Comparative Growth Outcome of Preterm Neonate Fed Post-Discharge Formula and Breast Milk after Discharge

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Objective: *To evaluate the post-discharge growth, laboratory outcome, neurodevelopment and safety of post-discharge formula in comparison to breast milk.*

Material and Method: *A prospective cohort of preterm infants, who were discharged on breast milk or post-discharge formula (PDF) were studied. Demographic data, post-discharge growth, laboratory outcome, neurodevelopment and complications were recorded. These infants were followed-up at 40 weeks' postmenstrual age (PMA) 2, 4 and 6 months' corrected age. The present study was conducted for 22 months (from September 1, 2011-May 31, 2013).*

Results: *Seventeen infants were enrolled in the study, 7 in the breastfed group and 10 in the PDF group. Mean maternal age in breastfed group were significantly younger compared with PDF-fed group. PDF-fed infants were longer with statistical significantly at 40 weeks PMA and 4 months' corrected age ($p<0.05$). At 2 months' corrected age, babies in breast milk group were significantly heavier compared to those in PDF group. Conversely, those in PDF group were heavier than the breastfed group at 4 months' corrected age ($p<0.05$). There was no difference of head circumference between groups at follow-up. A higher serum phosphorus and lower serum alkaline phosphatase were related to improve suspected osteopenia of prematurity at 2 months' corrected age in PDF group ($p = 0.007$). Hematocrit was higher in the PDF group than breastfed group, which was statistically significant at 40 weeks' postmenstrual age and 6 months' corrected age. There were no significant differences in developmental screening in both groups.*

Conclusion: *Post-discharge formula may improve growth, hematocrit and reduce suspected osteopenia of prematurity. However, neurodevelopment outcome and complications were similar to both groups.*

Keywords: *Preterm, Breast milk, Post-discharge formula*

J Med Assoc Thai 2014; 97 (Suppl. 6): S33-S39
Full text. e-Journal: *http://www.jmatonline.com*

Preterm babies typically have relatively low weight, low nutrition and incomplete body-systems. Furthermore, preterm babies are born with many problems including feeding intolerance causing insufficient nutritional intake.

Many factors prevent preterm babies from having the proper conditions to grow up, and this creates various health problems in the short and long term. In the short term, preterm babies will have below average weight, length, and head circumference[1]. This may slow down the baby's development[2]. The low level of bones mineral content may cause thin bones, shortness[3], or malfunctioned hormones[4]. In the long term as adults, these babies may be at risk of getting a heart attack, high blood pressure, diabetes, or spongy bones[5]. Preterm formula has been produced specifically for preterm babies while they are in hospital, which can be given along with breast milk. However, this may cause insufficient nutrition, disability, death[6,7], failure to thrive and slow long-term development once they are discharged from hospital with term formula.

When feeding preterm formula to preterm babies in hospital, the amount of protein and minerals are sufficient. However, after discharge from hospital, preterm babies who are only on breast milk may have nutritional deficiencies as it may have insufficiency amount of proteins and minerals to support the already deficient premie.

For these reasons, a post-discharge formula has been developed for preterm babies after they leave

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hospital to support the needs of these at risk babies.

Objective

Primary outcome

To compare the differences in growth, laboratory results, and development of preterm babies that are fed either with a post-discharge formula or breast milk after discharge.

Secondary outcome

To study complications including, feeding intolerance, enteritis, infections and number of hospital readmission.

Material and Method

This was a prospective study to compare the differences between neonates discharged on breast milk (BMG) and the post-discharge formula (PDF) at 40 weeks post-menstrual age, and two, four, and six months corrected age. Growth, development and laboratory results were monitored. In this study, the breastfed babies were given supplemental vitamin D of 400-800 IU/day, phosphorous 30 mg/kg/day, and calcium 70-120 mg/kg/day until four months old whereas the PDF babies were given a supplemental vitamin D of 400 IU/day until two months of age. The study was conducted on the preterm babies who were discharged from Queen Sirikit National Institute of Child Health during September 1, 2011-May 31, 2013.

