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2014 Update in Neonatal Nephrology
Mar. 28, 2014; NY, NY USA
http://neonate.kidneyurology.org

International Neonatology Association Conference (INAC 2014)
April 3-5, 2014; Valencia, Spain
www.worldneonatology.com

2014 Workshop on Perinatal Practice Strategies Innovation with Evidence
Apr. 4-6, 2014; Scottsdale, AZ USA
www.aap.org/livecme

11th National Advanced Practice Neonatal Nurses Conference
Apr. 23-26, 2014; Honolulu, HI USA
www.academyonline.org/APNNC

5th Phoenix Fetal Cardiology Symposium
Apr. 23-27, 2014; Phoenix, AZ USA
www.fetalcardio.com

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Acidification of Human Milk Fortifier for Low Birth Weight Infants Associated with Poor Growth and Acidosis

By Ann Anderson-Berry, MD; Melissa Thoene, RD; Elizabeth Lyden, MS; Laura Dugick, NNP; Leslie Ruybal, MD; Corrine Hanson, PhD

Human milk has been shown to be the best source of nutrition for infants, leading to improved neurodevelopmental outcomes as well as improvements in long-term health.[1,2] For preterm infants it is particularly important to provide a human milk diet. Premature infants fed human milk have decreased rates of necrotizing enterocolitis, nosocomial infections and have improved neurodevelopmental outcomes.[3] While preterm infants reap great benefit from a human milk diet, unfortified human milk does not provide complete nutrition for the smallest infants. In particular, preterm milk does not provide enough protein, carbohydrates, or fat to meet current estimated needs. Preterm infants fed unfortified human milk grow more poorly than preterm infants fed preterm or even term formula.[4,5,6] For this reason, recommendations to fortify human milk for preterm infants have been published for almost 15 years.[7] Fortification of human milk historically has provided additional protein calories, fats, and other micronutrients and vitamins in a powdered form. Two commercial powdered human milk fortifiers (PHMFs) have been available for approximately 15 years. These two products were very similar in from and nutritional composition with the exception of iron content.

Powdered human milk fortifiers have represented a major improvement in the nutrition of the preterm infant over the last decade.[8] There remain several areas that demand improvement to meet the clinical and safety needs of the premature infant. First, the products are a powder and are not sterile. Both the Center for Disease Control and the Academy of Nutrition and Dietetics have recommendations for the use of liquid products in the Neonatal Intensive Care (NICU) environment to prevent infection from a contaminant Cronobacter sakazakii (formerly known as Enterobacter sakazakii) a gram-negative bacteria.[9,10] Second, despite improved growth compared to unmodified human milk, infants fed human milk fortified with PHMF often develop extrauterine growth restriction (EUGR). EUGR is defined as growth below the 10th percentile at 36 weeks corrected gestational age (CGA) when an infant is born above the 10th percentile. Third, the PHMFs do not meet the current estimates of protein necessary for extremely low birth weight infants (ELBW) and for larger infants who require catch-up growth.[11]

Liquid Products

C. sakazakii infections in newborns have been associated with mortality and serious morbidities, including sepsis, meningitis and necrotizing enterocolitis. In addition, severe neurologic complications often develop when meningitis is present including large cerebral abscess causing profound disability. Death occurs in 33%-80% of cases making this infection worth prevention despite its rare causation of invasive disease, with estimates at 8.7 per 100,000 low birth weight infants yearly.[12-19] Reports in the literature including one in 2001 investigated by the CDC in a Tennessee NICU have associated C. sakazakii infections with the use of powdered formulas (Portagen® in this report).[20]

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- First and only extensively hydrolyzed casein protein fortifier for easy digestion and absorption

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References: 1. Barrett-Reis B, et al. *Pediatrics.* 2000;106:581-588. **2.** Erickson T, Gill G, Chan GM. *J Perinatol.* 2012:1-3. **3.** Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Professional.* 6th ed. St. Louis, MO: Elsevier Mosby, Inc; 2005:147.

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Ideally the NICU environment could deliver optimal nutrition without the use of powder additives. In many cases this is not possible, and in such situations, the CDC has given guidance on best practices for the use of powdered nutrition. In a document entitled "Summary Interim Recommendations for Preparation of Powdered Infant Formula in the Neonatal Intensive Care Unit Setting" the following recommendations are made:

1) Formula products should be selected based on nutritional needs; alternatives to powdered forms should be chosen when possible. Trained personnel should prepare powdered formula under aseptic technique in a designated preparation room.
2) Manufacturer's instructions should be followed; product should be refrigerated immediately and discarded if not used within 24 hours after preparation.
3) The administration or "hang" time for continuous enteral feeding should not exceed 4 hours.
4) Written hospital guidelines should be available in the event of a manufacturer product recall, including notification of health-care providers, a system for reporting and follow-up of specific formula products used, and retention of recall records.[20] Following these protocols can help to minimize risk of infection from contaminated powder, and minimize risk of external contamination.

Growth

The second area where PHMFs are not meeting the needs of our preterm infant patient population is in growth. Despite widespread use of these products, a majority of infants discharged from NICUs in the US have EUGR.[21] Multiple studies evaluating growth reach the conclusion that in utero growth rates cannot be maintained during hospitalization in the NICU.[22-25] When evaluating growth in the NICU, it is imperative to evaluate with a tool designed specifically for preterm neonates. There are several appropriate tools available, including Fenton 2003 and Fenton 2008 growth charts[23,25] In the study summarized in this article, we utilized the Fenton 2003.[23] This publication is particularly informative with regards to achieved growth in the NICU, as the authors note, "(on evaluation of infant growth)…at a weight of 2 kilograms provides evidence that, on average, preterm infants are growth retarded with respect to weight and length while their head size has caught up to birth percentiles."[23]

In 1999 Ehrenkranz et al. evaluated growth of preterm infants 24-29 weeks, and demonstrated mean weights at birth at the 50th percentile for this patient population. By 36 weeks CGA, this group of infants was growing well below the 10th percentile with the youngest infants showing the most severe EUGR.[22] A paper from 2013 continues to find a high incidence of EUGR, ranging from 43% to 97% depending on the center. In 2000–2001, 16% of VLBW infants were small for gestational age (SGA) at birth, yet 89% displayed growth failure at 36 weeks PMA, figures that outline how widespread this problem is in the preterm infant.

One troubling aspect of managing growth and preventing EUGR in the preterm infant is that it is not a disease that has significant clinical signs. Radmacher et al. evaluated growth in infants less than 1000g at birth, and found that aside from lower birth weight, increasing days on parenteral nutrition was predictive for EUGR.[24]
or falling blood pressure in a septic infant where the disease process demands clinical attention. In a clinical setting growth often is secondary to acute illness, and this sets the stage for EUGR.

