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Reduced Risk of Necrotizing Enterocolitis with Breastfeeding

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Abstract

Introduction: Necrotizing enterocolitis (NEC) is a life-threatening disease in infants that causes direct damage to the intestines and requires emergent treatment. The purpose of this clinical review is to analyze the prevention of NEC in preterm neonates with breastfeeding.

Methods: PubMed was searched using a specific search strategy using the key terms “breast,” “feed,” “formula,” “necrotizing,” and “enterocolitis.” Operators and filters applied narrowed the results to 4 quality articles for review.

Results: One RCT, and two meta-analyses, reviewed had a reduction in the development of necrotizing enterocolitis among breastfed neonates. One randomized noninferiority trial totaling 123 neonates did not favor breastfeeding, but the results were not statistically significant. All studies used a 95% Confidence Interval (CI) and p-values of $P<0.05$.

Discussion: The articles reviewed in this study supported breastfeeding in reducing the development of necrotizing enterocolitis in preterm neonates. The studies reviewed had several limitations. Further research is needed to replicate these results.

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INTRODUCTION

Breastfeeding is feeding an infant breast milk as their main source of nutrition, which can commence right after birth. The components of human milk include living biological substances that strengthen the newborn gut microbiome, lowering the risk of infection.[1] Preventing infection in the neonatal period is imperative to reduce the risk of morbidity and mortality.[1] The newborn's brain development can be impacted if they undergo an inflammatory response to fight an infection during those early stages of life.[1] A major risk for preterm neonates is the development of necrotizing enterocolitis (NEC), a life-threatening disease. NEC is a disease that causes direct damage to the intestines which requires emergent treatment to prevent detrimental progression.[1]

Necrotizing enterocolitis affects 5-12% of neonates born at a deficient birth weight making it the leading cause of death due to a gastrointestinal disease in a preterm neonate.[2] This disease starts slowly with signs of feeding intolerance and can quickly progress into pneumatosis intestinalis or portal venous gas.[2] Neonates that suffer from necrotic bowel due to NEC require surgery and have a mortality rate of 20-30%, making it the highest mortality rate for any neonate that requires surgery.[2] Preterm neonates have delayed microbiota colonization resulting in an increased inflammatory response and abnormal bacterial glycosylation patterns.[2] Other factors that have delayed colonization include delayed enteral feedings, early exposure to broad-spectrum antibiotics, and formula feeding.[2]

NEC is diagnosed using Bell's Modified Staging Criteria which has three levels Bell's Stage 1, Stage 2, and Stage 3.[2] Bell's Stage 1 is mild stage, classified with temperature instability, bradycardia, mild abdominal distention and occult blood in the stool.[2] Moderate NEC is classified as Bell's Stage 2, which includes radiographical findings of pneumatosis intestinalis

or portal venous gas.[2] The systemic signs of Bell's Stage 2 include abdominal tenderness, thrombocytopenia, and metabolic acidosis.[2] Advanced NEC known as Bell's Stage 3 requires surgical intervention. Stage 3 is classified with pneumoperitoneum, hypotension, signs of peritonitis, and severe metabolic acidosis.[2] Treatment for NEC varies based on the Bell's Stage. All Bell Stages will receive antibiotics, bowel rest, and have ionotropic and fluid support.[2] Broad-spectrum antibiotics will be given to cover anaerobic organisms with concern for sepsis.[2] Advanced NEC with a resultant ischemic bowl will require surgical intervention to resect portions of the dead bowel.[2] Prevention is important since the treatment of NEC has not impacted the frequency or severity of the disorder.[2]

Breast milk is a living biological substance, that continuously evolves based on the infant's needs at the current time. Based on the infant's age and immune system, the bioactivity of human milk can change to meet the infant's nourishment and immunologic requirements.[3] The World Health Organization (WHO) recommends breastfeeding through the child's second birthday.[4] WHO and United Nations International Children's Emergency Fund (UNICEF) recommend starting breastfeeding within the first hour of birth and continuing exclusive breastfeeding until the infant is 6 months of age. At 6 months of age, the infant can then be introduced to solid foods, alongside human milk until age 2.[4]

In the United States, the CDC reports that for infants born in 2020, more than 80 percent initiate breastfeeding at birth, but less than 60% are still breastfeeding at 6 months postpartum.[5] The percentage of infants breastfed at 1 year is less than 40%.[5] The overall percentage decreases when it is specified if the infant was exclusively breastfed. The CDC reports that the percentage of infants exclusively breastfed through 3 months of age is 45% and that through 6 months is 25%.[5] The amount of infants born in 2020 who were breastfed newborns that received formula

supplementation within the first 2 days of life is 20.8%.[5] The CDC reports suggest that many mothers and families decide to breastfeed at the start of a new life but do not continue it for the longevity the WHO recommends, or they are not exclusive to human milk.[4-5]

A newborn at birth has an immature immune system that is limited in antioxidant and anti-inflammatory activity.[3] The composition of human milk contains bioactive factors such as cytokines, hormones, leukocytes, immunoglobins, lactoferrin, lysozyme, stem cells, human milk oligosaccharides, microbiota, and microRNAs.[3] With these bioactive substances, breastfeeding can improve infants' gut microbiota colonization, immune system modulation, and overall gut health, and supplement their deficient antioxidant and anti-inflammatory activity levels.[3] Human milk introduces antigens to the infant allowing for a strong immune system against harmful pathogens early in life.[3] The composition of bioactive factors in human milk can build the infant's immune system and decrease the risk of gastrointestinal infections and necrotizing enterocolitis.[1-3]

