

## EFFECTS OF HUMAN MILK FORTIFICATION ON MORBIDITY FACTORS IN VERY LOW BIRTH WEIGHT INFANTS

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**Background:** The use of human milk as a sole source of nutrients for preterm infants has been the subject of debate in recent years. We studied the morbidity factors associated with hospitalization of very low birth weight (VLBW) infants fed human milk with and without fortification.

**Patients and Methods:** One hundred VLBW infants were randomly assigned to two groups with stratification for gestation and weight. The control group (n=50; mean birth weight 1239±186 g and mean gestation 29.3±2.1 wks) was fed human milk only, and in the fortifier group (n=50; mean birth weight 1245±191 g and mean gestation 29.5±2.1 wks), human milk was enriched with a fortifier after the babies reached a volume of 140 mL/kg/day by the enteral route. Weight was measured twice weekly, biochemical indices of nutritional and bone status and serum electrolytes were obtained weekly, and clinical evidence for sepsis, necrotizing enterocolitis and feeding intolerance was assessed regularly until infants were discharged.

**Result:** Hospital stay was less than 45 days in the majority (94%) of the babies in the fortifier group, whereas the majority (66%) of the babies in the control group stayed for more than 45 days ( $P<0.01$ ). Low serum phosphorus and raised alkaline phosphatase levels were seen more frequently in the control group without fortification ( $P<0.01$ ), as well as hyponatremia ( $P<0.01$ ), late metabolic acidosis of prematurity ( $P<0.01$ ) and culture-proven sepsis ( $P<0.05$ ). There was no significant difference in the occurrence of necrotizing enterocolitis between the two groups ( $P>0.05$ ).

**Conclusion:** Human milk fortification has beneficial effects on the growth of VLBW infants and decreases hospital stay and morbidity associated with prematurity and very low birth weight, with economic and psychological benefits for the parents.

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**Key Words:** Very low birth weight (VLBW) infant, human milk, fortification, morbidity.

Human milk provides adequate nutrition to facilitate optimal growth in term infants, and has potential beneficial effects on immunity and infant-mother bonding. Preterm infants are born with low skeletal stores of calcium and phosphates, and require large amounts of these minerals in order to attain adequate postnatal skeletal growth. The importance of meeting the increased nutritional needs of preterm infants, compared with those of term infants, has been emphasized by many previous studies.<sup>1-4</sup> The aim of this study was to analyze the rate of growth in a large sample of preterm very low birth weight (VLBW) babies fed exclusively on breast milk with or without fortifiers, and to compare the morbidities, including duration of hospitalization, in the two groups.

### Patients and Methods

A total of 100 VLBW infants who were appropriate for gestational age and admitted to the Special Care Baby Unit of Khoula Hospital, Muscat, between January 1997 and October 1999, were studied. Since the introduction of the Baby Friendly Hospital Initiative (BFHI) program in the country in 1992, parents have been routinely encouraged to feed all premature babies on breast milk alone. In this double-blind study, infants in one group (control group, n=50) received human milk only, while the other group (fortifier group, n=50) received fortified human milk. Group allocation was done on the criteria that the groups matched in number, gestational age and birth weight as far as possible. The infants were free of any congenital anomalies. Infants who needed prolonged ventilation were not included in the study.

All infants were fed their own mother's milk, and in case of insufficient breast milk, formula feeds were used to meet the total energy requirements on that particular day. Babies who needed more than 15% of energy from formula feeds for more than two days were not included in this

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TABLE 1. Nutritional comparison per 100 mL of preterm mother's milk assessed at two weeks postpartum and human milk fortified with 4 g of human milk fortifier.