The question then arises, why is growth critical to the NICU patient? There is strong evidence to support associations with improved pulmonary outcomes, improved temperature control, earlier discharge readiness, and most importantly, improved neurodevelopmental outcomes with improved growth in the preterm infant.[26,27]

Protein

Protein needs in the preterm patient population are not clearly defined. Published estimates of requirements for the smallest infants have increased over the last two decades. One recent estimate published by Hay et al. in 2008 determines the protein need of patients born between 24-30 weeks to be between 3.6 and 4.8 g/kg/day depending on gestational age and weight at birth, need for catch up growth, clinical course and acuity.[11] The current PHMFs do not meet the protein needs of the highest risk lowest birth weight infants, and they also do not provide enough protein for the estimated needs of the larger preterm infant with deficits from early hospitalization.

Lower than optimal protein may be one component of the growth failure that is so prevalent in the NICU environment. Table 2 shows estimated protein content of selected enteral feeding options. Increasing protein in enteral feedings has been shown to improve growth in this patient population.[26] One method of increasing protein has been to add a protein modular to breast milk fortified with human milk fortifier. Previously available protein modulars have been in a powdered and non-sterile form. The use of Beneprotein®, a cow's milk based protein modular, has been reported to improve growth in this patient population.[26, 28] This is an intact cow's milk based powdered product and there was mixed adop-

Table 1. Comparison of ingredients and Key Nutrients Using Powder and Liquid HMF

24-Calorie-Per-Ounce Fortified Premature Human Milk[34]		
Per 100 mL	**Powder HMF**	**Liquid HMF**
Protein (g)	2.35	3.2
Iron (mg)	0.46	1.85
Calcium (mg)	138	141
Phosphorus (mg)	78	78
Vitamin D (IU)	119	200
pH	-	4.7
Primary Fortifier Macronutrient Ingredients	Nonfat milk, whey protein concentrate, corn syrup solids, medium-chain triglycerides (MCT oil)	Water, whey protein isolate hydrolysate (milk), medium chain triglycerides (MCT oil), vegetable oil (soy and high oleic sunflower oils)

Table 2. Protein Amounts in Various Feeding Options for Preterm Infants[36-38]

Feeding Type	Protein g/ 100 ml	Protein g/kg at 150 ml/kg/day
Unfortified Breast Milk	0.9-1.4	1.65-1.95
Breast Milk Fortified with Similac HMF Liquid or Powder	2.35	3.525
Breast Milk Fortified with Enfamil ALHMF	3.2	4.8
Similac Special Care 24 cal/oz	2.43	3.65
Similac Special Care High Protein 24 cal/oz	2.68	4.02
Enfamil Premature 24 cal/oz	2.44	3.66
Enfamil Premature High Protein 24 cal/oz	2.85	4.28
Prolact+	2.3-3.7	3.45-5.55

tion of this method of increasing protein delivery. Product labeling was recently changed to indicate that Beneprotein® is not for use in infants under three years of age.[29] Dietary list serves have voiced concerns regarding tolerance of this product; this was not reported in our studies.[26]

Recent Product Introductions

To meet the need for a powder-free feeding option for preterm breastfed infants, several new products have been developed. A human milk fortifier, Prolacta®, which is liquid in form and is derived from donor human milk has been recently available. Published studies show the use of this product is associated with decreased rates of NEC and late-onset sepsis when compared to rates in infants fed preterm formula.[30] This product has not seen widespread implementation due to its considerable cost, high degree of dilution of mother's own milk, and concerns about poor growth on a pasteurized donor milk product. [31,32]

A second product, Enfamil® Human Milk Fortifier Acidified Liquid (ALHMF) manufactured by Mead Johnson Nutrition, USA was introduced in 2011.[33] This product has several changes from the previously available PHMFs (Table 1). Differences are seen in protein content and the method of sterilization, the addition of citrate to acidify the product.

A new liquid protein modular is now available to consider for use in place of Beneprotein® (Nestle, USA). This product is a hydrolyzed protein, and should improve tolerance issues with the sensitive premature gastrointestinal tract. The protein is a casein hydrolysate protein as opposed to a whey protein. Concentrated at 1 gm protein/6 ml, it is possible to dose this product to administer 4-4.8 gm/kg/day of estimated enteral protein, as previously recommended in the review by Hay, 2008.[11] As a concentrated liquid, the Liquid Protein Fortifier® (Abbott Nutrition, USA) will have some dilutional effect on mother's breast milk; this will be about 4-8% based on the desired protein concentration.[35]

Nutrition Delivery Protocols

Given the complex array of options available to provide enteral nutrition to preterm infants and the critical need to provide appropriate nutrition, our NICU constantly evaluates options to improve delivered nutrition. The Nebraska Medial Center has a Level IV 36 bed NICU that participates in the Vermont Oxford Network, is active in quality improvement, has published in nutrition management of the VLBW infant, and manages growth and nutrition very closely to minimize EUGR with good results. We have a baseline low incidence of NEC at 2-5%, and have established parenteral and enteral feeding protocols. Our enteral protocol prior to using the ALHMF called for initiation of enteral feeding on day 0-1 with either mother's own breast milk or donor breast milk. Feedings to be initiated at 20 ml/kg/day, maintained at that rate for 3-5 days, then advanced by 20 ml/kg/day to full enteral volumes of 150 ml/kg/day. Feedings to be fortified at 80ml/kg/day to 22 cal/oz and at 100ml/kg/day to 24 cal/oz. At 120 ml/kg/day additional protein to be added to provide an estimated 4 gm/kg/day of enteral protein at full feeds of 150 ml/kg/day. The unit standard at this time was to use Abbott Powdered Human Milk Fortifier and Beneprotein® protein modular.

These protocols were instituted to meet our units' nutrition goals of:

- meeting the ADA and CDC recommendations for a powder-free NICU,
- providing optimal nutrition for our ELBW and VLBW patient population,
- minimizing EUGR and optimizing neurodevelopmental outcomes, while
- minimizing risk of NEC and adverse outcomes, our NICU implemented a change in clinical practice in 2011.

