The influence of early postnatal nutrition on retinopathy of prematurity in extremely low birth weight infants

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is the most common serious ophthalmic disease in preterm infants. Human milk may provide a protective effect for ROP; however, beneficial effects of human milk preclude randomized trials. Therefore, we conducted a retrospective analysis comparing early postnatal nutrition with ROP development.

Objective: To evaluate relationship between early postnatal nutrition and ROP surgery.

Design/methods: Nutrition data was collected for inborn AGA infants, BW 700–1000 g. ROP surgery was the primary outcome variable. A single pediatric ophthalmologist supervised examinations. All infants received triweekly IM vitamin A as chronic lung disease prophylaxis (Tyson: NEJM, 1999).

Results: BW and gestational age were 867±85 g and 26.3±1.2 weeks (n=77, mean±1SD). ROP surgery infants (n=11) received more parenteral nutrition, 1648 mL, and less human milk, 13.8 mL/kg-day, and vitamin E, 1.4 mg/kg/day, during the second postnatal week. Human milk was a negative predictor for ROP surgery, odds ratio = 0.94. Both groups met vitamin A recommendations; however, 74% was administered via IM injections. Neither group met vitamin E recommendations.

Conclusions: Human milk feeding, parenteral nutrition volume and vitamin E intake were predictors for ROP surgery. IM vitamin A injections provided the majority of vitamin A; vitamin E administration was insufficient. Improving human milk feeding rates and vitamin dosing options may affect ROP surgery rates.

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1. Background

Retinopathy of prematurity (ROP) is the most common serious retinal disease in extremely low birth weight infants (ELBW). BW<1000 g, 2 lb 3 oz) infants during the neonatal period. [1,2] ROP is multifactorial in nature; oxygen [3] and its prooxidant metabolites are one factor which affect concentrations of retinal endothelial growth factors (VEGF), influencing retinal vessel overgrowth. [4] Early postnatal infant nutrition can affect oxidant balance and may affect ROP development. [5,6] More stringent respiratory care guidelines for oxygen saturation limits have reduced rates of ROP in preterm infants. [7,8] However, as the number of ELBW infants who have survived has increased over the last five years, [9] the number of infants with severe ROP also has risen. [10]

Human milk is the preferred source of nutrition for preterm infants, [11] containing unique nutrients, immunologic factors and enzymes which enhance the antioxidant potential of human milk compared to preterm infant formulas. These include the immunoglobulin IgA, [12] vitamins A, [13] E, [14,15] and C, [16] and the enzymes catalase [17] and glutathione peroxidase. [18] Hylander described reduced severity of retinopathy of prematurity in VLBW infants primarily receiving human milk feedings. [19] However, this protective effect was not shown in a later study comparing human milk intake with sepsis and severity of ROP. [20] Neither study used ROP surgery as the discriminating factor associated with the most severe grade of ROP. The medical benefits of human milk and the American Academy of Pediatric recommendation as the preferred feeding source for preterm infants [21] limit prospective randomization studies; therefore, we conducted a retrospective study comparing early postnatal nutrition with later development of ROP requiring surgery in ELBW infants. The hypothesis was human milk feeding would be associated with decreased rates of ROP surgery in ELBW infants. The specific aims were to 1) create a high resolution dataset of early postnatal nutrition of ELBW infants to identify nutritional factors predicting lower rates of ROP surgery, and 2) evaluate daily administration of antioxidant vitamins with respect to current recommendations.

Abbreviations: ROP, retinopathy of prematurity; ELBW, extremely low birth weight (birth weight<1000 g, about 2 lb, 3 oz); VLBW, very low birth weight (birth weight < 1500 g, about 3 lb, 5 oz); CRYO, cryosurgery.