Inclusion criterias

1. Preterm appropriate for their gestational age (AGA) babies with a weight of at least 1,800 g or a gestational age of at least 34 weeks.

2. All infants were followed by appointment for a total duration of six months.

Exclusion criterias

1. Small for gestational age (SGA) or have intrauterine growth restricted babies.

2. Neonate with major congenital anomalies, hypoxic ischemic encephalopathy, IVH grade 3-4, hydrocephalus, severe gastroesophageal reflux (GER) and bronchopulmonary dysplasia.

3. Baby of HIV infected mother.

Informed consent was obtained from all parents.

This research study received approval from the ethical committee of the Queen Sirikit National Institute of Child Health.

After consent for the present study, babies were divided into two groups namely the breast milk group (BMG) and the preterm formula group depending the intention of the mother. The preterm formula group will be fed with the post discharge formula (PDF, S26 Gold) after discharge. The breast milk group also receives supplementary calcium and phosphorus according to the American Academy of Pediatrics. Both groups receive supplementary iron (2-4 mg/kg/day) and multivitamin of 0.5 milliliters (ml) twice a day. The demographic data of maternal histories and the amounts of milk before discharge were recorded. Growth parameters (weight, height and head circumference) were measured at discharge and repeated at 40 weeks post-menstrual age, two, four and six months corrected age. Hematocrit, electrolytes, calcium, phosphorus, and alkaline phosphatase were measured at every follow-up visit. Denver Development Assessment (DENVER II) was performed on all the infants at four months corrected age by same pediatrician. Complications, such as flatulence, vomiting, constipation, and the number of hospital readmissions were recorded.

Data analysis

General data was summarized in terms of percentages, mean, and standard deviations ($x \pm SD$). Continuous data were analyzed using the Chi-square test or the Fisher's exact test while discontinuous data were analyzed using the ANOVA, the repeated ANOVA, and the Mann-Whiney U test. The *p*-value less than 0.05, was considered as statistically significant.

Results

There were 133 preterm babies who were discharged from the Queen Sirikit National Institute of Child Health between February 2012 and August 2012, of which 23 patients were included in the present study. The babies were divided into two groups: BMG 11 patients (47.8%) and PDF group 12 patients (52.2%). Six patients left the present study early. Four of them were in the BMG and two in PDF group. In BMG, two of the babies who dropped out, one stopped breastfeeding because the mother became ill and the other was diagnosed with severe gastroesophageal reflux after joining the project. Two patients in the PDF group could not be contacted. Out of the total 17 patients, 7 (41%) were in the breast milk group, whereas 10 (59%) were in the PDF group. All fundamental data (as shown in Table 1) were not significantly different between groups except maternal age. The average maternal age in BMG was significantly younger than in PDF group. For growth parameters, head circumference in both groups

Table 1. Fundamental data

Mother/baby details	BMG n = 7, (%)	PDF group n = 10, (%)	*p*-value
Mother age* (year)	25.85±6.08	33.5±3.14	0.037
Gestational age* (week)	32.28±2.49	30.7±2.36	0.420
Male baby (%)	4 (57)	4 (40)	
Birth weight* (gram)	1,547.71±255.12	1,318.3±290.65	0.39
Head circumference* (cm)	29±2.02	27.45±2.41	0.34
Birth length* (cm)	41.14±2.79	38.0±1.88	0.14
Oxygen usage time** (day)	3 (0, 17)	2 (1, 42)	
Respirator time** (day)	1 (0, 9)	2 (1, 42)	
Apgar score at 5th (minute)**	10 (7, 10)	9 (7, 10)	
TPN treatment** (day)	4 (0, 43)	11.5 (4, 43)	
Duration of admission* (day)	26 (14, 85)	44 (21, 76)	

*Mean ± SD, **Median (min, max), BMG = breast milk group; PDF = postdischarge group

were not significantly different at 40-week PMA until six months follow-up. The babies in PDF group were statistically heavier than in BMG at 4 months, but lighter at 2 months. Babies in PDF group were statistically longer than BMG at 40 weeks PMA and 4 months. There were 4 male, each in the breast milk group (57%) and in the PDF group (40%). The median oxygen and ventilator time was similar in both groups. The breast milk group had a median of 3 days (0-17) and 1 (0-9), whereas the PDF group has a median of 2 days (1-42) and 2 days (1-42) for the period of oxygen usage and ventilator time, respectively. The 5 minutes Apgar score was also found to be similar in both groups (Table 1).