At this time the ALHMF was made commercially available. The decision to use the protocols was based on the desire to utilize a sterile liquid

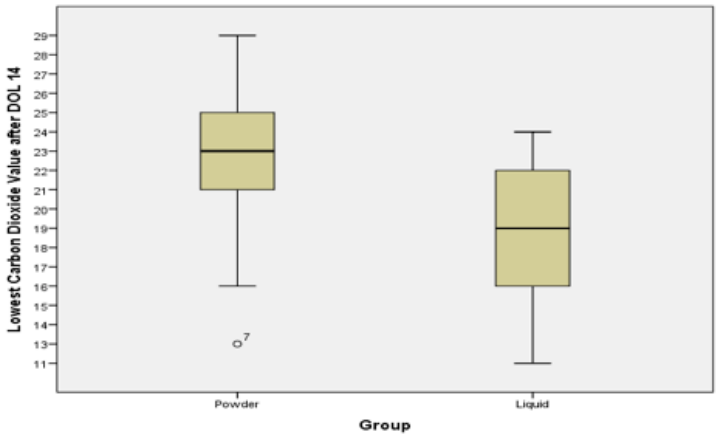

Figure 1. CO_2 levels between groups after Day of Life 14. The lowest CO_2 levels after DOL 14 were collected from metabolic panels. The mean level in the powder group was 23, the mean level in the liquid group was 18.5. Laboratory clinical reference range 22–32 mmol/L. The difference is statistically significant (p = 0.002).[34]

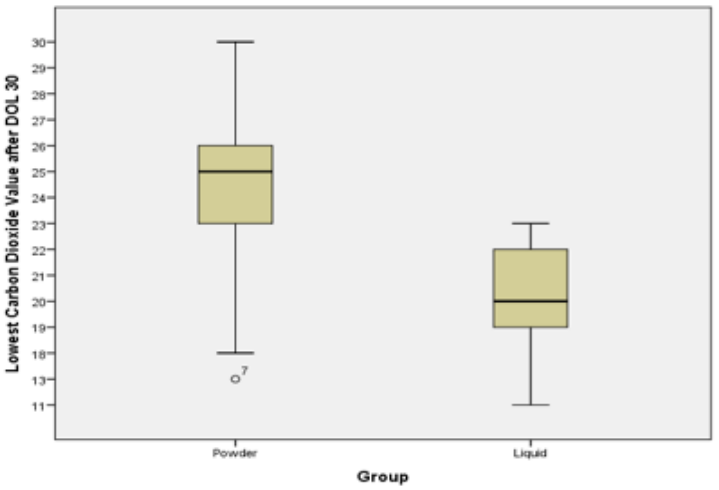

Figure 2. CO_2 levels between groups after Day of Life 30. The lowest CO_2 levels after DOL 30 were collected from metabolic panels. The mean level in the powder group was 25, the mean level in the liquid group was 20. Laboratory Clinical reference range 22–32 mmol/L. The difference is statistically significant (p = 0.002).[34]

product with higher protein content to replace our enteral protocol of fortifying human milk with PHMF and additional powdered protein modular. The product change was delayed secondary to FDA requirements that the fortifier labeling be changed to highlight the sterilization process was due to acidification, and the name was changed to add Acidified prior to its release. When the ALHMF was made available, our units trained our staff and updated our electronic medical record to reflect the new product and its additional protein content. After this was completed we changed all infants requiring human milk fortification to the ALHMF on the same day. After beginning use of the ALHMF, the medical team noted several changes in patient outcomes and conditions including: poor growth compared to previous fortification methods, increased need for caloric densities of human milk feedings over 24 cal/oz, metabolic acidosis requiring oral bicitra treatment to normalize pH, dark green fatty foul smelling stools, and excoriation of the diaper area at times so severe that wound nurse consultation was required. Because of these noted changes after 4 months of use, we decided to discontinue use of the ALHMF, and resume fortification with PHMF and additional powdered protein modular.

Retrospective Study

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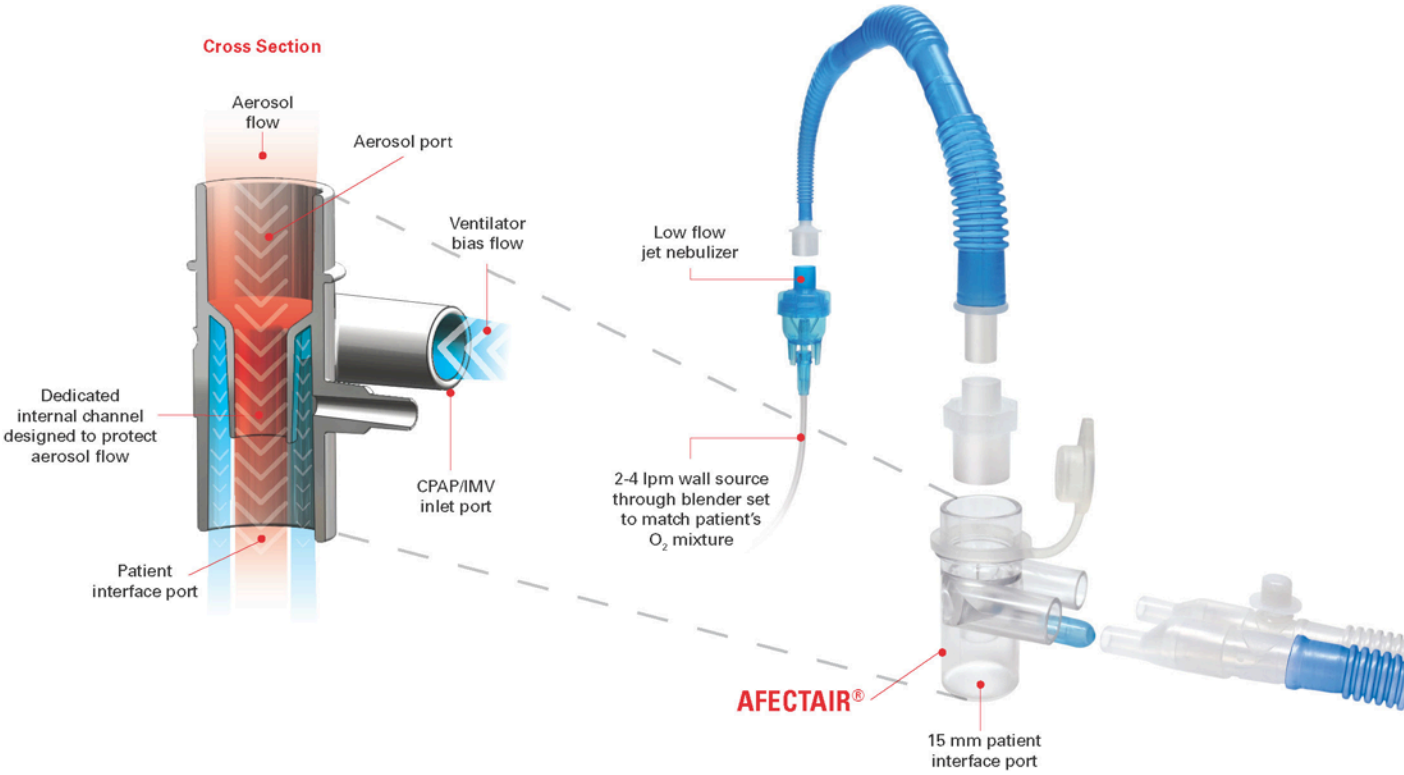