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2. Methods

2.1. Patient population

Clinical pulmonary and nutrition data were collected for infants delivered in Winston-Salem, NC from 1/1/2002-9/30/2003. Inclusion criteria included: birth weight 700–1000 g, anthropometric measurements average for gestational age, between 10 and 90% for gestational age using the Fenton growth chart, [22] received at least 1 week of parenteral nutrition, and survival through the first 6 weeks of life. Multiple gestation twin and triplet neonates who met the entry criteria were eligible for inclusion. We focused on infants 700–1000 g with 700 g as the lower birth weight limit because compared to sub-700 g infants, this cohort a) would survive at rates greater than the sub-700 g birth weight group, b) would stabilize sooner to allow enteral feedings, including human milk, during their first few weeks of life, c) should have fewer serious complications in the immediate postnatal period that might affect enteral feeding volumes, such as IVH and sepsis, and d) would present as AGA infants in greater numbers. Oxygen administration guidelines for infants <1500 g (VLBW infants) identified a target range from 85 to 94% with bedside alarm limits set for 84% (low end) and 95% (high end).

2.2. Retinopathy screening

Ophthalmology examinations were scheduled per the NICU protocol adapted from the American Academy of Ophthalmology and the American Academy of Pediatrics Section on Ophthalmology of screening examinations for Retinopathy of Prematurity in VLBW infants. [23] In brief, the initial examination was scheduled to coincide with 4–6 weeks postnatal age and 30–32 weeks postconceptual age. Infant retinal examinations were performed by a single pediatric ophthalmologist (RGW) and individual decisions regarding reexamination intervals and management with either continued examinations or retinal surgery also were independently made by the participating ophthalmologist. Decisions for retinal surgery were guided by the Cryotherapy for Retinopathy of Prematurity Cooperative Group guidelines which indicated surgery for patients with at least stage 3+ ROP with five or more contiguous or eight cumulative clock hours [30° sectors] of stage 3 ROP in zone I or II with plus disease. [24] ROP surgery was chosen as the primary outcome variable since it is an ‘event’ or hard variable and not related to subjective grading scales, and it represents the most severe degree of ROP associated with the most serious visual complications of blindness and significant vision loss. Ophthalmology records were reviewed for data collection.

2.3. Data collection

Patient demographic data were collected from an internal electronic database and the paper medical record. Standard nutrition sources and volumes per day for preterm infants were recorded: maternal human milk if available, or preterm infant formula feedings, Similac Special Care (Ross Laboratories, Columbus, OH) and Enfamil Premature Formula (Mead Johnson, Evansville, IN). Because of its multiple benefits, human milk was always provided as the primary enteral feeding source if available. Human Milk Fortifier powder (Mead Johnson) supplementation to infant human milk feedings was not initiated prior to reaching at least 100 mL/kg-day of enteral feeding volume. Neither banked nor donor human milk was provided. Parenteral nutrition contained MVI Pediatric (now) AAIPharma, Wilmington, NC) at a dose of 2.5 mL/kg-day. Nutrition data were collected using Neohal, [25] an electronic neonatal nutrition design system, and the patient paper medical record. Pulmonary data were collected from the preterm infant patient outcome database. The study was approved by the Wake Forest University Health Sciences Institutional Review Board. Clinical ophthalmology patient data was collected by chart review of the pediatric ophthalmology records.

2.4. Data collection and definitions

Baseline data collection included gestational age, birth weight, gender and race.

Pulmonary:

• Days on ventilator was defined as the total number of days the patient had an endotracheal tube in place.

Nutrition: daily enteral and parenteral feeding source and volume were recorded.

Enteral: formula name or human milk, nutritional additives such as human milk fortifier.

Parenteral vitamin administration was determined from manufacturer labeling. Parenteral admixture composition: dextrose, amino acids, lipid, electrolytes and minerals.

• Daily vitamin A and E administration recommendations were drawn from expert opinions, including the American Society of Clinical Nutrition (ASCN) recommendations. [28]

• The daily vitamin recommendation for vitamin A administration was 450 ucgm/kg-day [25–31] and 2.8 mg/kg-day for vitamin E administration. [28,32] Trweekly intramuscular vitamin A was administered per the Tyson protocol [33] and averaged to a per day dose: (5000 IU×3 per week)/7 days/week = 2143 IU/day. The vitamin A dose was irrespective of patient weight and therefore, a dose providing 2143 IU/kg-day for a 1 kg infant provided 4286 IU/kg-day for a 500 g infant.