The median of duration of TPN treatment (11.5, 4-43 days) in the PDF group was more than in the breast milk group (4, 0-43 days). The median of duration of the hospitalization, 44 (21-76 range) days, in the PDF group was also more than the median duration, 26 (14-85 range) days, in the breast milk group.

One baby from both groups had 1 intraventricular hemorrhage (IVH grade 1). One patient in the PDF group was found to have retinopathy of prematurity (ROP stage 3). All calcium, phosphorus and alkaline phosphatase were not significantly different between the two groups, except alkaline phosphatase at 40-week PMA and at 2 months.

The hematocrit in the PDF babies were significantly higher at 40 weeks old (PMA) and at 6 months old compared to the BMG as shown in Table 4. One patient in BMG received a blood transfusion due to a low hematocrit of only 17.7%.

Using the Denver test for developmental screening at four months corrected age, all infants had normal development. Among infants in PDF group, one patient developed enteritis, one bronchitis (10%), and two common cold (20%). Only one patient (14%) in the BMG developed the upper respiratory tract infection.

The excretory system and the ability to accept milk of both groups were equally good. Constipation, vomiting, and colic were not found in any infant.

Discussion

Due to improvement in the care of preterm infants, their survival is increasing. However, preterm babies have a high risk of complications. There have been many comparative studies between PDF and preterm formula in babies after discharge. Lucas et al[8] compared PDF, the preterm formula, and breast milk. The average gestational ages of infants in that studies was similar to the number reported in this study but differed from what Koo et al[9] reported where the average gestational ages were 29 and 28.4 week for PDF and preterm formula fed babies, respectively. In the present study, there were statistically significant differences in weight and length. The breastfed babies were heavier at two months old, whereas the PDF-fed babies were heavier at four months of age and were also longer at 40 weeks and four months corrected ages. It reported that the PDF-fed babies have a greater weight and length than the preterm formula fed babies at six and nine months of age[8] while the head circumference were not different. Other studies have revealed that the growth in terms of weight and length at nine months of age[10] were similar. However, two studies demonstrated that the weight of PDF babies were greater than that of the standard term formula fed babies, but the length and head circumference were not different[11,12]. On the contrary, recent studies showed

Table 2. Growth parameters of the breast milk and PDF groups

Baby detail	BMG, n = 7	PDF group, n = 10	*p*-value
Baby weight (gram)			
40 weeks (PMA)	2,824.86±227.08	3,140.33±371.78	0.120
2 months	5,014.29±474.09	4,980.00±239.44	0.030
4 months	6,257.14±618.75	6,440.00±239.44	0.006
6 months	7,256.00±273.28	7,500.00±578.17	0.080
Head circumference (cm)			
40 weeks (PMA)	34.13±0.82	34.98±1.27	0.120
2 months	38.04±1.33	38.25±0.78	0.070
4 months	40.35±0.89	41.02±0.80	0.370
6 months	42.50±0.70	43.02±0.89	0.340
Body length (cm)			
40 weeks (PMA)	48.46±0.52	48.77±2.06	0.001
2 months	55.29±2.58	56.15±1.49	0.067
4 months	60.79±2.58	61.80±0.79	0.001
6 months	64.40±1.71	65.88±1.88	0.450