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Table 3. Baseline Characteristics of the Subjects[34]							
Variable	**PHMF**			**ALHMF**			
	n	**Mean**	**SD (±)**	***n***	**Mean**	**SD (±)**	**p-value**
CGA at Birth	46	29.5	3.0	23	30.3	2.5	0.21
Birth Weight (g)	46	1293.7	407.5	23	1437.3	375.6	0.13
Birth Weight Percentile	46	31.4	24.7	23	36	26.5	0.82
Weight at 36 Weeks CGA (g) #	44	2245.9	450.72	18	2071.2	367.4	0.17
Weight Percentile at 36 Weeks CGA #	44	18.6	24.4	18	10.3	13.8	0.22
HC at Birth (cm)	46	27.2	3.4	22	27.9	2.1	0.19
HC Percentile at Birth	46	29.9	23.1	22	33.6	26.3	0.7
HC at 36 Weeks CGA (cm) #	42	32.5	2.6	19	31.9	1.5	0.37
HC Percentile at 36 Weeks CGA #	42	38.8	30.7	19	31.4	24.6	0.5
Length at Birth (cm)	46	38.6	3.9	21	40.4	2.8	0.07
Length Percentile at Birth	46	31.4	24.6	22	32.8	21.9	0.68
Length at 36 Weeks CGA (cm) #	42	44.2	3.3	19	43.5	4.6	0.44
Length Percentile at 36 Weeks CGA #	42	17.3	22.3	19	21.3	28.1	0.93
# Growth at these time points represents nutrition delivery throughout hospitalization, not just breast milk with PHMF and ALHMF.							

Table 4. Enteral Feeding, Growth and Laboratory Data[34]					
Variable	**PHMF**		**ALHMF**		**p-Value**
	N	**Median**	***N***	**Median**	
Average Daily Provision of Protein per kg Weight	42	3.9	18	4.3	0.0014
CO_2 Minimum after DOL 14	33	23	16	18.5	0.002
CO2 Minimum after DOL 30	23	25	8	20	0.002
Growth Velocity (g/kg/day) while on HMF	46	15.37	21	10.59	<0.0001
Growth (g/day, while on HMF)	46	31.27	21	23.66	0.0001
DOL Enteral Feedings Started	46	3.0	22	1.1	0.12
Calcium Maximum	34	10.3	16	10.45	0.17
BUN Maximum after DOL 14	33	18	16	20	0.28
BUN Maximum after DOL 30	23	18	8	16	0.91
Creatinine Maximum	46	0.92	22	0.9	0.52

We received IRB approval for a retrospective study comparing infants fed human milk fortified with ALHMF to infants fed PHMF with additional protein modular. Our hypothesis was that the acidification of the breast milk led to acidosis and poor growth in preterm infants. We identified 23 infants who were fed human milk fortified with ALHMF and matched them 2 to 1 to 46 infants fed human milk fortified with PHMF and additional protein. Infants who were given PHMF, and were changed to ALHMF on the first day of use, were excluded from the study, as was one infant with Trisomy.[13] We evaluated growth, acidosis, nutrient intake, and NICU outcomes between the two groups. Records were retrieved from our electronic medical record, Intuacare®, which calculates percent breast milk, protein in gm/kg/day and calories/kg/day based on nursing documentation of administered feedings. This data was collected on infants receiving these products who were given >50% fortified breast milk, and were given 140 ml/kg/day of enteral feedings. Laboratory data including creatinine, blood urea nitrogen, maximum base deficit, maximum calcium level, lowest CO_2 after DOL 14, and lowest CO_2 after DOL 30, and pH after DOL 14 were collected from the medical records as available.

All fortification was according to manufacturer directions. Nutritional estimates are based on online nutritional references. Infants who were given powdered human milk fortifier were also given a powdered protein modular to provide an estimated 4 gm/kg/day of protein at a goal volume of 150 ml/kg/day. Infants who required feedings with a caloric density greater than 24 cal/oz had additional Neosure® powder added to fortified breast milk.

Statistical Analysis

As was described in our original publication, "Descriptive statistics were displayed for all variables by type of milk (powder vs. liquid) given. The Wilcoxon rank sum test was used to compare continuous data between the milk groups. Associations of categorical variables were assessed with the Fisher's Exact Test. A p-value ≤0.05 was considered statistically significant. To assess the difference in growth patterns between infants given powder and infants given liquid, a mixed effects model was used. We included random slopes and intercepts for each subject to capture individual growth pattern as well as fixed effects for group and day and a group day interaction term. A significant interaction of day and group indicates differing growth patterns based on group. Growth Velocity (GV) was calculated using Equation 1: [34]

$$GV = [1000 \times ln(Wn/W1)]/(Dn - D1)\ 1" 34$$

Results

Infants in the ALHMF group did not have significantly different baseline characteristics than the infants in the PHMF group, who were non-significantly smaller and younger [Table 3[34]]. Infants in the ALHMF group were more acidotic as measured by CO_2 from basic metabolic panel as measured after the 14th and 30th Day of Life (DOL) [Figures 1 and 2[34]]. Growth as measured in grams/day and grams/kg/day was significantly different between the two groups with much slower growth in the ALHMF infants [Table 4[34]]. Growth was

also evaluated by modeling day and group and showed slower growth on the ALHMF [Figure 3[34]].

Infants in the ALHMF group were given more protein than infants in the powder group [Table 3[34]]. Additionally, although p-values did not reach significance, infants in the ALHMF group required more frequent fortification above 24 cal/oz feeds (48% vs. 26%), and were given more calories/kg/day (128.7 vs 117.3, a difference of 11.4 cal/kg/day) than infants in the PHMF group.[34] Growth was also slower throughout the hospitalization when evaluated from DOL 14 to 36 weeks; CGA infants in the PHMF group had a mean growth of 23.65 g/day while infants in the ALHMF group had a mean growth of 18.77 g/day (p=0.057). Clinical outcomes are summarized in Table 5.[34]

Discussion

Given the results above, our group concludes that acidification of human milk with the AHMF may not provide optimal growth outcomes for preterm infants. Clinically and statistically significant acidosis may lead to poor growth as noted in both human and animal models.[39-41] Even with increased protein and calories, infants in our study receiving ALHMF grew more poorly than infants fed with PHMF and Beneprotein®. The degree of growth failure seen in our study with use of ALHMF as compared to PHMF has the potential to impact outcomes such as EUGR which is known to be associated with negative outcomes.[42]

Table 5. Clinical Outcomes[34]