• The daily vitamin E recommendation of 2.8 mg/kg-day was derived from the ASCN recommendation [28] and endorsed by the American Academy of Pediatrics. [32] and reflected in expert consensus opinion in relevant literature. [34,35]

2.5. Data analysis

Data were stored in a Dbase3+ electronic database and analyzed using Crunch® (Oakland, CA). For continuous data, t-test was applied to compare means for normally distributed data and Mann–Whitney for non-normally distributed data. 95% confidence intervals were determined for continuous variables. A p value <0.05 was considered significant. Fisher’s exact test was applied for categorical data with the small samples sizes in the ROP surgery group. An ANOVA model was created using nutrition factors as predictor variables and ROP surgery as the dependent variable and using a backward elimination method, variables were removed at the 0.05 level. The primary analytic interest was to identify early postnatal nutrition factors associated with development of ROP requiring surgery. Secondary analysis involved determining daily vitamin A and E intake from enteral, parenteral and intramuscular records with respect to the American Society of Clinical Nutrition recommendations. [28] Days of ventilation were collected as a marker for degree of illness early after delivery. Regression analysis was performed using human milk as the predictor variable and ROP surgery as the dependent variable to adjust for days of ventilation. Human milk and formula intake during postnatal week two were adjusted for days of ventilation and compared using 95% CI.

2.6. Power analysis

We evaluated similar published studies examining the relationship between early postnatal nutrition and development of ROP to
estimate an appropriate study subject number. There were no other studies specifically comparing human milk nutrition volume to surgery for ROP; however, Hylander [19] compared human milk feeding as a categorical variable to grades of ROP. Their data described an ROP rate of 64% in the non human milk fed group compared to 41% in the human milk fed group. We created a two sided test using the 23% difference, an alpha of 0.05 and power of 80% to apply to the One-Sample Inference for a Binomial Proportion from Rosner [36] for an estimated sample size of 35 patients. We enrolled more than 35 because of the possibility that the expected number patients with ROP and the relationship of ROP surgery to infants human milk intake could have been different than those used from the power calculations.

3. Results

During the data collection period, 389 VLBW infants were admitted to the NICU. Of these, 85 were less than 700 g and 203 were ≥1000 g. Seven died in the immediate postnatal period. Thirteen were SGA and 1 was LGA, and complete chart information was available for ROP surgery patients and the 66 who did not. There were more males in both groups; however, no demographic differences existed between the 11 patients who required ROP surgery and the 66 who did not. There were more males in both groups; however, no demographic differences existed between the ROP/non-ROP surgery groups regarding gender or race.

Table 1

<table>
<thead>
<tr>
<th>Control vs surgery group</th>
<th>Control</th>
<th>Surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>66</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>873 ± 85</td>
<td>842 ± 78</td>
<td>0.262</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>26.4 ± 1.3</td>
<td>25.9 ± 0.9</td>
<td>0.238</td>
</tr>
<tr>
<td>Race (White: Black: Hispanic)</td>
<td>33:</td>
<td>25:</td>
<td>6:</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>35:31</td>
<td>7:4</td>
<td>0.513</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator days</td>
<td>12.4 ± 12.8</td>
<td>33.6 ± 16.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Days on oxygen</td>
<td>33.9 ± 22.7</td>
<td>45.8 ± 25.4</td>
<td>0.118</td>
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</table>

Nutrition

Table 1 (continued)

