Breast Milk vs. Donor Milk vs. Formula: An Analysis of Premature Growth in the Neonatal Intensive Care Unit (NICU)

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Abstract:

Premature babies are born before 36 weeks. Since these babies are not fully developed, they need extra nutrients. There are three types of milk that infants can receive: mother's, donor's, and formula. Mother's milk is provided by the mother; donor milk is provided by a donor milk bank, which requires hospitals to be on such a program. If donor milk isn't available, then the substitute is formula.

In addition to the type of nutrients the baby receives, milk has to be fortified. Initially, mother's milk and donor milk are 20 cal/oz. Progressively, the milk ends up getting fortified to 22 cal/oz then 24 cal/oz. There are two types of fortifiers: cow milk based and human milk based. Cow milk based fortifier taints the breast milk composition making washing away any nutrients in the original breast milk. The human milk fortifier keeps the composition of the breast milk intact.

This research will focus on the effects of breast milk vs. donor milk vs. formula on preterm infants with respect to cognitive development, neurological outcomes, and risk for diseases. For this experiment, I will conduct a meta-analysis of previous research and use the hospital's data that doctors have started recording.

Premature babies are babies that are born before the typical term of 36 weeks. These babies tend to be weaker than normal babies. Because these babies are weaker their body requires a great amount of nutrients to complete normal processes. Before babies can eat solid foods, milk is the primary source of nutrition. Babies can receive 3 types of milk: mother's own milk, donor human milk or formula milk. Breast milk is the milk produced by the mother to feed their infants. Donor milk is produced from a different mother but given to the neonate. Formula milk is substituted for breast milk and is typically based of cow milk; thus when mixing formula and breast milk, the breast milk becomes tainted to cow milk. For premature babies, the type of milk they receive depends on many factors.

Since 1939 studies have shown mother's own milk has beneficial effects to the baby including reduced risk of eczema and increased cognitive development. This is because mother-infant bonding can occur if the baby receives mother’s milk. Also, the mother's milk is specifically tailored to her baby. The mother and the baby are living in the same microbiome (the microorganisms in an environment), which can help the baby fight diseases. It is stated that mammary gland receptors interpret the baby's spit for bacteria and viruses and, the glands can even detect something amiss. The mom's body will actually change the milk's immunological composition, tailoring it to the baby's particular pathogens by producing customized antibodies for that baby, (Belfort et al., 2008). Other than tailoring composition to their own baby, breast milk in general has a number of protective benefits. In a study done by Radmacher et al., 2016 there was a reduction in bronchopulmonary dysplasia and retinopathy of prematurity. But, the most noticeable short-term effect of breast milk compared to formula is that breast milk lowers

the rate of Necrotizing Enter colitis (NEC), (Lucas and Cole 1990). One study in 2010 particularly compared donor milk and formula milk on just the risk for NEC. An Exclusively Human Milk-Based Diet is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk Based Products instituted donor milk banks in their study only when mothers cannot provide sufficient breast milk. The study reported that donor milk and formula milk do not affect cognitive development differently but donor milk significantly lowers the risk of NEC by about 50% and 90% surgery. Breast milk seems to have different antibodies than formula milk, which provides exertive effects with respect to NEC, (Sullivan et al., 2010). This is consistent with earlier reports, dating back to 1990. In 1990 Lucas and Cole reported a reduction in NEC among infants who received only human milk compared to infants who received all bovine milk-based formula. The formula milk only provided an intermediate level of protection while the breast milk provides and advanced level of protection, (Lucas and Cole 1990). This makes a huge difference in avoiding surgery as well.