Variable	PHMF	LHMF	p-Value
	n (%)	n (%)	
NEC	0 (0%)	3 (13%)	0.03
ROP	16 (35%)	3 (13%)	0.09
ROP Procedure	3 (7%)	2 (9%)	1.00
IVH (any)	18 (39%)	4 (17%)	0.10
Dexamethasone Treatment	9 (20%)	1 (5%)	0.15
Bicitra Treatment	0 (0%)	1 (5%)	0.31
Death	0 (0%)	1 (4%)	0.33
Diaper Dermatitis	5 (11%)	4 (18%)	0.46
BPD	9 (20%)	3 (14%)	0.74

We chose to discontinue use of the ALHMF due to poor growth, acidosis, and intolerance including diaper dermatitis, which was not accurately documented in the electronic medical record and is underrepresented in the numbers reported in this study. Other institutions are beginning to describe similar outcomes to those reported here including Cibulskis et al., 2013.[43] In a study which acidified human milk to the pH achieved with the ALHMF evaluating cellular and nutritional components of milk, Erikson et al. found a 76% decrease in white cells, a 56% decrease in lipase activity, a 14% decrease in the total protein, and 36% increase in the creamatocrit.[44] The study concludes that acidification causes significant changes to milk's cellular and nutritional components that may not be beneficial to preterm infants.[44] The industry-sponsored study evaluating ALHMF enrolled 150 infants, 106 completed the 28-day study. The authors report minimal improvement in growth in the ALHMF group as compared to the control group fed Mead Johnson Powdered Human Milk Fortifier, no significant difference in rates of mean growth in the entire population, a modest (0.02 cm/week) increase in length growth rate, and a modest weight and length improvement on Day 28 in a subset of infants (n=51).[45]

Infants in the ALHMF group also had a lower pH on Day 6, a lower CO_2 on Day 14, and a lower HCO_3 on Days 6 and 14. These values were thought to be clinically insignificant by the authors.[45] This study had many exclusion criteria unlike ours where infants of all acuities were included.

To our knowledge we are the first study to quantify our clinical observations with the use of ALHMF in a general Level IIIc NICU patient population. For a retrospective study, we have detailed data on delivered nutrition, and we have standardized feeding and nutrition protocols making the two groups care very similar. As we used the project for only a short time we have a limited number of subjects to evaluate retrospectively. Additionally, we were not powered as a primary outcome to study NEC due to our low baseline rate and small number of study subjects. This and other outcomes should be closely evaluated in a larger trial.

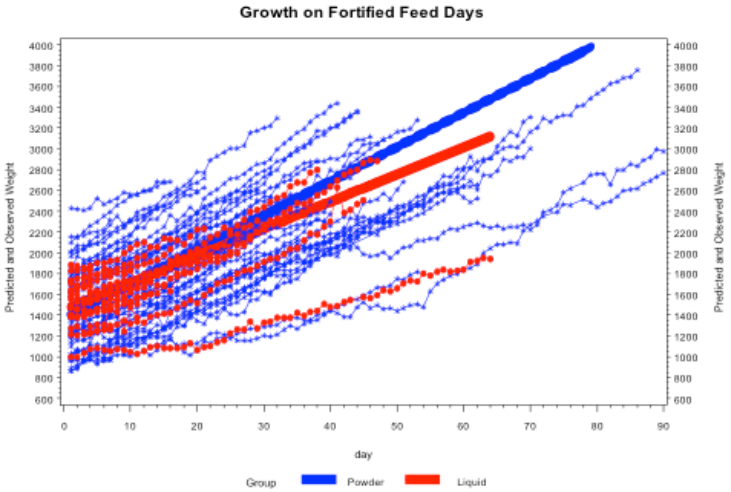

Figure 3. The growth pattern of infants receiving powder differs from the growth pattern of infants receiving liquid on fortified feed days. The plot shows the growth pattern for each infant and the fitted line by group. Based on the plot, infants on powder grow at a faster rate than infants receiving liquid. Evaluation of growth in gm/kg/day for the days infants were fed fortified breast milk, based on the mixed effects model, shows a significant interaction between day and group (p = 0.0022). Truncating the analysis at 45 days did not attenuate the results.[34]

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See the "Human Milk Fortification Lecture" video
by Dr. Ann Anderson Berry, MD at
http://youtu.be/Vj7wdjjFwO4

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"The study concludes that acidification causes significant changes to milk's cellular and nutritional components that may not be beneficial to preterm infants.[44]"

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INDICATION

SURFAXIN® (lucinactant) Intratracheal Suspension is approved by the FDA for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.

IMPORTANT SAFETY INFORMATION

SURFAXIN (lucinactant) Intratracheal Suspension is intended for intratracheal use only. The administration of exogenous surfactants, including SURFAXIN, can rapidly affect oxygenation and lung compliance. SURFAXIN should be administered only by clinicians trained and experienced with intubation, ventilator management, and general care of premature infants in a highly supervised clinical setting. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Most common adverse reactions associated with the use of SURFAXIN are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. During SURFAXIN administration, if bradycardia, oxygen desaturation, endotracheal tube reflux, or airway obstruction occurs, administration should be interrupted and the infant's clinical condition assessed and stabilized. Overall the incidence of administration-related adverse events did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants.

SURFAXIN is not indicated for use in acute respiratory distress syndrome (ARDS).

For more information about SURFAXIN, please visit **www.SURFAXIN.com** and see accompanying brief summary on the next page.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full prescribing information.

INDICATIONS AND USAGE

SURFAXIN® is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Acute Changes in Lung Compliance

Administration of exogenous surfactants, including SURFAXIN, can rapidly affect lung compliance and oxygenation. SURFAXIN should be administered only by clinicians trained and experienced in the resuscitation, intubation, stabilization, and ventilatory management of premature infants in a clinical setting with the capacity to care for critically ill neonates. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Administration-Related Adverse Reactions

Frequently occurring adverse reactions related to the administration of SURFAXIN include bradycardia, oxygen desaturation, reflux of drug into the endotracheal tube (ETT), and airway/ETT obstruction.

Increased Serious Adverse Reactions in Adults with Acute Respiratory Distress Syndrome (ARDS)

Adults with ARDS who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in ARDS.

Clinical Trials Experience

The efficacy and safety of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a single randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants (Study 1). Infants weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Infants were randomized to received 1 of 3 surfactants, SURFAXIN (N = 524), colfosceril palmitate (N = 506), or beractant (N = 258). Co-primary endpoints were the incidence of RDS (defined as having a chest x-ray consistent with RDS and an $FiO_2 \geq 0.30$) at 24 hours and RDS-related mortality at 14 days. The primary comparison of interest was between SURFAXIN and colfosceril palmitate with the intent of demonstrating superiority. Beractant served as an additional active comparator. Compared to colfosceril palmitate, SURFAXIN demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through Day 14. A second multicenter, double-blind, active-controlled study involving 252 premature infants was also conducted to support the safety of SURFAXIN (Study 2). Infants weighed between 600 g and 1250 g and were less than 29 weeks in gestational age. Infants received 1 of 2 surfactants, SURFAXIN (N = 119) or poractant alfa (N = 124).