<table>
<thead>
<tr>
<th>Parenteral nutrition volumes</th>
<th>Control</th>
<th>Surgery</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Total PN volume (mL)</td>
<td>1221.5 ± 616.9</td>
<td>1648.6 ± 667.5</td>
<td>0.039*</td>
</tr>
<tr>
<td>Postnatal week 1 (mL/kg-day)</td>
<td>90.9 ± 14.1</td>
<td>93.5 ± 21.9</td>
<td>0.601</td>
</tr>
<tr>
<td>Postnatal week 2 (mL/kg-day)</td>
<td>79.0 ± 24.7</td>
<td>98.5 ± 29.5</td>
<td>0.021*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human milk enteral feeding</th>
<th>Control</th>
<th>Surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total human milk volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total 1st postnatal month (mL)</td>
<td>316.5 ± 256.8</td>
<td>297.5 ± 294.6</td>
<td>0.825</td>
</tr>
<tr>
<td>Postnatal week 1 (mL/kg-day)</td>
<td>10.5 ± 7.7</td>
<td>5.8 ± 7.9</td>
<td>0.066</td>
</tr>
<tr>
<td>Postnatal week 2 (mL/kg-day)</td>
<td>36.9 ± 30.2</td>
<td>13.9 ± 16.9</td>
<td>0.016*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamin A administration (μg/cm/kg-day)</th>
<th>Control</th>
<th>Surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total vitamin A</td>
<td>990.3 ± 99.1</td>
<td>997.3 ± 69.9</td>
<td>0.822</td>
</tr>
<tr>
<td>Enteral vitamin A</td>
<td>54.7 ± 48.4</td>
<td>27.9 ± 26.2</td>
<td>0.078</td>
</tr>
<tr>
<td>Enteral (postnatal week 1)</td>
<td>18.1 ± 19.8</td>
<td>7.1 ± 10.4</td>
<td>0.075</td>
</tr>
</tbody>
</table>
| Enteral (postnatal week 2)              | 90.4 ± 87.5| 13.2 ± 13.4| <0.005*
| Parenteral vitamin A                    | 198.9 ± 15.2| 196.2 ± 22.0| 0.613|
| Intramuscular (given triweekly)         | 736.7 ± 88.2| 773.2 ± 76.4| 0.199|

<table>
<thead>
<tr>
<th>Vitamin E administration (mg/kg-day)</th>
<th>Control</th>
<th>Surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total vitamin E</td>
<td>1.89 ± 0.70</td>
<td>1.58 ± 0.48</td>
<td>0.167</td>
</tr>
<tr>
<td>Total (postnatal week 1)</td>
<td>1.50 ± 0.33</td>
<td>1.37 ± 0.11</td>
<td>0.181</td>
</tr>
<tr>
<td>Total (postnatal week 2)</td>
<td>2.24 ± 1.20</td>
<td>1.42 ± 0.21</td>
<td>0.027*</td>
</tr>
<tr>
<td>Enteral vitamin E</td>
<td>0.54 ± 0.72</td>
<td>0.25 ± 0.43</td>
<td>0.205</td>
</tr>
<tr>
<td>Parenteral vitamin E</td>
<td>1.35 ± 0.10</td>
<td>1.31 ± 0.15</td>
<td>0.613</td>
</tr>
</tbody>
</table>

Values reflect mean ± standard deviation.

The analysis of variance model identified four variables associated with increased ROP surgery: days of ventilation, parenteral nutrition volume, and daily human milk and vitamin E intake during the second postnatal week. ROP surgery patients required 33.6 ± 16.9 ventilator days compared to 12.4 ± 12.8 ventilator days in the non-ROP surgery group, p < 0.01 (Fig. 1). The volume of parenteral nutrition administered during the first postnatal month, 1648.6 ± 667.5 mL, and the volume received during postnatal week 2, 98.5 ± 29.5 mL/kg/day, were both greater in the ROP surgery group compared to the non-ROP surgery group. Both groups received small volumes of human milk or formula during the first postnatal week; however, human milk intake in the non-ROP surgery group during postnatal week 2 was greater, 36.9 ± 30.2 mL/kg/day, compared to the ROP surgery group. The volume of enteral feedings between the groups during the first month were compared after adjusting for days of ventilation because days of ventilation may be a marker for degree of illness during the early postnatal period, and may influence the need for ROP surgery. There was no difference between the groups for total enteral volume: ROP surgery 305.3 ± 296.4 mL vs 334.9 ± 247.1 mL. However, there was a difference between the amount of human milk consumed between the two groups during their second postnatal week, ROP surgery, 13.1 ± 15.1 mL/kg-day (95% CI: 4.2–22.1) vs 36.7 ± 25.9 mL/kg-day (30.5–43.0) p < 0.05, with data adjusted for days of ventilation. In a logistic regression model adjusting for days of ventilation, human milk intake during postnatal week two emerged as an independent predictor for ROP surgery with an odds ratio = 0.94.

