Human Milk Feeding as a Protective Factor for Retinopathy of Prematurity: A Meta-analysis

Jianguo Zhou, MD, Vivek V. Shukla, MD, Denny John, MBA, MPH, Chao Chen, MD, PhD

abstract

CONTEXT: Studies have suggested that human milk feeding decreases the incidence of retinopathy of prematurity (ROP); however, conflicting results have been reported.

OBJECTIVE: The aim of this meta-analysis was to pool currently available data on incidence of ROP in infants fed human milk versus formula.

DATA SOURCES: Medline, PubMed, and EBSCO were searched for articles published through February 2015.

STUDY SELECTION: Longitudinal studies comparing the incidence of ROP in infants who were fed human milk and formula were selected. Studies involving donor milk were not included.

DATA EXTRACTION: Two independent reviewers conducted the searches and extracted data. Meta-analysis used odds ratios (ORs), and subgroup analyses were performed.

RESULTS: Five studies with 2208 preterm infants were included. Searches including various proportions of human milk versus formula, any-stage ROP, and severe ROP were defined to pool data for analyses. For any-stage ROP, the ORs (95% confidence intervals [CIs]) were as follows: exclusive human milk versus any formula, 0.29 (0.12 to 0.72); mainly human milk versus mainly formula, 0.51 (0.26 to 1.03); any human milk versus exclusive formula, 0.54 (0.15 to 1.96); and exclusive human milk versus exclusive formula, 0.25 (0.13 to 0.49). For severe ROP, they were 0.11 (0.04 to 0.30), 0.16 (0.06 to 0.43), 0.42 (0.08 to 2.18), and 0.10 (0.04 to 0.29), respectively.

LIMITATIONS: Prospective randomized studies being impossible because of ethical issues, we chose observational studies for analysis. A few studies involving subgroup analyses presented high heterogeneity.

CONCLUSIONS: Based on current limited evidence, in very preterm newborns, human milk feeding potentially plays a protective role in preventing any-stage ROP and severe ROP.
Prematurity is a major contributor to global neonatal mortality. With increases in preterm births globally and major recent advances in management for preterm neonates, the survival of the smallest and sickest neonates has significantly increased. Recent studies have shown increased incidence of retinopathy of prematurity (ROP) in developed and developing countries, such as the United States, Sweden, China, and Turkey. In extremely preterm infants with a gestational age of 22 to 28 weeks, the incidence of ROP was 59% (96% at 22 weeks and 32% at 28 weeks) according to a large US cohort study. In China, the incidence was >50% in infants with birth weight <1000 g based on a multicenter epidemiologic study. Globally, ROP has become a leading cause of childhood blindness in recent times. ROP is a multifactorial disease, and risk factors such as low gestational age, oxygen therapy, and oxidative stress have been associated with its development. Human milk is recommended to all preterm infants after birth and has been shown to be effective in preventing necrotizing enterocolitis and late-onset sepsis. Human milk also contains a number of antioxidant components that could be potentially protective against ROP.

There has not been sufficient focus on this subject, and scientific analysis regarding the possible beneficial effect of breast milk on preventing ROP is lacking. The data until now have been scattered and limited to a few clinical studies. Given the ethical implications in conducting a randomized, controlled trial of comparing human milk feeding to formula feeding and the effects on ROP, it is imperative that observational studies provide high-quality evidence for comparison.

We systematically reviewed the evidence from observational studies comparing human milk and formula feeding for preventing ROP and present the meta-analysis results.

METHODS

Our study was undertaken to investigate whether human milk is protective against any-stage ROP and severe ROP in comparison with formula feeding. We have followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines in reporting our study.

Systematic Search Strategy and Study Selection

Studies published in English were systematically identified through a database search of PubMed, Medline, and EBSCO from their earliest available dates up to February 28, 2015, using (human milk OR breast milk) AND (retinopathy of prematurity OR necrotizing enterocolitis) as search keywords. We used necrotizing enterocolitis as a search keyword to isolate studies with ROP as secondary outcome, as the topic of "necrotizing enterocolitis and human milk" is widely studied all over the world. In addition, we manually searched relevant journals related to pediatrics and ophthalmology.