The safety data described below reflect exposure to SURFAXIN administered intratracheally to infants at a dose of 5.8 mL per kg (up to 4 doses) in either 4 aliquots (Study 1) or 2 aliquots (Study 2) in 643 premature infants.

Comparator surfactants colfosceril palmitate and beractant were administered at the recommended doses (5.0 and 4.0 mL per kg, respectively) while the first dose of poractant alfa administered (2.2 mL per kg) was less than the recommended dose of 2.5 mL per kg. Any subsequent doses of poractant alfa were at the recommended 1.25 mL per kg dose.

Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants (Table 1) and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia. For Study 1, oxygen desaturation was reported in 17%, 9%, and 13% and bradycardia for 5%, 2%, and 3% of infants treated with SURFAXIN, colfosceril palmitate, and beractant, respectively. For Study 2, oxygen desaturation was reported in 8% and 2% and bradycardia in 3% and 2% of infants treated with SURFAXIN and poractant alfa, respectively. These adverse reactions did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants (Table 2).

Table 1. Administration-Related Adverse Reactions in SURFAXIN Controlled Clinical Studies[a]

	Study 1[b]			Study 2[c]	
	SURFAXIN (N = 524)	Colfosceril palmitate (N = 506)	Beractant (N = 258)	SURFAXIN (N = 119)	Poractant alfa (N = 124)
Total Doses Administered	994	1038	444	174	160
	Total Number of Events (Events per 100 Doses)				
ETT Reflux	183 (18)	161 (16)	67 (15)	47 (27)	31 (19)
Pallor	88 (9)	46 (4)	38 (9)	18 (10)	7 (4)
Dose Interruption	87 (9)	46 (4)	30 (7)	7 (4)	2 (1)
ETT Obstruction	55 (6)	21 (2)	19 (4)	27 (16)	1 (1)

[a] Table includes only infants who received study treatment.
[b] Study 1 doses were administered in 4 aliquots.
[c] Study 2 doses were administered in 2 aliquots.

Table 2. Common Serious Complications Associated with Prematurity and RDS in SURFAXIN Controlled Clinical Studies Through 36-Weeks Post-Conceptual Age (PCA)

	Study 1			Study 2	
	SURFAXIN (N = 527) %	Colfosceril palmitate (N = 509) %	Beractant (N = 258) %	SURFAXIN (N = 119) %	Poractant alfa (N = 124) %
Apnea	52	52	46	66	75
Intraventricular hemorrhage, all grades	52	57	54	39	38
-Grade 3/4	19	18	21	13	8
Periventricular leukomalacia	10	10	12	4	9
Acquired sepsis	44	44	44	45	52
Patent ductus arteriosus	37	35	37	43	44
Retinopathy of prematurity, all grades	27	26	25	32	31
-Grade 3/4	6	7	6	5	9
Necrotizing enterocolitis, all grades	17	17	19	13	15
-Grade 2/3	6	8	14	8	8
Pulmonary air leak through Day 7, all types	15	17	14	9	7
-Pulmonary interstitial emphysema	9	10	10	3	5
-Pneumothorax	3	4	2	4	1
Pulmonary hemorrhage	10	12	14	6	9

All-cause mortality through 36-weeks PCA was similar regardless of which exogenous surfactant was administered.

Adverse reactions reported in the controlled clinical studies through 36-weeks PCA occurring in at least 10% of infants were anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia. These reactions occurred at rates similar to the comparator surfactants.

No assessments for immunogenicity to SURFAXIN were performed in these clinical studies.

Follow-up Evaluations

Twelve-month corrected-age follow-up of 1546 infants enrolled in the 2 controlled clinical studies demonstrated no significant differences in mortality or gross neurologic findings between infants treated with SURFAXIN and those treated with the comparator surfactants (colfosceril palmitate, beractant, or poractant alfa).

OVERDOSAGE

There have been no reports of overdose following the administration of SURFAXIN.

HOW SUPPLIED/STORAGE AND HANDLING

SURFAXIN (lucinactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension (NDC 68628-500-31). One vial per carton.

Store SURFAXIN in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze. Vials are for single use only. Discard any unused portion of SURFAXIN. Discard warmed vials of SURFAXIN if not used within 2 hours of warming.

To report SUSPECTED ADVERSE REACTIONS, contact Discovery Laboratories, Inc. at 1-877-SURFAXN (877-787-3296) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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National Perinatal Association Position Statement – Ethical Use of Assisted Reproductive Technologies: A Call for Greater Transparency, Better Counseling of Prospective Parents and Single Embryo Transfer to Improve Outcomes for Mothers and Babies

By T. Allen Merritt, MD; Raylene Phillips, MD; Mitchell Goldstein, MD; Bernadette Hoppe, JD

Background

The development of Assisted Reproductive Technologies (ART) is credited to Dr. Patrick Steptoe and Dr. Robert Edwards (a Nobel Prize Recipient) who developed the technology leading to the world's first "test-tube baby," a scientific breakthrough that has led to the conception of 5 million babies worldwide.[1] In the United States, ART is responsible for approximately 1.4% of all infants born annually.[2] While there are many unanswered questions regarding the outcomes of infants conceived outside the womb, ART and related pharmacologic ovarian stimulation has permitted children to be born to many welcoming families who would otherwise be unable to conceive due to infertility.