PMA = postmenstrual age

Table 3. Biochemical values of the breast milk and PDF groups

	Breast milk n = 7	PDF milk n = 10	*p*-value
Alkaline phosphatse (U/L)			
40 weeks (PMA)	411.71±166.01	258.50±64.90	0.006
2 months	405.67±93.23	252.40±45.50	0.030
6 months	282.40±49.50	211.25±39.80	0.280
Calcium			
40 weeks (PMA)	2.53±0.12	2.495±0.11	0.390
2 months	2.61±0.09	2.64±0.07	0.240
6 months	2.62±0.04	2.66±0.07	0.150
Phosphorus			
40 weeks (PMA)	6.12±0.55	6.58±0.87	0.140
2 months	5.96±0.85	6.53±0.34	0.070
6 months	6.09±0.54	6.27±0.52	0.430

Table 4. Blood concentration (hematocrit) of breast milk and PDF groups

Blood concentration	Breast milk n = 7	PDF milk n = 10	*p*-value
40 weeks	27.24±4.88	28.57±2.28	0.02
2 months	31.66±2.396	33.94±1.43	0.08
6 months	33.46±2.90	35.36±1.32	0.03

that the weight, height, and head circumference of the PDF-fed babies were lower than the babies fed preterm formula at 6, 9 and 12 months old[9].

The growth and bone mass evaluation for the preterm babies can be carried out using the DEXA scan[13] technique. However, in the present study the biochemical values of calcium, phosphorous and alkaline phosphatase were measured in order to diagnose the osteopenia of prematurity[14]. It has been reported that the use of phosphorous and alkaline phosphatase together may improve the screening process[15].

The present study of the biochemical value of the bone mass and bone mass growth obtained from the preterm babies by Bishop et al showed that PDF babies had higher bone mass than standard term formula fed babies at three months of age with statistical significance[16].

Wheeler and Hall[17] compared the values of calcium, phosphorous, and alkaline phosphatase from three groups of babies: Breastfed, preterm formula fed, and PDF-fed. This was carried out eight weeks after leaving the hospital and found that the calcium levels were similar, phosphorous levels were lowest in the breast-fed babies, and the alkaline phosphatase levels were lowest in the PDF babies. This present shows that the alkaline phosphates at 40 weeks postmenstrual age and 2 months corrected age in PDF group were lower than that of the BMG similar to Wheeler and Hall. These data may indicated lower bone mass in BMG. However, one study revealed that there was no statistically significant difference in bone mass when the alkaline phosphatase were lower than 600 IU/L or higher than 1,200 IU/L[18].

Preterm babies tend to encounter iron deficiency anemia due to a lower iron storage compared to term babies. The American Academy of Pediatrics (AAP) suggests that supplemental iron (2 mg/kg) must be given to the breastfed preterm babies[17].

Despite iron supplementation of 2-4 mg/kg for 6 months, the BMG still had significantly lower hematocrit level at 40 weeks and 6 months corrected age compared to PDF group who were supplemented to only 2 mg/kg for two months. These data correspond to Wheeler and Hall report that ferritin was lowest in the breast milk group compared to PDF-fed and full-term formula fed babies, which confirms that the supplemental iron must be given to all preterm breastfed babies[7]. Lucas et al found that Bayley Psychomotor Developmental Indices in the PDF group was not different statistically[8] at 9 and 18 months compared to standard term formula. In this present, the development, screening tool (Denver II) was used during the first four months. It was found that the two groups have a similar developmental screening which is, along with those studied by Knobloch, Passamanick, and Sherrards, during the first nine months[9].

Conclusion and suggestion

The PDF helps preterm babies in terms of growth and development in the short term. These findings are supported by the babies that increase in weight at the same rate as those with the same gestational ages. However, further studies should be done to study of the short and long-term effects and the benefits of the PDF. The limitations of the present study are as follows: small populations may lead to some deviation, and the use of laboratory results to diagnose the osteopenia of prematurity may not be as accurate as the bone density measurement. This present demonstrates the benefits of PDF milk in terms of growth, bone strength, blood concentration, which can be applied to the preterm babies in Thailand, who have difficulty in receiving breast milk. To study in more detail, long term effects must be observed.

Potential conflicts of interest

None.