Analysis of daily vitamin intake during the first two postnatal weeks showed daily vitamin A intake met administration recommendations; however, the combined daily intake from the parenteral nutrition multivitamin supplement and enteral feedings for the first two postnatal weeks showed these two sources provided less than the daily recommendation of 450 ucgm/kg-day. Triweekly intramuscular vitamin A supplementation provided the majority of vitamin A intake, 74%, during this period (Fig. 2), 741.9 ± 87.1 ucgm/kg-day, and was necessary to achieve recommended daily vitamin A administration. Similarly, average daily vitamin E intake from enteral and parenteral nutrition sources did not meet the current daily recommendation of

Fig. 1. Nutrition factors associated with ROP surgery. This box plot shows nutrition factors associated with ROP surgery. Infants requiring ROP surgery (left-sided boxes, n = 11) received a greater volume of parenteral nutrition during their first postnatal month, 1648.6 ± 667.5 mL, compared to the non-ROP surgery group (right-sided clear boxes, n = 66). Infants in the non-ROP surgery group received more human milk, 36.9 ± 30.2 mL, and more vitamin E, 2.24 ± 1.20 mg/kg-day, during their second postnatal week compared to the ROP surgery group. These three factors emerged as independent predictors for ROP surgery. These clinical characteristics reflect ELBW infants with more complicated pulmonary and gastrointestinal neonatal courses. The boxes indicate the mean ± SE; whiskers indicate the 10th and 90th percentiles.
4. Discussion

Retinopathy of prematurity is the most serious clinical ophthalmic disease in preterm infants with the smallest, most preterm infants at greatest risk. As survival has improved over the last 20 years, the rate of severe ROP also has increased, from 27% in the 1988 CRYO-ROP report [37] to 37% in the 2004 ET-ROP report. [38] Despite more extensive knowledge of and greater experience with ROP, individual reports from different countries confirm the phenomenon that as preterm infant care and survival increases, so does the rate and severity of ROP. As these are inversely related to birth weight. While diagnosis and management of ROP has been maturing in the United States over the last 15–20 years, in other countries significant ROP morbidity is increasing as ELBW infant survival increases. In southern Brazil, 48% of ELBW infants developed ROP and 36% of surviving ELBW infants reached threshold disease. [39] China’s rising rate of ROP incidence and management of ROP has been maturing in the United States over the last 15 years, in other countries significant ROP morbidity is increasing as ELBW infant survival increases. In southern Brazil, 48% of ELBW infants developed ROP and 36% of surviving ELBW infants reached threshold disease. [39] China’s rising rate of ROP.

Advances in pediatric ophthalmology have improved the diagnostic evaluation and efficacy of therapeutic interventions for ROP. These include developing standard classification criteria in 1984 [42] and application of early laser surgery following the ET-ROP report in 2004. [38] While improved classification of ROP with better treatment options represent valuable advances, the relatively high medical and societal cost resulting from severe ROP encourages strategies to reduce severe ROP compared to better diagnosis and treatment. We chose the ‘hard’ parameter, ROP surgery, as the outcome variable because of its binary nature. Whereas ROP grading is a subjective process, ROP surgery indicated infants with the most severe form of ROP, often associated with the worst ophthalmic outcomes, blindness and extensive vision loss. Effective preventive strategies include preterm delivery prevention, [43,44] antenatal dexamethasone therapy, [45,46] oxygen targeting [7,47] and D-Penicillamine [48] therapy. We chose to evaluate early postnatal human milk feeding to reduce ROP requiring surgery for several reasons: a) human milk is the best feeding source for infants [49] and many neonatal units already have programs to encourage human milk feedings, [50] b) there are few clinical situations in which human milk is not the preferred feeding source, [51] c) intervention programs can improve rates of human milk feedings to preterm infants, [52,53] and d) relative costs to provide human milk rather than formula are nominal and competitive. [54,55]