Infertility and subfertility are defined by various entities as failure to conceive after unprotected intercourse for one year or more.[3] There are many factors that contribute to infertility in both women and men. In addition to a variety of medical factors, there are social, economic and personal pressures as well as life circumstances that contribute to the decision of many woman and men to reproduce later in life. If the decision to delay parenthood is a personal choice, it should be done with a full knowledge and understanding of the consequences of delaying reproduction. Physicians and other health professions should begin to discuss fertility preservation early during an adult's life and help young women and men to understand all options regarding childbearing.[4] Infertility in both men and women contributes to anxiety and grief and should be recognized as a medical issue. It is the ethical responsibility of physicians and society to provide available solutions and offer support to those experiencing this life crisis.[5]

There have been considerable medical and ethical concerns about the generally unregulated expansion of ART, including the use of surrogacy, international medical tourism to seek less expensive access to these technologies, and the exploitation of women in less developed countries as gestational carriers for embryos conceived in the U.S. and taken abroad. Because the use of ART is largely unregulated, there is wide variation on how the technologies are used. Although guidelines are available, compliance is purely voluntary and the transparency of some ART practices has been questioned. A workshop of the Eunice Shriver National Institute of Child Health and Human Development in 2007 regarding Detection, Prevention, and Management of Infertility[6] developed the following recommendations:

1. Emphasis of Assisted Reproductive Technologies should be on the birth of healthy infants primarily using elective single embryo transfer.
2. Counseling of prospective parents using ART should be in a nondirective manner and provided well in advance of any invasive procedures, as well as in a relaxed and unrushed environment.
3. Couples should be informed of treatment risks and pregnancy rates, as well as of adverse pregnancy/birth outcomes for which well-documented outcome data exist (i.e. multi-fetal gestation, number of embryos transferred, congenital anomalies [including imprinting disorders], and other genetic abnormalities [parental risk factors and the use of prenatal diagnosis]).
4. Couples should be informed of maternal risk factors including increased risk for preeclampsia and risks of multi-fetal gestation, including requirement for cesarean delivery among others.

It is estimated that 36% of twin births and 77% of triplet and higher-order multiples in the United States were attributable to medically assisted conceptions. Kulkami et al recently summarized their findings that the high incidence of multiple births in the U.S. is a consequence of two factors:

1. increased rates of advanced maternal age at delivery and
2. increased rates of fertility treatments.

Some providers have begun to recognize this trend and have decreased the number of embryo transfers involving three or more embryos during IVF. These changes have resulted in a 33% decrease in the proportion of triplet and higher-order multiple births attributable to IVF since the peak rates in 1998.[7] Many IVF providers, however, have not adhered to professional guidelines regarding the number of embryo transfers. It is clear that reducing the rate of multiple-embryo transfers must be of the highest priority if we are to successfully reduce the rate of multiple births and the associated risks of prematurity and low birth weight.

Ovarian induction and hyperstimulation are also leading causes of multiple births according to Reynolds and colleagues who evaluated non-IVF fertility treatments from 1997-2000.[8] Guzick and colleagues also evaluated women who underwent ovarian superovulation and intrauterine insemination and found a large proportion of pregnancies resulted in multiple births including twins, triplets, and quadruplets.[9] A clinical shift from ovarian hyperstimulation to elective single embryo transfer after IVF is likely to lower the unacceptably high rate of multiple births in women utilizing ART.

Dr. Eli Adashi, former President of the American Gynecological and Obstetrical Society, declares that while "alleviation of barrenness [is] a laudable goal….multiple gestation challenge by its very nature is a public health issue," and "our ultimate, if not immediate goal is clear: healthy singleton births."[10] He champions the concept that "the last disabled child should be born" by using artificial reproductive technologies. Canadian ethicists Raymond Lambert and Marcel Melánçon have stated that protection of the vulnerable is a physician's moral and ethical responsibility, and that physicians are responsible for risk reduction or prevention when future generations are at stake."[11]

Prospective mothers and fathers may benefit from the experience of others who have undergone ART procedures. George J. Annas, Professor of Health Law, Bioethics and Human Rights at Boston University has suggested the book "Cracked Open" by Miriam Zoll,[12] described as a compelling narrative that speaks for a generation of women who, like the author, delayed parenthood only to find themselves unable to conceive a child using all of the benefits of contemporary reproductive science. As summarized by obstetrician and gynecologist, Dr. Christiana Northup, "the brave new world of ART…isn't nearly as rosy as we've all been led to believe."[13]

Law Professor Michele Goodwin at the University of Minnesota and Judy Norsigian have described the "raw and debilitating physical, emotional and spiritual challenges created by deeply personal and life-altering pro-

cedures" experienced by some women seeking ART and support the need for additional regulation.[14] In addition to the invasive processes involved in conception, the ethical quandary created by a recommendation for fetal reduction and the emotional toll on women and couples may be profound and is incompletely studied. Professor Goodwin asserts there is a "much needed public discourse that could also become the clarion call for regulation of a field of medicine that has thus far unsuccessfully regulated itself."

Recommendations of the National Perinatal Association on the Ethical Use of Artificial Reproductive Technology:

1. **Prospective parents should receive informed consent before using ART. Note: While it has been argued that infertility itself bestows the additional risks of prematurity and birth defects, it is evident that the use of ART adds to these risks.**
   a. Informed consent should be required in every jurisdiction and should communicate information in appropriate language that conveys the relative risk or odds ratios of prematurity, low birth weight, birth defects and imprinting disorders with respect to each procedure including ovarian hyperstimulation, intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI).
   b. The most current data available from peer reviewed research and meta-analysis should be used when conveying relative risks and odds ratios.
2. **Prospective parents should receive counsel from a multidisciplinary team prior to initiating ART.**
   a. Multidisciplinary teams should include representatives from maternal-fetal medicine, genetics, neonatology and psychology.
   b. Thorough discussion of the potential emotional and economic costs of having a premature and/or low birth weight infant or infant with birth defects should be offered and documented. Grief counseling should be available to address issues relating to infertility.
3. **Prospective parents should be counseled regarding the need for adequate health insurance to assist if the pregnancy results in a child with special needs.**
   a. The well-documented higher rate of multi-fetal gestations, premature births, low birth weight infants, and a higher risk for selected birth defects[15, 16, 17] and imprinting disorders[18, 19] often results in substantially increased costs of neonatal intensive care for infants.
   b. This can lead to unforeseen economic burden for parents without adequate insurance coverage.
4. **Pregnant women using ART should receive comprehensive obstetric care.**
   a. Comprehensive care should include immediate access to specialists in Maternal-Fetal Medicine
   b. Proximity to a Neonatal Intensive Care Unit should be ensured to maximize optimal birth outcomes.
5. **Insurance companies should pay for evaluations of women and men presenting with infertility.** *Note: Current access to ART services in most states is primarily for those with sufficient resources to pay out-of-pocket and excludes many from seeking medical help for infertility.*
6. **Insurance companies should pay only centers that meet professional standards.**
   a. Professional guidelines, such as those published by the Society for Assisted Reproductive Technology, should be followed by centers receiving third-party payment.
   b. This should include the substantial preference for elective single embryo transfer.[20]
7. **Insurance companies should pay only centers that provide annual reports to the Centers for Disease Control and Prevention.** *Note: Current reporting of fertility clinic outcomes is voluntary under federal law.*
   a. Reports should include number of pregnancies per patient, number of cycles required for pregnancy with live birth, infants born per cycle, birth weights, gestational age, multiples or singletons, congenital/genetic abnormalities and additional costs for infants born with special needs.
   b. In unique circumstances when more than a single embryo transfer is desired, prior approval from insurance companies should be a requirement for coverage.
8. **Prospective parents and surrogates should receive independent legal counsel.**
   a. Contractual arrangements should be performed prior to in vitro conception embryo transfer.
   b. As the procedure for legalization of intended parents is a legal proceeding, ideally the gestational carrier and intended parents should reside in the same jurisdiction and be subject to the same legal due process.
9. **Agencies who represent women wishing to be compensated for being a gestational carrier should be governed by state regulations.**
   a. Financial transactions between intended parents and surrogates should comply with federal and state taxation regulations.
   b. All parties should adhere to state privacy rules.
10. **"Medical tourism" for the use of surrogacy should be discouraged.**
    a. Citizens of another country seeking surrogacy in the United States should be discouraged.
    b. US citizens should be discouraged from seeking surrogacy abroad, which may be viewed as exploitation of women from that country.
    c. Surrogacy using a family member may be an acceptable exception.
11. **State regulatory agencies who license and provide oversight for collection and use of human tissues should provide the same level of oversight for sperm banks, the selling of human eggs and egg "donation."** *Note: A bill permitting the selling of oocytes for in vitro fertilization and use in ART or research was recently vetoed by Governor Brown in California. This legislation would have made human eggs just another commodity to be bought and sold.*