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ความแตกต่างในการเจริญเติบโตผลทางห้องปฏิบัติการและพัฒนาการในทารกเกิดก่อนกำหนดที่จำหน่ายออกจากโรงพยาบาลที่ได้รับนมสูตรต่อเนื่องเปรียบเทียบกับทารกที่ได้นมแม่

อุไรวรรณ โชติเกียรติ, จรินทรณ์ วงค์ภากรณ์

วัตถุประสงค์: เพื่อศึกษาความแตกต่างในการเจริญเติบโต ผลทางห้องปฏิบัติการและพัฒนาการในทารกเกิดก่อนกำหนดที่จำหน่ายออกจากโรงพยาบาลที่ได้รับนมสูตรต่อเนื่องเปรียบเทียบกับทารกที่ได้นมแม่ และติดตามภาวะแทรกซ้อน

วัสดุและวิธีการ: การศึกษาไปข้างหน้า ทำการศึกษาเปรียบเทียบความแตกต่างของการเจริญเติบโตผลทางห้องปฏิบัติการ (แคลเซียม ฟอสฟอรัส อัลคาร์ไลน์ ฟอสฟาเตส และความเข้มข้นเลือด) และพัฒนาการในช่วงอายุครรภ์ 40 สัปดาห์ 2, 4 และ 6 เดือนระหว่างกลุ่มนมแม่และนม postdischarge (PDF) ในผู้ป่วยทารกแรกเกิดก่อนกำหนดที่ได้รับการรักษาในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี และจำหน่ายออกจากโรงพยาบาล โดยทำการศึกษาเป็นระยะเวลา 22 เดือน (1 กันยายน พ.ศ. 2554 ถึง 31 พฤษภาคม พ.ศ. 2556)

ผลการศึกษา: ทารกที่เข้าร่วมโครงการทั้งสิ้น 17 ราย เป็นกลุ่มนมแม่ 7 ราย และกลุ่ม PDF 10 ราย พบว่าอายุของมารดามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ น้ำหนักตัวของทารกกลุ่มนมแม่มากกว่ากลุ่มนม PDF ช่วงอายุ 2 เดือน ($p = 0.03$) แต่ที่อายุ 4 เดือน ทารกที่ได้รับนม PDF มีน้ำหนักตัวและส่วนสูงมากกว่า เมื่อเปรียบเทียบกับกลุ่มนมแม่ ($p<0.05$) โดยส่วนสูงของกลุ่มนม PDF มากกว่ากลุ่มนมแม่ในช่วงอายุ 40 สัปดาห์ด้วย ($p = 0.001$) แต่ไม่มีความแตกต่างของรอบศีรษะ ค่าอัลคาร์ไลน์ ฟอสฟาเตส ในกลุ่มนม PDF ต่ำกว่ากลุ่มนมแม่ ทั้งช่วงอายุ 40 สัปดาห์ (PMA) และ 2 เดือน ($p<0.05$) อย่างมีนัยสำคัญทางสถิติและค่าฟอสฟอรัสของกลุ่มนม PDF ที่อายุ 2 เดือนสูงกว่าอย่างมีนัยสำคัญทางสถิติ ($p = 0.007$) แต่ค่าแคลเซียมไม่พบความแตกต่างทางสถิติระหว่าง 2 กลุ่ม ทารกกลุ่มนม PDF มีความเข้มข้นเลือดสูงกว่าแต่มีความแตกต่างทางสถิติที่อายุ 40 สัปดาห์ (PMA) และ 6 เดือน และไม่มีความแตกต่างในผลการคัดกรองพัฒนาการที่อายุ 4 เดือน

สรุป: การให้นม PDF ช่วยให้การเจริญเติบโต ความเข้มข้นเลือดและผลเลือดที่บ่งถึงภาวะกระดูกอ่อนของทารกเกิดก่อนกำหนดดีขึ้น โดยไม่มีความแตกต่างกันในด้านพัฒนาการ และไม่พบภาวะแทรกซ้อนจากการใช้นม PDF