Study Selection Criteria

Two authors independently performed study screening of all citations by title and abstract in pairs. The full texts of these studies were then retrieved, and 2 authors independently screened them for inclusion. In both stages, disagreements about inclusion were resolved by discussion or by consulting a third author.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Site</th>
<th>Design</th>
<th>Sample Size</th>
<th>Study Duration</th>
<th>Patient Characteristics</th>
<th>Feeding Categories, n</th>
<th>ROP Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hylander et al, 2001</td>
<td>us</td>
<td>NICU, university hospital</td>
<td>Cohort</td>
<td>174</td>
<td>January 1992 to September 1993</td>
<td>Gestational Age, wk 28.0 ± 2.2, Birth Weight, g 1044 ± 251</td>
<td>Other Factors Reported Prenatal care, health insurance, maternal smoking, alcohol use, illegal drug use</td>
<td>Stages 1–4</td>
</tr>
<tr>
<td>Furman et al, 2003</td>
<td>US</td>
<td>NICU, university hospital</td>
<td>Cohort</td>
<td>119</td>
<td>January 1997 to February 1999</td>
<td>Gestational Age, wk 27.5 ± 2.4, Birth Weight, g 948 ± 223</td>
<td>Other Factors Reported Ethnicity, ventilator dependence</td>
<td>Stages 1–4</td>
</tr>
<tr>
<td>Heller et al, 2007</td>
<td>US</td>
<td>NICU, multicenter hospitals</td>
<td>Cohort</td>
<td>1057</td>
<td>October 1999 to September 2001</td>
<td>Gestational Age, wk 28 ± 2, Birth Weight, g 1103 ± 260</td>
<td>Other Factors Reported Pneumothorax, ethnicity, maternal hypertension, day of first feeding, human milk proportion, antenatal steroids</td>
<td>Surgical ROP</td>
</tr>
<tr>
<td>Maayan-Metzger et al, 2012</td>
<td>Israel</td>
<td>NICU, university hospital</td>
<td>Cohort</td>
<td>360</td>
<td>2008 to 2008</td>
<td>Gestational Age, wk 30.5 (24–32), Birth Weight, g 1305 ± 388</td>
<td>Other Factors Reported Small for gestational age, gender, multiple pregnancy, mechanical ventilation</td>
<td>Stages 1–3</td>
</tr>
<tr>
<td>Manzoni et al, 2013</td>
<td>Italy</td>
<td>NICU, multicenter hospitals</td>
<td>Cohort</td>
<td>498</td>
<td>2004 to 2008</td>
<td>Gestational Age, wk 29.4 ± 2.5, Birth Weight, g 1125 ± 247</td>
<td>Other Factors Reported Hypermeclemia</td>
<td>All stages ROP</td>
</tr>
</tbody>
</table>

**Note:**
- ROP: Retinopathy of Prematurity
- NICU: Neonatal Intensive Care Unit
We followed a priori study eligibility criteria for study selection. Any type of observational study (cohort or case-control) was included that compared human milk feeding and formula feeding. We excluded studies that reported only donor human milk feeding.

We determined a priori to report the studies on outcomes that reported ROP at any stage, including severe ROP.

**Data Extraction and Quality Assessment**

Two authors extracted data from the included studies separately using a structured data extraction sheet. The following details were extracted from each study: authors, year of publication, geographical area, study site, study design, population (gestational age and birth weight), feeding type, ROP diagnosis, relative risk/odds ratio (OR) and 95% confidence interval (CI), and relevant risk factors for ROP besides feeding. If the abstracted data differed between the 2 authors, resolution was conducted through discussion or discussion with a third author.

A critical appraisal was conducted for the observational studies included in the meta-analysis, using the Critical Appraisal Skills Programme (UK) checklist, assessing the validity of the results from each study on a scale of high, medium, and satisfactory:20 high quality, the study was prospective and scored well on main quality parameters such as study method, result validity, precision of outcomes, and generalizability; medium quality, study method was sound and results were presented with precision; satisfactory quality, the study did not score well or did not contain any information on the main quality parameters such as study method, result validity, precision of outcomes, or generalizability.