Another study also reported the differences between donors' human milk compared with preterm formula. Effect of Supplemental Donor Human Milk Compared with Preterm Formula on Neurodevelopment of VLBW Infants at 18 months instituted a double blind, randomized trial. The infants were split into random groups (donor milk and formula) and were fed that type of milk for 90 days or to discharge. This study reports that Breast milk promotes gastrointestinal development better than formula milk does. When the GI tract is developed more it actually reduces the risk of GI diseases, (Gibson et al., 2009). This also looked at the risk of NEC and they found that

formula milk increases risk of NEC and risk of NEC requiring surgery. But in addition this study reported that the weight length and head circumference gains were greater. A plausible reason for this is that donor milk in most studies wasn't fortified with nutrients so these findings are not surprising. This study instituted a cognitive development test called the Bayley. On this test the donor milk group did better at 18 months. The donor milk had many more babies that had a neuroimpairment score lower than 85 (which is a great sign). 27.2% of babies had a cognitive score of <85, 46.7% of babies had a language score of <85 and 25.5% of babies had a motor score of <85. This is compared to the formula milk group which had 16.2% of babies had a cognitive score of <85, 37.2% of babies had a language score of <85 and 20.4% of babies had a motor score of <85. This also carried over to a disability score of <70 where the donor milk group had more babies reach below that score. These results weren't great enough to report significant clinical differences. This study concluded "among VLBW infants, the use of supplemental donor milk compared with preterm formula did not result in an improvement in a measure of neurodevelopment at 18 months corrected age," (O'Connor et al., 2016). This is consistent with another study done by Polishook et al., in 2016. Human milk intake in preterm infants and neurodevelopment at 18 months corrected age also administered the Bayley to babies at 18 months corrected age. This study was done to examine associations of human milk intake with neurodevelopment at 18 months corrected age only for babies born <33 weeks' gestation. They hypothesized that greater dose of human milk intake during the neonatal hospitalization and longer duration of human milk (even after discharge) would be associated with better outcomes; and that associations would be stronger in infants more vulnerable to neurodevelopmental

impairment. Another thing this study noted was they expected a stronger association in female infants vs. male because of docosahexaenoic acid, a key nutrient in human milk but appears greater in females. This study also administered the Bayley at 18 months corrected age. They did not find statistically or clinically significant association of the volume of human milk intake during the neonatal hospitalization or total duration period and concluded no substantial associations of human milk intake compared to formula.

With human milk and formula milk also comes the fortifying of both of these milks. As of now, two main fortifiers are on the market. One is cow milk based and the other is derived from human milk itself. The cow milk based is inexpensive but this price comes with effects on the breast milk. Once this bovine based product is added to the breast ilk it changes the breast milk to cow milk; meaning that any effects the breast milk might have had on the baby are all gone. With the human milk fortifiers it doesn't change the milk so the breast milk can still have positive effects on the baby. Fortification of human milk for the premature infant reported on the main three strategies of fortification. Standard fortification is the most widely used and a fixed dosage of fortifier is added to the milk over the fortification period. Adjustable fortification is all based on changes in the blood urea nitrogen level (BUN), which is an indicator of how well protein is broken down in the body. Additional fortifier is added if the BUN is below a critical threshold and the fortifier is lowered is the BUN level is too high. The last is targeted fortification, the most time consuming and not really available in real time. This requires analyzers to tailor the macronutrient content based on real time analysis of human milk; thus providing the infant with a constant and defined intake. This study concluded that human milk must be fortified in order to provide sufficient support for growth and development.