Nutrient	Preterm milk	Fortified human milk
Calories (Kcal)	67	81
Protein (g)	1.4	2.4
Fats (g)	3.9	4.06
Carbohydrates (g)	6.6	9.0
Vitamins		
Vitamin A (IU)	389	1289
Vitamin D (IU)	2.0	302
Vitamin E (IU)	1	5.6
Vitamin K ( $\mu$ g)	0.21	11.2
Vitamin B <sub>1</sub> -thiamine ( $\mu$ g)	21	247
B <sub>2</sub> -riboflavin ( $\mu$ g)	48	298
B <sub>6</sub> -pyridoxine ( $\mu$ g)	15	265
B <sub>12</sub> cyanocobalamin ( $\mu$ g)	0.05	0.35
Niacin ( $\mu$ g)	150	3650
Folic acid ( $\mu$ g)	3.3	33.3
Panthenic acid ( $\mu$ g)	180	1080
Biotin ( $\mu$ g)	0.6	2.1
Vitamin C (mg)	11	51
Minerals		
Calcium (mg)	25	115
Phosphorus (mg)	13	58
Iron (mg)	0.12	-
Zinc (mg)	0.34	0.60
Magnesium (mg)	3.2	6.2
Sodium (mg)	25	43
Potassium (mg)	57	84
Chloride (mg)	55	72

Milk nutrient composition values from Wyeth-Ayerst International 1999; milk composition literature was used from studies that reported data on milk samples collected from mothers who delivered prematurely.

TABLE 2. Data of infants fed human milk with fortifier (fortifier group) or without fortifier (control group).

	Fortifier group (n=50)	Control group (n=50)
Gestational age (wk)		
26-27	8	10
28-30	30	27
31-34	12	13
Mean gestational age $\pm$ SD (wks)	29.5 $\pm$ 2.1	29.3 $\pm$ 2.1
Birth weight (g)		
600-1000	4	5
1001-1250	20	19
1251-1500	26	26
Mean birth weight $\pm$ SD (g)	1245 $\pm$ 191	1239 $\pm$ 186

study. Milk was expressed by the mothers using Medela breast pump (Medela AG, Medical Technology, Switzerland). Infants were started on feeds as soon as clinical conditions permitted. When the infants tolerated a volume of >140 mL/kg/day by the enteral route, the milk in the fortifier group was enriched with a multinutrient fortifier in the form of a powder in packets, manufactured by a leading multinational drug company. Fortification was started with 1 g of fortifier added to 100 mL of milk on day 1, and gradually increased to 4 g of fortifier added to 100 mL on day 3 or 4 to improve tolerance of fortified milk. Feedings were initially given by continuous and later by intermittent gavage feeding, and finally the infants were

cup and breast fed before discharge. Maximum enteral milk intake was kept at 180 mL of milk/kg/day until the infants were breast fed. The nutrient content of 100 mL of fortified human milk (with 4 g of fortifier) and mother's milk at two weeks postpartum is shown in Table 1.

Weight was measured twice weekly throughout the study period. Data regarding gestation, birth weight, duration of hospital stay and average daily weight gain were analyzed. Biochemical indices of nutritional and bone mineral status were obtained on the first day of study and weekly thereafter until the infants were discharged from hospital. These indices included serum calcium, phosphorus and alkaline phosphatase levels. Serum electrolytes were also checked weekly after infants were on full enteral feeds. Clinical evidence for sepsis, feeding intolerance and necrotizing enterocolitis was monitored and assessed regularly. The data were analyzed and statistical significance of the observed data was derived using the chi-squared method.

## Results

Demographic data shows that the gestational age at birth ranged from 26 to 34 weeks while the birth weight ranged between 600 and 1500 g in both study groups, and that there were no significant weight and gestational age differences in the two groups (Table 2). Overall, insufficient breast milk was not a problem in this study, but 6 infants (3 in the control group and 3 in the fortifier group) received supplemental formula milk over a total period of 7 study days (4 days in the control group and 3 days in the fortifier group) to meet the total energy requirements. The total energy intake from formula over these days was less than 15% on each day. This had no statistical significance on the study objectives both in terms of the number of the patients who received formula supplements in each of the two groups ( $P>0.05$ ), or on the total caloric intake from human milk during the entire period of hospitalization.