**Data Synthesis and Statistical Analysis**

Data were abstracted from all the studies that met eligibility criteria. All statistical tests in the analysis were 2-tailed, and P values of ≤ .05 were considered significant. Statistical analysis was done using SPSS (version 22, IBM SPSS Statistics, Chicago, IL). Estimates of association between human milk feeding and ROP risk were evaluated by ORs and corresponding 95% CIs. I² statistics were applied for the assessment of statistical heterogeneity.
heterogeneity among studies in the meta-analysis using RevMan (version 5.3.5, Nordic Cochrane Centre, Cochrane Collaboration, London, UK). Evidence summaries were prepared for the included studies by using predetermined output tables.

**Role of the Funding Source**

This review was conducted as a collaboration of researchers with diverse backgrounds (neonatology, gastroenterology, and public health). No funding was obtained for conducting this study, and all the authors contributed through voluntary efforts.

**RESULTS**

**Selection Results and Included Studies**

We identified 1270 citations from the electronic search of the databases from earliest date until February 28, 2015. After duplicate studies were removed, 728 studies were subjected to title and abstract screening. After excluding 418 studies and later including 2 additional studies based on manual searching from relevant journals, 312 studies were subjected to full-text review. Finally, we identified 5 cohort studies for qualitative synthesis and meta-analysis after excluding 307 studies. Fig 1 provides a summary of the evidence search and literature review. The background information of these studies is presented in Table 1. Average gestational age and birth weight of participants ranged from 26 to 30.2 weeks and 775 to 1376 g, respectively. Definitions of feeding type and ROP varied across studies. To pool data, we classified feeding into 6 categories: exclusive human milk (100% human milk feeding), any human milk, mainly human milk (>50%), exclusive formula (100% formula feeding), any formula, and mainly formula (>50%). We defined ROP as any-stage ROP or severe ROP (including stage 3 or 4, surgical, and threshold ROP).

**Feeding and Any-Stage ROP**

Based on the feeding categories, we conducted 4 groups of meta-analyses. The results are presented in Fig 2. Each group includes 2 to 4 studies as detailed in Table 2. The estimated ORs (95% CIs) were 0.29 (0.12 to 0.72), 0.51 (0.26 to 1.03), 0.54 (0.15 to 1.96), and 0.25 (0.13 to 0.49), respectively, for exclusive human milk versus any formula, human milk versus mainly formula, human milk versus exclusively formula, and any human milk versus exclusive formula. Human milk feeding acted as a protective factor for any-stage ROP. Heterogeneity tests in 4 analyses showed I² values of 53%, 74%, 90%, and 18%. In comparing mainly human milk versus mainly formula and any human milk versus exclusive formula, the outcomes of the individual studies showed poor consistency.

**Feeding and Severe ROP**

Four groups of meta-analyses were done with the target outcome of severe ROP, with each group comprising 2 to 3 studies. The results are presented in Fig 3. The estimated ORs (95% CIs) were 0.11 (0.04 to 0.30), 0.16 (0.06 to 0.43), 0.42 (0.08 to 2.18), and 0.10 (0.04 to 0.29), respectively, for exclusive human milk versus any formula, mainly human milk versus mainly formula, any human milk versus exclusive formula, and exclusive human milk versus exclusive formula. Human milk feeding acted as a protective factor for severe ROP in all analyses except any human milk versus exclusive formula. Heterogeneity tests in 4 analyses showed I² values of 0%, 27%, 91%, and 0%. In comparing any human milk versus exclusive formula, the outcomes of the individual studies showed poor consistency.

