean birth weight of 900-1850 grams (Kuschel and Hardling, 2004). The mean of body length was born in breastmilk group 41,58±2,92 cm and breastfeeding group was fortified HMF 41,58±3,04 cm. Both groups had normal mean birth rates and no significant differences. Research by Arslanoglu showed prematurity infants has a mean length of body born 38,9±2,2 cm (Arslanoglu *et al*., 2006). In this study, head circumference was born in the ASI group of 29 (25-32) cm and the breastfed group was fortified HMF 29 (22-31) cm. Both groups had normal head circumference and no significant differences. In contrast to previous studies, the mean birth circumference of underweight infants who received breast milk fortification was 27.7±2.2 cm (Arslanoglu *et al*., 2006).

Both groups showed no significant differences in body weight, body length (cm) and head circumference (cm). Body weight in breastfed group 1590 (1070-1950) grams and breastfed groups fortified HMF 1620 (1160-1770) grams. The mean body length in the breastmilk group was 42.53±2,70 cm and the breastfed group was fortified HMF 43,09±2,50 cm. The breastmilk group had a head circumference of 29 (25-32) cm and the breastmilk group fortified HMF 29 (22-31) cm (Table 4). In previous RCT studies showed the initial weight of the study 1189±209 grams (Mukhopadhyay *et al*., 2007). The study by Morlacchi *et al*. also showed less-than-matured infants with an initial body weight of 1412±231 gram (Morlacchi *et al*., 2016). The mean weight-to-age (z-score) and length-for-age (z-score), body weight before breast milk fortification showed a decline compared to birth weight and length of birth. However, both groups showed no meaningful differences (Figure 1).

Prematurity Infants get breastfeeding fortified HMF at chronological age of 11.41 ± 3.54 days. Both groups showed no significant difference (Table 4). Breastfeeding fortification begins at the age of chronologically 11 days (Adamkin, 2009) or at chronological age 4-15 days (Kuschel and Hardling, 2004). RCT study in 85 under-term infants stated that breastfeeding fortification was performed at the age of 11.8 ± 5.7 days (Mukhopadhyay *et al*., 2012). Other studies initiated breastfeeding fortification in underweight infants at chronological age of 13 (10-16) days (Miller *et al*., 2012).

Breastmilk fortification was given when the study subjects had enteral nutrition ability of 140.94±22.7 ml / kg / day. Both groups showed no significant difference to the mean enteral volume at baseline (Table 4). Previous studies have found that breastfeeding fortification begins when the prematurity infant had an enteral ability on 150 ml / kg / day (Arslanoglu *et al*. 2006, Adamkin, 2009), 45-170 ml / kg / day (Kuschel and Hardling, 2004). An RCT study of 85 underweight babies mentioned fortification when achieving enteral ability of 168±14.4 ml / kgbb / day (Mukhopadhyay *et al.*, 2012). Miller *et al*. did fortification of breastfeeding when prematurity infant had an enteral ability of 120 (94-140) ml / kg / day (Miller *et al*., 2012).

In this research, 4 underweight infants (gestational age 28-33 weeks and birth weight 750-1500 grams) who received HMF of 24 kcal / oz showed sepsis incidence with feeding intolerance more often than 2 infants less months (gestational age 31-33 week and birth weight 1400-1500 gram) that get HMF of 22 kcal / oz. Schutzman et al. mentions the fortification technique of ASK 22 kkal / oz given to prematurity infants with birth weight 1000-1500 gram since chronological age 10 days for 6 days continued fortification of ASK 24 kkal / oz. While in prematurity infants with birth weight 1500-2000 gram get fortification 22 kcal / oz since chronological age 9 days for 4 days (Schutzman *et al*., 2012). Radmacher and Adamkin recommend giving fortification of breastmilk for 2-8 weeks with protein intake of 3.5-4.4 g / kg / day and calories of 24 kcal / oz (Radmacher and Adamkin, 2016).

In this study, the growth rate of body weight showed significant differences between the two groups. The growth rate of breastfeeding fortification HMF group weight was found on 22 (12,86-51,76) g / kg / day to be greater than breastfeeding group 14,28 (-12,86 - (+ 32,86)) g / kg / day (Table 6). Changes in weight (grams) and age-related weight (z-score) also showed significant differences (Table 5). Other studies with fortified breastfeeding techniques of 24 kcal / oz had a lower body weight growth rate of 18.2 ± 0.7 g / kg / day (Barrus *et al*., 2012) and 15.1 ± 4 g / kg / day (Mukhopadhay *et al*., 2007). The differences in the rate of weight gain can be influenced by the characteristics of the study subjects (low birth weight, gestational age, history of steroid delivery before delivery, gender and APGAR score) and HMF composition (Kartal *et al*., 2016). In this study, only a small proportion of preterm infants had prematurely ruptured membranes and no significant difference was found (Table 3).