Conclusions

The National Perinatal Association (www.nationalperinatal.org) advocates the position that greater public awareness and professional transparency should assist prospective parents in making informed decisions regarding their potential choices in seeking ART as well as their options involving adoption of the many infants already born who are in need of loving parents.

Studies are urgently needed regarding every aspect of ART, including neurodevelopment outcomes, school performance, and differences in the incidence and onset of adult diseases when conceived using ART versus naturally. As with other technologies that may impact the human genome through epigenetic modification, continued research into the influences of emerging technologies on the health and well being of the infants born should be a national priority.

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"As with other technologies that may impact the human genome through epigenetic modification, continued research into the influences of emerging technologies on the health and well-being of the infants born should be a national priority."

NT

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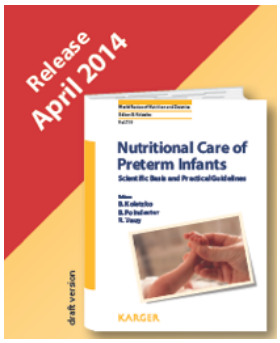
Medical News, Products & Information

Nutritional Care of Preterm Infants (book)
Scientific Basis and Practical Guidelines
Editor(s): B. Koletzko, B. Poindexter, R. Uauy

This book continues the tradition established with the previous books edited by Reginald Tsang et al.

Improved conditions of care for premature infants have led to markedly increased survival rates over the last few decades, particularly in very low and extremely low birth weight infants. Nutritional measures play a central role in the long-term outcome, health and quality of life of these premature infants. In this publication, leading experts from all 5 continents present the most recent evidence and critical analyses of nutrient requirements and the practice of nutritional care (with the focus on very low birth weight infants) to provide guidance for clinical application. After the introductory chapters covering nutritional needs and research evidence in a more general manner, topics such as: amino acids and proteins, lipids, microminerals and vitamins, parenteral and enteral nutrition as well as approaches to various disease conditions are addressed.



Due to its focus on critical appraisals and recommendations, this book is of interest not only for the researcher who wants to keep up-to-date, but also for the clinician faced with premature infants in his practice. For more information or to order, www.karger.com/Book/Order/261508.

Preterm Infants with Severe Retinopathy More Likely to Have Non-Visual Disabilities at Age 5

In a group of very low-birth-weight infants, severe retinopathy of prematurity was associated with nonvisual disabilities at age 5 years, according to a study in the February 5*th* issue of *JAMA*.

Severe retinopathy (disease of the retina) of prematurity occurs in premature infants treated with excessive concentrations of oxygen and is a serious complication of neonatal intensive care for preterm infants. "Although the incidence of severe retinopathy has increased since the late 1980s, blindness caused by retinopathy has become rare in developed countries. Consequently, clinicians and parents may conclude that severe retinopathy is no longer associated with childhood impairments," according to background information in the article.

Barbara Schmidt, MD, MSc, of Children's Hospital of Philadelphia, and colleagues investigated whether infants with severe retinopathy retain an increased risk of nonvisual disabilities compared with those without severe retinopathy. This analysis (using data from a trial, Caffeine for Apnea of Prematurity), included infants with birth weights between 1.1 and 2.8 lbs. who were born between 1999 and 2004 and followed-up at age 5 years (2005-2011).

Of 1,815 eligible infants, 1,582 (87%) had complete (n = 1,523) or partial (n = 59) 5-year assessments. Of 95 with severe retinopathy, 40% had at least 1 nonvisual disability at 5 years compared with 16% of children without it. Fourteen of 94 children (15%) with and 36 of 1,487 children (2.4%) without severe retinopathy had more than 1 nonvisual disability. Motor impairment, cognitive impairment, and severe hearing loss were 3 to 4 times more common in children with severe retinopathy than those without severe retinopathy.

The authors write that these findings may help improve the ability to counsel parents and to select high-risk infants for long-term follow-up.

"Severe retinopathy of prematurity remains an adverse outcome of neonatal intensive care with poor prognosis for child development, although blindness can mostly be prevented by timely retinal therapy."

The Caffeine Apnea of Prematurity trial was supported by a grant from the Canadian Institutes of Health Research and by the National Health and Medical Research Council of Australia. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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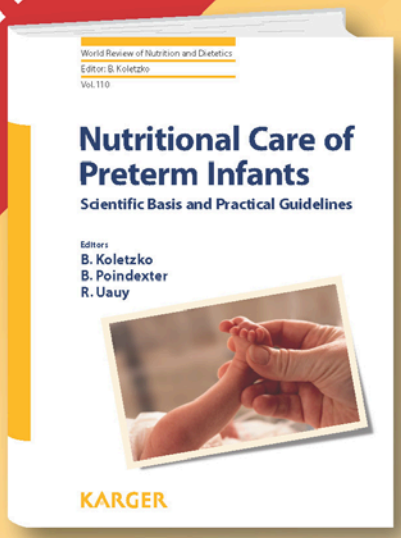

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Nutritional Care of Preterm Infants

Scientific Basis and Practical Guidelines

Editors

B. Koletzko, B. Poindexter, R. Uauy

Nutritional care plays a central role in the long-term outcome, health and quality of life of premature infants. In this publication, leading experts from all 5 continents present most recent evidence and critical analyses of nutrient requirements and the practice of nutritional care – with a focus on very low birth weight infants – to provide guidance for clinical application.

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Appendix: Composition of Selected Human Milk Fortifyers and Preterm Formulas

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