**Quality Assessment of Observational Studies**

The 5 observational studies included in the meta-analysis were further assessed independently using the Critical Appraisal Skills Program checklist for cohort studies (Table 3). Based on our assessment, 1 study17 was rated high, 2 studies18,21 were rated medium, and 2 studies22,23 were rated satisfactory. This implies that the medium-quality studies scored well on all the

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**TABLE 2 ORs of group analyses**

<table>
<thead>
<tr>
<th>Group and Reference Patients, n</th>
<th>Any-stage ROP</th>
<th>Stage 3 or 4, surgical ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n OR (95% CI)</td>
<td>n OR (95% CI)</td>
<td></td>
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<td>--------------------------------</td>
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<td></td>
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<tr>
<td><strong>Exclusive human milk versus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>any formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylander et al, 200121</td>
<td>17 vs 157</td>
<td>0.50 (0.18–1.42)</td>
</tr>
<tr>
<td>Manzoni et al, 201317</td>
<td>314 vs 184</td>
<td>0.19 (0.09–0.40)</td>
</tr>
<tr>
<td><strong>Mainly human milk versus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mainly formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylander et al, 200121</td>
<td>45 vs 90</td>
<td>0.51 (0.25–1.05)</td>
</tr>
<tr>
<td>Furman et al, 200322</td>
<td>32 vs 87</td>
<td>0.73 (0.32–1.64)</td>
</tr>
<tr>
<td>Maayan-Metzger et al, 201223</td>
<td>188 vs 172</td>
<td>0.95 (0.51–1.78)</td>
</tr>
<tr>
<td>Manzoni et al, 201317</td>
<td>314 vs 184</td>
<td>0.19 (0.09–0.40)</td>
</tr>
<tr>
<td><strong>Any human milk versus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exclusive formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylander et al, 200121</td>
<td>100 vs 74</td>
<td>0.40 (0.22–0.74)</td>
</tr>
<tr>
<td>Furman et al, 200322</td>
<td>79 vs 40</td>
<td>2.10 (0.96–4.57)</td>
</tr>
<tr>
<td>Heller et al, 200718</td>
<td>788 vs 289</td>
<td>No data</td>
</tr>
<tr>
<td>Manzoni et al, 201317</td>
<td>314 vs 184</td>
<td>0.19 (0.09–0.40)</td>
</tr>
<tr>
<td><strong>Exclusive human milk</strong></td>
<td></td>
<td></td>
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<tr>
<td>versus exclusive formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hylander et al, 200121</td>
<td>17 vs 74</td>
<td>0.40 (0.22–0.74)</td>
</tr>
<tr>
<td>Manzoni et al, 201317</td>
<td>314 vs 184</td>
<td>0.19 (0.09–0.40)</td>
</tr>
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</table>
checklist parameters related to study method and results validity. Whereas the satisfactory-quality studies scored well on parameters related to study method and results validity, specific information pertaining to certain parameters was either unclear or not reported in the studies.

**DISCUSSION**

ROP is a vasoproliferative disorder of immature retina affecting the vast majority of preterm newborns. The incidence of severe ROP in very-preterm infants weighing <1250 g could be as high as 37%. Low birth weight and prematurity are strongly associated with increased risk for the disease. ROP is currently the biggest contributor to infant blindness in developed countries, as vision loss occurs secondary to retinal detachment that may occur in the most severe cases. In addition, myopia, strabismus, and amblyopia also occur frequently. The pathogenesis of ROP is multifactorial: besides prematurity and low birth weight, factors such as high-concentration oxygen therapy and suboptimal postnatal nutrition could put infants at significant risk for this devastating eye disease, as established by clinical studies and animal studies.

The meta-analysis results of our study indicate that the overall incidence of ROP was reduced among infants fed human milk compared with those fed formula, and exclusive or mainly human milk feeding showed significant benefits in preventing severe ROP.