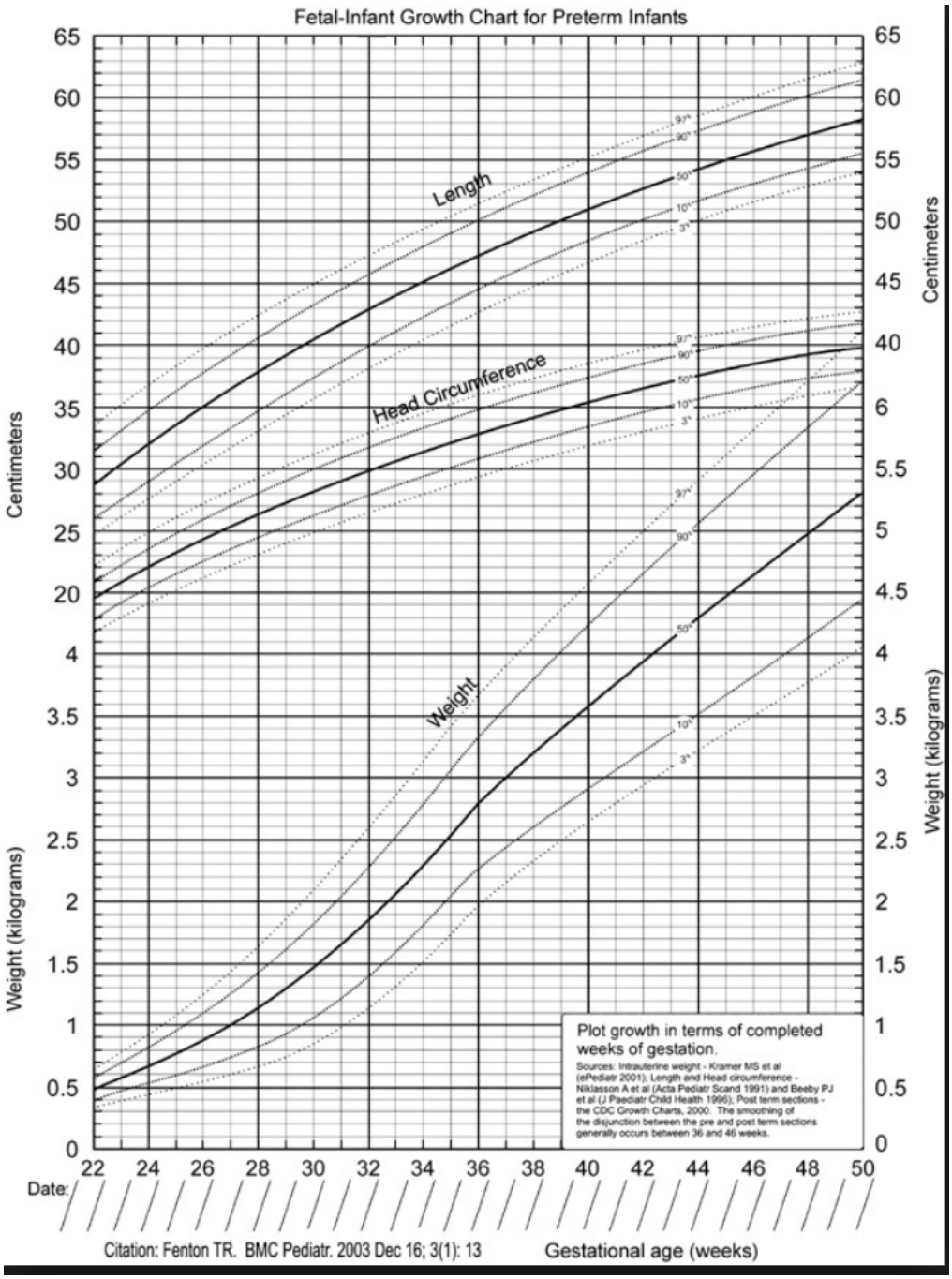
Various clinicians can decide which strategy/ fortifier they prefer. (Radmacher et al., 2016)

This led me to my research question. My research question was: What are the effects of breast milk vs. donor breast milk vs. premature formula with respect to risk for necrotizing enterocolitis?

In order to study the effects of different formulas on premature babies I analyzed premature babies' growth at the Valley Hospital Neonatal Intensive Care Unit (NICU). The hospital used a Similac fortifier as their main fortifier until they switched over to Enfamil at the beginning of 2017. The reason for the switch was economic. The hospital signed a contract with both Similac and Enfamil: the conditions are that the hospital switches fortifiers every six months and in exchange they receive the two fortifiers for no cost. Since the switch to Enfamil two babies have gotten necrotizing enterocolitis (NEC). This is a disease when bacteria invade the intestinal tissue, cause local inflammation and ultimately can destroy the intestine wall. In severe cases the intestine can perforate and some of the fluid can leak into the abdomen causing infection. It is the leading cause of death in premature infants and affects thousands of babies a year. (NEC Society 2017)

Valley Hospital decided to analyze growth and feeding patterns to see if there is a correlation between NEC and the type of formula. My mentor and I created a comprehensive Excel spreadsheet at the hospital to analyze babies' growth data on Enfamil and analyze babies' growth data on Similac. This spreadsheet examines many factors of each baby. First the chart looks at their gestational age and birth weight. Since NEC is more common among premature babies less than 3lbs 5oz and premature babies

less than 31 weeks, this is an important data point. (NEC Society 2017) First, I used Fenton growth charts to graph babies weight, head circumference and length. The x-axis represents the gestational age. The y-axis represents either kilograms or centimeters. The chart displays whether each baby is a singleton or a multiple. This matters because multiples are more prone to get NEC, but singletons can still acquire the disease.