The researchers used the fortification technique of ASK 22 kkal / oz of 2 sachets of HMF + 100 ml of breast milk. HMF product in this study contains protein 0.6 g / 100 ml of milk, fat 0.18 g / 100 ml of milk and carbohydrate 0.9 g / 100 ml of breastmilk. The fortified milk fortification technique 24 kcal / oz in the Porcelli *et al*. study contained 1g / 100 ml of milk protein, 0.05 g / 100 ml of breast milk and 2 g / 100 ml of breast milk and the study showed 27% feeding intolerance, 30% respiratory distress and 36% cardiovascular disorders (Porcelli *et al*., 2000).

The caloric value used in the study was 144.47 ± 10.03 kcal / kg / day (HMF fortified breastfeeding group) and 119.17±141.7 kcal / kg / day (breastfeeding group) (Table 8). Caloric mean of both study groups was in accordance with the recommendation of prematurity infants' caloric needs on 105-135 kcal / kg / day (Canadian pediatric society nutrition committee, 1995). Caloric mean showed significant differences (Table 8).

The mean of enteral volume in this study did not show significant difference (Table 7). The mean of enteral volume in breastmilk group was fortified HMF 175.04±13,91 ml/ kg/day and breastfeeding group 178,42±17,85 ml / kg / day. The mean of breast milk protein content of prematurity infants with chronological age 15,3±1,5 day is 2g/100 ml of breastmilk (Porcelli *et al*., 2000). The HMF product used contained 0.6 g /100 ml of breastmilk in this study. Thus, the mean protein was 5.44±0.49 g /kg/day (HMF fortified breastfeeding group) and 3.43±0.42 (breastfeeding group). The breastfed group of fortified HMF had a higher mean protein and was significantly different for the breastmilk group (Table 9). Levels of protein intake in this study have been in accordance with the recommendation of protein needs for prematurity infants 3-3.6 g/kg/day (Canadian pediatric society nutrition committee, 1995). Systematic reviews indicate that administration of high-dose protein (3-4 g/kg/day) may increase body weight by 23.6 g/kg/day (Miller *et al*. 2008). Other studies have suggested that giving 2-4 g/kg /day protein can increase BB, linear growth, nitrogen retention and albumin levels (Kuschel and Hardling, 2004). The HMF product in this study contains MCT of 9.6%. Meta-analysis showed no significant difference between the number of doses of MCT on weight gain, body length (Klenoff-Blumberg and Genen, 2003).

Breastfed fortified HMF groups had a higher mean age-to-weight (z-score). The breastfed fortified HMF group had a positive effect on the mean age weight (z-score) (Figure 1). In this study, mean age weight (z-score) showed a decrease in both groups. The decrease in body length by age (z-score) is greater than the z-score (Figure 1 and 2). Previous research has shown that age-related z-score is greater than z-score (Ramel *et al*., 2012; Olsen *et al*., 2014). Z-score weight loss was lower in the group receiving high-dose calories and protein (5 grams FM 85 + 100 ml of breast milk and 1-2.5 grams of Protifar + 100 ml of breast milk). The administration of high-dose protein had a significant difference to age-z-score (Roggero *et* *al*., 2012). Larger weight growth rates (36 g/kg/day and levels of 6.3 g/kg/day) are expected to match the intrauterine growth rate (Olsen *et al*., 2010).

Table 5. Changes in anthropometric and immunoglobulin A values during the study

Changes	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Anthropometry			
Weight (g)	192,65±170,78	355,88±162,30	**0,008**[2]
Weight to Age (z-score)	-0,52±0,46	-0,18±0,36	**0,022**[2]
Length (cm)	1(0-5)	1,5(0-4)	0,146[1]
Length to Age (z-score)	-0,51(-1,01-(+1,28))	-0,39(-0,86-(+0,80))	0,185[1]
Head Circumference (cm)	1(0-3,5)	1,5(1-3)	0,154[1]
Head Circumference to Age (z-score)	-0,14±0,55	0,18±0,43	0,068[2]
Immunoglobulin A			
IgA secretory fecal (μg/ml)	32,92(5,13-1172,77)	46,18(0,43-1269,39)	0,796[1]

Description: The value of p is significant when the value <0,05. Mann-Whitney[1] test and t-test independent sample[2] test.

Table 6. Rate of short-term growth

Characteristic	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Weight (g/kg/day)	14,28(-12,86-(+32,86))	22(12,86-51,76)	**0,020**
Length(cm/week)	0,50(0-2,50)	0,75(0-2)	0,257
Head Circumference (cm/week)	0,50(0-1,75)	0,75(0,50-1,50)	0,215

Description: The value of p is significant when the value <0,05Mann-Whitney Test.

Table 7. The average of enteral volume

Volume	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Enteral Volume (ml/kg)	298,43(232,29-338,57)	304,29(219,43-334,39)	0,809[1]
Enteral Volume (ml/kg/day)	178,42±17,85	175,04±13,91	0,151[2]

Description: The value of p is significant when the value <0,05. Mann-Whitney[1] test and independent t-test sample[2].