The underlying physiologic mechanism through which breast milk may protect against the development of ROP may reflect the antioxidant and immune-protective properties of human milk. In vitro chemical analysis of antioxidant content consistently shows that human milk contains vitamin C, vitamin E, and β-carotene and has greater antioxidant properties than formula. In addition to the antioxidant properties, human milk also contains immunomodulatory substances such as secretory immunoglobulin A, lactoferrin, lysozyme, cytokines, oligosaccharides, antioxidant enzymes, and cellular components. These factors are thought to influence immune defenses of the infant, which may explain the lower risk of necrotizing enterocolitis and sepsis among infants fed human milk.
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Are the results of the study valid?</td>
<td>Did the study address a clearly focused issue?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Was the cohort recruited in an acceptable way?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Was the exposure accurately measured to minimize bias?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Was the outcome accurately measured to minimize bias?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5a</td>
<td></td>
<td>Have the authors identified all important confounding factors?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>Have they taken account of the confounding factors in the design and/or analysis?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes. Associations between potential variables and presence of ROP was identified through bivariate analysis.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6a</td>
<td></td>
<td>Was the follow-up of subjects complete enough?</td>
<td>Yes/Can’t tell/No</td>
<td>No. Missing data, through comprising only 2.4% of the total number of data elements, occurred in one-sixth of the cases.</td>
<td>Yes. Results of all 119 infants are reported.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>Was the follow-up of subjects long enough?</td>
<td>Yes/Can’t tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

What are the results of this study?
<table>
<thead>
<tr>
<th>Section and number</th>
<th>Question</th>
<th>Option</th>
<th>Hylander et al, 2001&lt;sup&gt;21&lt;/sup&gt;</th>
<th>Furman et al, 2003&lt;sup&gt;22&lt;/sup&gt;</th>
<th>Heller et al, 2007&lt;sup&gt;18&lt;/sup&gt;</th>
<th>Maayan-Metzger et al, 2012&lt;sup&gt;23&lt;/sup&gt;</th>
<th>Manzoni et al, 2013&lt;sup&gt;17&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>What are the results of this study?</td>
<td>Explain in 1 sentence</td>
<td>Incidence of ROP was significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants.</td>
<td>Rates of ROP did not differ according to the amounts of maternal milk received.</td>
<td>Neither receipt nor increasing intake of human milk was associated with a decreased risk of developing severe ROP.</td>
<td>Lower rates of ROP were also detected in infants born at 24–28 wks who were breastfed, but the results did not reach statistical significance using univariate analysis ($P &lt; .06$). Using multivariate analysis, however, ROP stage III among this subgroup was significantly lower ($P &lt; .022$).</td>
<td>Overall, ROP incidence (at any stage) was significantly lower in infants fed maternal milk compared with formula-fed neonates.</td>
</tr>
<tr>
<td>8</td>
<td>How precise are the results?</td>
<td>Explain/ comment</td>
<td>Dose–response effect was not observed when categories of human milk were entered into logistic regression results, as duration of feeding was not included; hence results would be precise only to some extent.</td>
<td>Results are not precise, as sample size was not large enough to adequately assess ROP.</td>
<td>Results are precise, as power calculation was conducted for adequate sample size of included infants.</td>
<td>Results are precise to some extent due to the fact that study lacked precise knowledge regarding feeding days and amounts, as well as the use of human milk fortifier consisting of cow milk protein in the HM group.</td>
<td>Good, as multivariate logistic regression controlling for potentially confounding factors to ROP at any stage at univariate analysis showed type of milk feeding retained significance, maternal milk being protective at $P = .01$.</td>
</tr>
<tr>
<td>9</td>
<td>Do you believe the results?</td>
<td>Yes/Can't tell/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Can the results be applied to the local population?</td>
<td>Yes/Can't tell/No</td>
<td>No. The study was limited to 1 tertiary center with extensive resources through the Milk Bank and Lactation Center available to mothers who choose to provide human milk to their VLBW infants, thus allowing relatively high rate of providing human milk to VLBW infants in the study sample.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Do the results of this study fit with other available evidence?</td>
<td>Yes/Can't tell/No</td>
<td>Yes</td>
<td>No. Maternal milk has been reported to reduce rate of and severity of ROP in VLBW infants.</td>
<td>No. HM has been associated with decreased risk of ROP.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
This meta-analysis did not include studies on donor human milk. In 2005, Schanler et al. conducted a randomized trial of donor human milk versus preterm formula as a substitute for mother's milk in the feeding of extremely low birth weight premature infants. The stage 3 ROP incidences were 19% and 14% in the donor milk and formula groups, respectively. The study did not reveal any benefit of donor milk in terms of preventing severe ROP. Another study comparing donor milk and formula feeding also did not demonstrate any benefit in preventing ROP. This contrast may be possibly related to loss of the protective factors during processing and storage. The medical benefits of human milk and the recommendation of human milk as the preferred feeding source for preterm infants limit prospective randomized studies; we therefore selected observational studies for our meta-analysis. This selection could be a limitation to the current meta-analysis. The diagnosis of ROP also varied among studies, further complicating analysis. We resolved this by pooling stage 3 and 4 ROP, surgical ROP, and threshold ROP as a single definition of severe ROP. However, there was lack of long-term prognostic information. Our analysis showed high heterogeneity in some subgroup analyses, so the results in the corresponding analyses should be accepted cautiously and not considered a definitive statement.