Birth and Discharge Data Numbers and Percentiles for 7 Babies Fed Similac

GA	BW	BW (dis)	%//%	Length	Length (dis)	%/%	HC	HC (dis)	%/%
28 weeks 3/7	1.104 kg	2.527 kg	55--12	37 cm	46 cm	70--12	27 cm	33.5 cm	90--50
32 weeks 1/7	1.205 kg	2.255 kg	<10--<3	40.5 cm	45 cm	35--3	28 cm	32 cm	10--10
27 weeks 6/7	0.730 kg	2.430 kg	<10--<3	31 cm	45 cm	<10--<3	24.5 cm	32 cm	15--10
25 weeks 1/7	0.792 kg	2.294 kg	85--7	35.5 cm	44.5 cm	97--5	23.5 cm	31 cm	75--7
28 weeks	0.750 kg	2.25 kg	10--3	31 cm	41 cm	<3--<3	24 cm	30.5 cm	10--3
26 weeks	1.010 kg	2.808 kg	90--10	35.5 cm	45 cm	85--<3	24 cm	36.2 cm	75--75
27 weeks 4/7	1.190 kg	3.306 kg	80--50	38.1 cm	48.26 cm	85--10	26.5 cm	35.5 cm	75--90

Note: Gestation age is based on how many weeks and days the babies were. (i.e. 5/7 is 5 days out of 7 days). BW stands for birth weight. Dis stands for discharge. HC stands for head circumference. The percentile columns analyze the percentiles of weight, length and head circumference along with the data of when the baby was born and when the baby was discharged. The first number in the column is the percentile at birth. The second number in the column after the dashes is the percentile at discharge.

Birth and Discharge Data Numbers and Percentiles for 8 Babies Fed Enfamil

GA	BW	BW (dis)	%//%	Length	Length (dis)	%/%	HC	HC (dis)	%/%
30 weeks 6/7	1.075 kg	2.076 kg	10--<3	40 cm	41.5 cm	50--<3	27 cm	32 cm	25--25
30 weeks 6/7	1.262 kg	2.340 kg	25--10	39 cm	45 cm	40--10	28.5 cm	33 cm	75--50
27 weeks	0.952 kg	3.039 kg	50--<10	36 cm	48 cm	60--<10	25.5 cm	35 cm	75--50
28 weeks 3/7	0.965 kg	2.708 kg	25--<3	34 cm	45.5 cm	10--<3	25.5 cm	32.5 cm	40--<3
28 weeks 3/7	0.829 kg	2.679 kg	<10--<3	33.25 cm	45.5 cm	3--<3	23.5 cm	33.5 cm	<10--25
28 weeks 3/7	1.398 kg	3.295 kg	40--60	38 cm	47 cm	80--55	28 cm	36 cm	97--97
28 weeks 3/7	1.355 kg	3.75 kg	90--50	40 cm	50 cm	90--20	28 cm	37 cm	97--90
26 weeks 2/7	0.746 kg	2.099 kg	40--<10	33 cm	45 cm	50--30	22.5 cm	28 cm	10--<3

Note: Gestation age is based on how many weeks and days the babies were. (i.e. 5/7 is 5 days out of 7 days). BW stands for birth weight. Dis stands for discharge. HC stands for head circumference. The percentile columns analyze the percentiles of weight, length and head circumference along with the data of when the baby was born and when the baby was discharged. The first number in the column is the percentile at birth. The second number in the column after the dashes is the percentile at discharge.