Table 8. Caloric average

Caloric	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Caloric (kkal/day)	190,72±27,69	227,53±21,81	**<0,0001**
Caloric (kkal/kg/day)	119,17±14,17	144,47±10,03	**<0,0001**

Description: The value of p is significant when the value <0,05. Test t-test independent sample.

Table 9. The mean protein

Protein	Breastfed (n=17)	Breastfed Fortification HMF (n=17)	p
Protein (gram/day)	5,82(4,65-6,77)	9,26(6,78-10,17)	**<0,0001[1]**
Protein (gram/kg/day)	3,43±0,42	5,44±0,49	**<0,0001[2]**

Description: The value of p is significant when the value <0,05. Mann-Whitney[1] test and independent t-test sample[2].

The growth rate of body length showed no significant difference. The breastfed milk group HMF has a growth rate of body length of 0.75 (0-2) cm / week (Table 6). The growth rate of length breastfeeding fortified HMF group showed that varied results on recommendation of ideal infant growth less than 0.9 cm / week (Bertino *et al.*, 2008). Breast fortification 24 kcal / oz for 2 weeks showed growth rate of body length 0,9±0,1 cm / week and did not show significant difference. The protein content in this study was 1 g / 100 ml of breast milk (Porcelli *et al.*, 2000). Breastfed fortification 24kcal / oz other shows the growth rate of body length is 0.86±0,2 cm / week while breastfeeding group 1.04±0,3 cm. HMF is given in prematurity infants until it reaches 2000 grams (Mukhopadhyay *et al.*, 2007). Research by Reis *et al* showed that a growth rate is 1.09±29 cm / week (Reis *et al.* 2000). HMF with high-dose protein has a growth rate of 1.15 (1.10-1.19) cm / week (Miller *et al.*, 2012). Administration of adjustable fortification (1,3±0,5 cm / week) did not show significantly different body length growth rate against standard fortification (1,1,0,4 cm / week) (Arslanoglu *et al.*, 2006). High doses of protein did not show any significant difference to the increase in body length (Miller *et al.*, 2012; Roggero *et al.*, 2012). This is caused by the level of milk protein is dynamic (Gidrewic *et al.*, 2014). Thus, the calorie and protein levels given in this study, Miller et al and Roggero *et al.* were lower than those of Arslanoglu *et al.*

The breastfed fortified HMF group had a mean length of body-age (z-score) higher than the breastmilk group and showed a significant difference. The breastfeeding fortified HMF group was able to maintain a z-score average in the normal range (Figure 2). A z-score reduction in mean age was greater than the mean z-score (Figure 1 and Figure 2). In line with previous studies, breastfeeding fortified HMF showed a decline in mean age-for-age (z-score) (Miller *et al.*, 2012; Ramel *et al.*, 2012; Olsen *et al.,* 2014).

The HMF product in this study contained 58.4 mg calcium and 33.6 mg phosphorus per 100 ml of breast milk. The use of HMF products with calcium 87 mg and phosphorus 50 mg to body weight 2000 gram showed growth rate of body length is 0.86 ± 0.08 cm. The rate of body length growth in the Gross et al study, have not met the recommended recommendation of 0.9 cm / week (Bertino *et al.*, 2008). Although the mineral content in this study was lower but the growth rate of body length was faster than that of Gross *et al*. This is due to the composition of breastmilk and the characteristics of research subjects.

In this study, head circumference growth rate showed no significant difference (p = 0,215)

(Table 6). The breastfed group of fortified HMF had a larger head circumference growth rate of 0.75 (0.50 to 1.50) cm / week than the breastmilk group of 0.50 (0-1.75) cm / week (Table 6). Fortification techniques of 24 kcal / oz milk and protein 0.9 g / 100 ml of breast milk showed a change in head circumference of 1.04□0.23 cm / week (p = 0.743) (Reis et al., 2000). A study by Porcelli et al. gave HMF to less than 2 months of gestational weight to a body weight of 2000 grams but this did not show any significant difference (Porcelli et al. 2000). High doses of protein did not show significantly different head circumference growth rates (p = 0.330). The rate of head circumference growth in less-than-term infants who received high-dose protein was 0.94 (0.9-0.98) cm / week (Miller et al., 2012). In contrast to the milk fortification technique of 24 kcal / oz with protein of 0.9 g / 100 ml of breast milk and 0.8 g / 100 ml showed a larger head circumference growth rate of 1±0.1 cm / week and 0.8 ± , 1 cm / week (Porcelli *et al*., 2000). The mean age-zero head circumference (z-score) of breastmilk group was fortified with HMF higher than in breastmilk group. Breastfeeding fortification maintains an average z-score head circumference in the normal range (Figure 4). Higher calorie and protein intake showed significant differences in mean age-added z-score (Miller *et al*., 2012).

4. Conclusions

Short-term growth rate based on body weight showed significant differences while the parameters of body length and head circumference did not show significant differences between prematurity infants of breastfeeding and breastfeeding were fortified with HMF, and the secretory IgA fecal content showed no significant difference between breastfed infants who were breastfed and breast milk fortified with HMF.

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