Weight gained in grams per day is shown in Table 3. The rate of gain was less than 20 g/day in 43 infants (90%) in the control group and more than 20 g/day in 41 (90%) infants in the fortifier group ( $P<0.01$ ). Duration of hospital stay (from admission date until a weight of 2000 g was achieved) shows that all the infants in the fortifier group were discharged within 60 days, as compared to only 34 (60%) infants in the control group ( $P<0.05$ ) (Table 3).

Serum biochemical values are shown in Table 4. Low serum phosphorus (<1.55 mmol/L) and raised alkaline phosphatase levels (>450 mmol/L) were seen in a significantly higher proportion of infants in the control group as compared to the fortifier group ( $P<0.01$ ). Hyponatremia (<130 mmol/L) and late metabolic acidosis of prematurity were also more evident in the control group ( $P<0.01$ ). Similarly, culture-proven sepsis was seen in 3 (6%) infants in the fortifier group, compared to 7 (14%) in the control group ( $P<0.05$ ). A look at the incidence of

necrotizing enterocolitis (NEC) shows that there was no significant difference between the two groups in the number of infants (6% vs. 8%) who had this condition during hospitalization ( $P>0.05$ ).

### Discussion

Human milk feeding has potentially significant immunologic, nutritional and psychological advantages for the small preterm infant, and there is increasing scientific evidence supporting its value in neonatal care.<sup>5-7</sup> However, the low phosphorus content of human milk may be inadequate for bone mineralization during and after hospitalization,<sup>1</sup> and previous studies have shown improved bone mineralization and growth in premature infants fed fortified mother's milk<sup>3,8</sup> and higher prevalence of osteopenia and rickets in the VLBW infants without mineral supplementation.<sup>4,9</sup> Estimates of calcium and phosphorus needs for infants <1800 g and gestational age of 26-32 weeks are 140-180 mg calcium and 70-90 mg phosphorus/kg body weight/day.<sup>10</sup>

Many studies in the past have focused on various aspects of fortifier-enriched milk for preterm infants.<sup>11-13</sup> The last reported study by Schanler et al.<sup>12</sup> focused on the effects on growth, feed intolerance and health of participating infants who were fed fortified human milk, in comparison with those who were fed exclusively with preterm formula.

Our case-control study focuses mainly on the subject of nutritional morbidity factors in preterm babies. Though bone density could not be measured in this study, the biochemical indices of osteopenia of prematurity clearly show that neonatal well-being during the lengthy hospitalization of VLBW babies can be further improved by the addition of human milk fortifier to breast milk. There is a significant reduction in the duration of hospitalization because of faster growth rate in babies receiving fortification, with economic and psychological benefits for the parents. The shorter duration of hospitalization may decrease exposure of these babies to nosocomial sepsis and thus contribute to the overall reduction of sepsis and the associated morbidity in VLBW babies. Similar observations have been made by Reiss et al.,<sup>13</sup> who found enhanced growth of preterm babies with human milk fortification, and also by Schanler et al.,<sup>12</sup> who noticed that infants fed fortified human milk were discharged earlier and had less incidence of late-onset sepsis and NEC. The other study by Lucas et al.<sup>11</sup> reported higher plasma calcium, more clinical infections and non-significant increased incidence of NEC in the fortifier group. The problem with the study by Lucas et al. has been that the breast milk intake comprised only 47.6% of total enteral intake, and more than 50% of the enteral intake was supplemented by a preterm formula. Therefore, this mixed feeding pattern cannot be relied on to draw conclusions on the complications of fortification of human milk.