We also looked at how babies progressed from week to week. Our chart first measures week-to-week progress when babies started the 24-calorie fortifier. Initially babies start out with just breast milk, which is around 20 calories per oz. They can receive it through a feeding tube or by mouth. Then they progress to 22 cal/oz but only for a short time. After the 22 cal/oz they get 24 cal/oz. This was a good place to start our data collection because it meant that most babies were strong and mature enough to handle a feed by mouth and have been in the NICU for a time. The American Academy of Pediatrics has general guidelines about babies' growth rates. Since Valley Hospital has a level III NICU that can only hold 10-18 babies, the hospital sets its own standards. For Valley Hospital the target amount of intake was around 150 ml/kg/day. This number is based on weight but each baby's target intake was 150 ml/kg/day. This meant babies were receiving optimal nutrients. When babies were getting optimal nutrients, weight gain was supposed to be 20-30 grams per day and head circumference was supposed to be .5-1 inch per week. In the Valley Hospital NICU we look for length growth but sometimes the length can go down and up from week to week. It is the most inaccurate measure for how a baby is growing at this age. When babies are in the NICU all of their energy goes towards growing their brain and muscles. The length comes second. More intake is ok and it is also ok for the total intake to be less than 150ml/kg/day. If the total intake was less we had to look at factors that can make the number go down. The most common factor that made the numbers drop was if the baby was on Total Parenteral Nutrition (TPN). This was giving the baby nutrients in addition to the milk so they didn't need to get the whole serving of milk. The ml/kg/day for these babies was a much lower value, which was 100 ml/kg/day.

Babies on IV Fluid in Conjunction With Milk

5-Aug-17	1.037 kg	93 ml/kg/day
7-Sep-17	1.390 kg	98 ml/kg/day

Note: This is a sample of babies on 24-calorie fortifier win conjunction with IV fluid so the intakes are much lower than 150ml/kg/day.

The intake could be over 150ml/kg/day at times as well. This occurred when the baby was at the end of the NICU course. When a baby was at the end of the NICU course they most likely graduated from a 24-calorie fortifier to a 27-calorie fortifier or a rice cereal mix.

Sample of Babies' Intakes that are greater than 150ml/kg/day

6-Apr-17	2.494 kg	160 ml/kg/day
29-May-17	2.099 kg	190 ml/kg/day

Note: This is a sample of babies who were almost ready to be discharged, which is why their intakes are high. It is to get them extra healthy just before they go home.

After we made the Excel spreadsheet my mentor and I made a PowerPoint to present it to the other staff at Valley Hospital. From here we condensed the results of the data so it was easier to explain to the other staff. In the PowerPoint, we analyzed the ingredients of the fortifiers more closely.

Nutrients in Similac and Enfamil. PowerPoint Presented to Staff

	EBM/Sim	EBM/ENF	Similac 24	Enfamil 24
Calories per oz	24	24	24	24
Protein g	2.84	3.2	2.68	2.9
Protein g/kg/day at 150 ml/kg/day	4.26	4.8	4.02	4.35
Calcium Mg/kg/day at 150 ml/kg/day	180	177	219	201
Phosphorous Mg	67	65	81	73
Sodium meq	1.6	2	1.5	2.47
Potassium meq	2.9	2	2.7	2.05
Iron mg	0.47	1.54	1.46	1.46
Vitamin D	118	167	121	240

The only striking difference in the ingredients was the iron milligrams in the Similac Express Breast Milk there was a whole mg less. We then looked at the full workup of ingredients for each fortifier and they were very similar. Since this was not enough to prove any correlation between fortifier and NEC we looked further. We looked at how many babies had to progress to 27 calorie formula after the 24 calorie formula. There was a striking difference in the amount of babies that had to switch to the 27-calorie fortifier

while on the 24 in order to get extra nutrients. We found that in the Similac group 2/7 (29%) babies moved up to 27 calorie fortifier. In the Enfamil group 4/8 (50%) babies had to be moved up to 27 calories.

Similac Ingredients

Water, Nonfat Milk, Corn Syrup Solids, Medium-Chain Triglycerides, Lactose, Whey Protein Concentrate, Soy Oil, Coconut Oil. Less than 0.5% of: C. Cohnii Oil, M. Alpina Oil, Beta-Carotene, Lutein, Calcium Phosphate, Ascorbic Acid, Potassium Citrate, Calcium Carbonate, Soy Lecithin, Monoglycerides, Magnesium Chloride, m-Inositol, Sodium Citrate, Carrageenan, Potassium Hydroxide, Ferrous Sulfate, Choline Bitartrate, Taurine, Choline Chloride, Niacinamide, L-Carnitine, Zinc Sulfate, Potassium Chloride, Salt, Potassium Phosphate, d-Alpha-Tocopheryl Acetate, Calcium Pantothenate, Vitamin A Palmitate, Cupric Sulfate, Riboflavin, Thiamine Chloride Hydrochloride, Pyridoxine Hydrochloride, Folic Acid, Manganese Sulfate, Biotin, Phylloquinone, Sodium Selenate, Vitamin D3, Cyanocobalamin, and Nucleotides (Cytidine 5'-Monophosphate, Disodium Guanosine 5'-Monophosphate, Disodium Uridine 5'-Monophosphate, Adenosine 5'-Monophosphate).