The finding that human milk feeding was associated with a reduced ROP surgery rate should encourage human milk feeding programs for preterm infants during the neonatal period. The antioxidant [16,17] and immunoprotective [56,57] properties of human milk are reflected by reduced rates of necrotizing enterocolitis [58,59] and neonatal sepsis. [60,61] As preterm infants have immature antioxidant systems and are exposed to high oxygen environments per their respiratory care, they experience higher risk for oxidant injury. In vitro chemical analysis of antioxidant content consistently shows human milk contains greater antioxidant properties compared to formula. [62,63] No group difference was found for human milk feeding during the first postnatal week as enteral feeding volumes were small for both groups; however, human milk feeding volume during the second postnatal week was an independent predictor for ROP surgery. We suggest that early exposure to specific medications or nutrients, even in small amounts, may provide beneficial effects days or weeks later, and that human milk contains a variety of antioxidants [64,65] which serve to prevent or reduce effects of prematurity-related illnesses. Meinen–Derr showed lower rates of necrotizing enterocolitis in infants who received relatively small volumes of human milk, 11 mL/kg/day, compared to patients in the group that developed NEC, [66] recognizing that patients in this study received 3 times as much human milk per day. Because days of ventilation was a predictor for ROP surgery and could be a marker of early postnatal degree of illness, a secondary analysis of human milk intake as a predictor for ROP surgery was performed. After adjusting for days of ventilation, human milk feeding volume continued to be an independent negative predictor for ROP surgery.

Our evaluation shows increased human milk feeding volume is required more days of ventilation and received nutrition characterized by greater parenteral nutrition volume, and less human milk and vitamin E during the second postnatal week.

![Vitamin A & E Intake](image)

Fig. 2. Vitamin A and E Administration. Average daily vitamin A (µg/kg-day) and vitamin E administration (mg/kg-day) during the first two postnatal weeks reflect daily intake from intravenous (backslash), enteral (clear), and triweekly intramuscular (forward slash) sources for vitamin A. Triweekly IM vitamin A was administered per the Tyson chronic lung disease prophylaxis protocol. [33] The ‘Recommended’ black bar indicates the daily dose for VLBW infants from the American Society of Clinical Nutrition [28] and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. [80] Vitamin A intake from only enteral and parenteral sources did not achieve the recommended daily vitamin A dose. The triweekly intramuscular vitamin A injections accounted for the majority of vitamin A intake. Vitamin E intake was low during the first postnatal week and increased during the second week to 2.12–1.15 mg/kg-day. However, average daily vitamin E administration did not achieve the recommended daily dosage of 2.8 mg/kg-day, and routine supplemental intramuscular vitamin E administration is not currently practiced.

2.8 mg/kg-day. Parenteral sources provided more vitamin E than enteral during the first two weeks, and infants in the non-ROP surgery group received more vitamin E during the second week compared to the ROP surgery group. (1.321–1.372 mg/kg-day vs 0.362–0.717 mg/kg-day, 95% CI), p<0.05. No supplemental vitamin E was administered.

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Our evaluation shows increased human milk feeding volume is associated with a lower rate of ROP surgery; however, there are conflicting reports regarding the association of human milk with development and severity of ROP. Schanler [67] described 243 infants who received human milk, donor milk or formula; infants who received only human milk developed a milder form of ROP, stage 1 ROP (median), compared to stage 2 for the donor milk group. Also, human milk fed infants developed stage 3 ROP at lower rates, 5.6%, compared to the donor milk and formula fed groups, 18% and 14%. Hylander [19] evaluated 283 VLBW infants; those who fed human milk had lower rates of ROP, 35.3% vs 51.6%. Human milk feeding was
vitamin A administration achieve the recommended doses; Vitamin E intake was deficient. New opportunities using electronic health records may facilitate examination of infant nutrition on a larger scale, and new techniques and/or products may be needed to address vitamin administration deficiencies.

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