We noted that in addition to hypophosphatemia, hyponatremia is also frequently seen in VLBW babies, especially during the initial stabilization and early recovery periods of hospitalization. Our study demonstrated that the frequency of hyponatremia can be reduced by the additional amounts of sodium present in the fortifier, and may alleviate the need for sodium supplementation in recovering LBW babies with hyponatremia. In spite of the marginally higher content of sodium in the milk of babies receiving human milk fortifier, there was no significant difference in the frequency of feed intolerance and NEC in the two groups. This may also be related to the fact that human milk-fed babies have a very low incidence of NEC, as compared to babies on artificial feeds,<sup>14</sup> and fortified human milk, though marginally hyperosmolar than human milk alone,<sup>15</sup> does not predispose to the development of NEC and may be better than hypertonic saline added to the feeds in situations of hyponatremia during recovery periods of these LBW infants.

All these facts further point to the need for initiating fortification of human milk feeds in VLBW babies as soon as these infants tolerate enteral feeds. Though the current practice in most places is to initiate fortification at an enteral volume of 140 mL/kg/day, some recent studies have encouraged the use of fortification beginning at an enteral volume of 100 mL/kg/day.<sup>13</sup> The tolerance of fortified human milk can be further improved by the gradual increase to full strength fortification over a period of 3 to 4 days.

Overall, the benefits of a shorter hospital stay with decrease in hospital infections, better bone mineralization, fewer electrolyte disturbances and other potential benefits of human milk feeding strongly advocate the use of human milk with fortification for optimum growth of preterm VLBW infants.

The effects of human milk fortification on immunological factors present in human milk have yet to be finally evaluated and further studies are needed to explain this aspect of human milk fortification. Future studies should also be aimed at achieving optimum caloric intake through fortified human milk without a substantial increase in osmolality. This could be achieved by enhancing the fat content of the fortifier marginally to replace a fraction of the carbohydrates in the fortifier.

### References

1. Hall RT, Wheeler RE, Rippetoe LE. Calcium and phosphorus supplementation after initial hospital discharge in breast-fed infants of less than 1800 grams birth weight. *J Perinatol* 1993;13:272-8.
2. Davies DP. Adequacy of expressed breast milk for early growth of preterm infants. *Arch Dis Child* 1977;52:296-301.
3. Greer FR, McCormick A. Improved bone mineralization and growth in preterm infants fed fortified own mother's milk. *J Pediatr* 1988;112:961-9.
4. Laing IA, Glass EJ, Hendry GM, et al. Rickets of prematurity: calcium and phosphate supplementation. *J Pediatr* 1985;106:265-8.

5. Lucas A, Morley RM, Cole TJ, Lister G, Leeson Payne C. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 1992;339:261-4.
6. American Academy of Pediatrics Work Group on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* 1997;100:1035-9.
7. Neuringer M, Connor WE. n-3 fatty acids in the brain and retina: evidence for their essentiality. *Nutr Rev* 1986;44:285-94.
8. Schanler RJ, Garza C. Improved mineral balance in very low birth weight infants fed fortified human milk. *J Pediatr* 1988;112:452-6.
9. Rowe JC, Wood DH, Rowe DW, Raisz LG. Nutritional hypophosphatemic rickets in a premature infant fed breast milk. *N Engl J Med* 1979;300:293-6.
10. Ehrenkranz R. Mineral needs of the very low birth weight infant. *Semin Perinatol* 1989;13:142-5.
11. Lucas A, Fewtrell MS, Morley R, Lucas PJ, et al. Randomized outcomes trial of human milk fortification and developmental outcome in preterm infants. *Am J Clin Nutr* 1996;64:142-51.
12. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics* 1999;103:1150-7.
13. Reiss BB, Hall RT, Schanler RJ, Berseth CL, et al. Enhanced growth of preterm infants fed a new powdered human milk fortifier: a randomized, controlled trial. *Pediatrics* 2000;106:581-8.
14. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet* 1990;336:1519-23.
15. De Curtis M, Candusso M, Pieltain C, Rigo J. Effect of fortification on the osmolality of human milk. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F141-3.