Enfamil Ingredients

INGREDIENTS: WATER, NONFAT MILK, CORN SYRUP SOLIDS, WHEY PROTEIN CONCENTRATE, LACTOSE, MEDIUM CHAIN TRIGLYCERIDES (MCT OIL), SOY OIL, HIGH OLEIC SUNFLOWER OIL, AND LESS THAN 0.5%: MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, CALCIUM PHOSPHATE, CALCIUM HYDROXIDE, POTASSIUM CITRATE, SODIUM CHLORIDE, CALCIUM CARBONATE, MAGNESIUM PHOSPHATE, CALCIUM CHLORIDE, POTASSIUM CHLORIDE, FERROUS SULFATE, ZINC SULFATE, CUPRIC SULFATE, POTASSIUM IODIDE, SODIUM SELENITE, RICE STARCH, SODIUM ASCORBATE, VITAMIN E ACETATE, NIACINAMIDE, CALCIUM PANTOTHENATE, VITAMIN A PALMITATE, THIAMIN HYDROCHLORIDE, RIBOFLAVIN, VITAMIN B_6 HYDROCHLORIDE, FOLIC ACID, VITAMIN K_1, BIOTIN, VITAMIN B_{12}, MONO- AND DIGLYCERIDES, INOSITOL, SOY LECITHIN, CHOLINE CHLORIDE, VITAMIN D_3, NUCLEOTIDES (CYTIDINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE, ADENOSINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE), TAURINE, L-CARNITINE.

Growth Data For 7 Babies Fed Similac

Average ml/kg/day	Average weight gain per day (g)	Went to 27 calorie formula after __ days of being on 24 calorie formula
128.6	22.6	N/A
146	28	N/A
141.4	24	1
114	19.8	20
139	24.2	N/A
137	26	N/A
134	27.6	N/A

Data for 7 babies in Similac group
Average weight gain: 24.6 grams per day
Average intake: 134.2 ml/kg/day

Growth Data For 8 Babies Fed Enfamil

Average ml/kg/day	Average Weight Gain per day (g)	Went to 27 calorie formula after __ days of being on 24 calorie formula
143.4	20	N/A
136.4	25.4	N/A
124.8	27.6	10
128	17.8	9
136	28.4	7
136.8	32.4	N/A
142.8	24.6	N/A
150.2	22.4	7

Data for 8 babies in Enfamil Group
Average weight gain: 24.8 grams per day
Average intake: 137.3 ml/kg/day

Conclusion:

From thoroughly looking through and analyzing the results my mentors and I came to a conclusion that neither fortifier was more effective. As previously discussed, the cost effectiveness for Enfamil and Similac are the same. After analyzing both fortifiers we concluded that neither fortifier is better. The hospital should continue to use both fortifiers and switch every six months.

Discussion:

After looking at the results we can conclude that breast milk is the best option for the baby for numerous reasons. But the breast milk has shortcomings, which is why discussion is needed. Since breast milk lacks enough calories for premature infant growth. Thus fortifiers are beneficial because they provide extra nutrients. But the problem with Similac and Enfamil is that when added to breast milk, the milk Similac and Enfamil used at Valley Hospital are both very similar but they both taint the effects of breast milk. There is one fortifier that doesn't taint the effects of breast milk when it is added. That is because the fortifier has a human milk base instead of the standard cow milk base. It is called Prolacta and it is the leading brand in human milk fortifiers. The only problem with it now is that it is too expensive. If the studies show that breast milk and donor milk only protect against NEC and Valley hospital only gets 2-3 cases of NEC a year; is it really worth it to implement?

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