### TABLE 3

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>What are the implications of this study for practice?</td>
<td>Explain/comment</td>
<td>Findings suggest a protective effect of human milk feedings against ROP after controlling for potential confounding variables.</td>
<td>Results cannot be generalized, as sample size was too low to assess the effect of maternal milk feeding on neonatal morbidities that occur at lower rates such as ROP.</td>
<td>Limitations such as lack of data collection of eye examinations after discharge, missing data of &gt;10% of sample who did not require surgery for ROP before discharge and did not return for follow-up visits at 18 or 30 mo corrected age, and absence of defined definition of ROP across study centers.</td>
<td>Human milk is ROP protective even if partially administered.</td>
<td>Exclusive maternal milk feeding since birth may prevent ROP of any stage in VLBW infants in the NICU.</td>
</tr>
</tbody>
</table>

Overall quality: Medium, Satisfactory, Medium, Satisfactory, High.
The heterogeneity among studies could be attributable to two factors. First, variations in study duration: the studies included in meta analyses were from 1992 to 2008. With the advancement of respiratory support, standardization of oxygen utilization, and increased survival rate of very preterm infants, the incidence of ROP varied from study to study. Second, variation in gestational age and birth weight: the 2 most relevant risk factors for ROP ranged from 28 to 30 weeks and 775 to 1425 g, respectively. It has been observed that a 1-week increment in gestational age could change ROP rate significantly. A random-effects model for conducting meta-analysis has been suggested as a reasonable way of addressing heterogeneity in pooled studies, and in such cases narratively explaining the reasons for heterogeneity has been proposed. We justify using our meta-analysis approach on the basis of these methodological suggestions.

Notwithstanding these limitations, our meta-analysis has several strengths. Ours is the first systematic analysis of evidence to date regarding the possible benefits of human milk on ROP. We have done multiple database searches, including manually searching relevant journals in pediatrics and ophthalmology, to incorporate maximum published studies concerning our focus. We have followed expected guidelines for meta-analysis of observational studies, which increases the applicability of our results.

We have also reported quality assessment of the included studies in the meta-analysis. Our objective in conducting this exercise was not to assess if the quality of publication should be a criterion for inclusion in the meta-analysis, such that only the high-quality studies are included, but to present how confident can one be in the results presented in the published studies. In doing so, it enables the methodology in these studies to be understood and appraised for the reader.

CONCLUSIONS

In our meta-analysis, longitudinal studies comparing the incidence of ROP in infants who were fed human milk versus formula were selected. Studies involved donor milk were not included. After unifying the definitions of feeding and ROP diagnosis and pooling the data, we found that human milk feeding potentially plays a strong role in protecting very preterm newborns from any-stage ROP and severe ROP.

ABBREVIATIONS

Cl: confidence interval MOOSE: Meta-analysis of Observational Studies in Epidemiology OR: odds ratio ROP: retinopathy of prematurity

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Jianguo Zhou, Vivek V. Shukla, Denny John and Chao Chen
Pediatrics; originally published online November 16, 2015;
DOI: 10.1542/peds.2015-2372

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Jianguo Zhou, Vivek V. Shukla, Denny John and Chao Chen
*Pediatrics*; originally published online November 16, 2015;
DOI: 10.1542/peds.2015-2372

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