The alternative to breastmilk for feeding a neonate is infant formula. Milk formulas are divided into subgroups based on the child's age. The composition of milk formulas includes milk proteins, lactose or other sugars, vegetable oils, and micronutrients.[6] Other bioactive compounds included in the formula are lactoferrin, osteopontin, probiotics, prebiotics, choline, miRNA, L-carnitine, lutein, taurine, ganglioside, and inositol, improving the nutritional value.[6] The infant formula rate is increasing in the modern era due to the growing number of working mothers, malnutrition rates, a concern for nutrition in the neonate, and the increasing income of the middle class.[6] Infant formulas come in liquid, powder, and ready-to-feed preparations.[6] New combinations and components are continuously being tried to align the formula ingredients with the infant's needs.[6] This review aims to analyze recent literature on the benefits of breastfeeding

to reduce the risk of NEC in discussing infant health with new and expectant mothers and families.

METHODS

PubMed was searched using the key terms “breast,” “feed,” “formula,” “necrotizing,” and “enterocolitis”. MeSH terms were added to produce a final search of “breast” AND “feed*” AND “formula” AND “necrotizing” AND “enterocolitis”. This resulted in 215 articles. Additional search filters were applied for free full text, dates were restricted within the past five years, RCTs, meta-analyses, systemic reviews, and restrictions for the English language only. This yielded 13 results.

Five of the articles that were not selected did not include necrotizing enterocolitis. Two articles were excluded due to bovine milk use, another article was not chosen due to enteral feeding. One article comparing high versus low medium chain triglyceride formulas was not included. Four articles were reviewed in this paper comparing the risk of developing necrotizing enterocolitis (NEC) in breastfed and formula-fed neonates.

RESULTS

Altobelli et al[7]: This article produced a systemic review and meta-analysis of human milk impact on preventing necrotizing enterocolitis in premature infants compared to preterm formula-fed infants. The meta-analysis included six RCTs and 26 observational studies.[7] The study considered NEC in patients with a Bell score greater than or equal to two. The effect size was measured using relative risk (RR) reduction, with 95% CI and p-value.[7] Heterogeneity in these studies was assessed using Q statistics and I^2.[7] The meta-analysis had a total sample size of 1626 newborns.[7] The meta-analysis results showed a decreased risk of NEC when fed human milk compared to formula. The RR was 0.62 (0.42-0.93).[7] These results had statistical

heterogeneity with an I^2 of 47.03 and a p-value of 0.009.[7] The meta-regression analyses by year of publication, gender, birth weight, gestational age, and ethnicity did not show significant results.

Eighteen of the observational studies compared 6,405 newborns' diets and their risk of NEC. The relative risk result was 0.45 (0.32-0.62), p-value less than 0.001, and statistically significant heterogeneity ($I^2 = 55.25$, $p=0.002$).[7] The overall result of these observational studies indicated a reduction in the risk of NEC with human milk-fed infants.[7] The geographical area showed differences with a reduction in Europe and USA, but not in Japan.[7] This is thought to be because one small study was done in Japan, with a sample size of 18. The other meta-regression analyses by year of publication, gender, birth weight, gestational age, and ethnicity do not show significant results.[7]

The other observational studies in this article were not included in this review, which compared the high consumption of breast milk vs low consumption on the decrease of NEC risk. Seven of the observational studies not included also compared mixed feeding vs breastfeeding and formula feeding.

Lapidaire et al[1]: This article was a randomized control trial that included preterm infants who were randomized to receive preterm formula, term formula, banked donor breast milk as a sole diet, or in addition to maternal breast milk. The researchers had consent from the families of the randomized infants. The trial consisted of 926 infants who had weighed less than 1850g at birth and were recruited for diet intervention.[1] The randomized design split the infants, assigning an intervention diet (preterm formula), or the standard diet (term formula, banked donor breast milk or breast milk). The mother had the choice to provide breast milk, so the infants had solely the randomized standard diet, or the supplement of the breast milk in addition

to the randomized diet. The proportion of maternal breast milk varied between infants, therefore a proportional intake for each diet was calculated.[1] In this trial, NEC was determined using the British Association for Perinatal Pediatrics classification.[1] NEC grades I and 2 were distinguished. The cases of NEC were further classified as confirmed by surgery or radiological studies or labeled as unconfirmed.[1]

A sample size of 765 infants was studied to determine the relationship between diet and NEC. This study used a logistic regression model that was adjusted for maternal education, sex, birth weight, gestational age, days of ventilation, and the number of days until 150 ml/kg/day of enteral feeds.[1] The results showed that each 10% increase in maternal breast milk and bank-donor breast milk intake was associated with an 8 and 12% lower chance of NEC. In comparison, a 10% increase in term formula was associated with a 12% increased chance of NEC.[1] The standard term formula with donor breast milk compared with the intervention group of preterm formula had no difference in odds with increased diet intake.[1] The maternal breast milk percentage showed a 0.992 infection change in odds ratio per percent increase in diet intake, with a p-value <0.05 and 95% CI (0.984-1.000).[1] The donor breast milk showed a 0.988 infection change in odds ratio with p<0.001 and 95% CI (0.976-0.997).[1] The term formula showed 1.012 infection ratio odds per percent increase in diet intake with p<0.001, 95% CI (1.004-1.019).[1] This study, which compared diet and NEC, showed that increased human milk intake (maternal and donor) was associated with a reduced risk of NEC.[1]

Li et al[8]: Meta-analysis reviewed preterm infants' diet with the occurrence of NEC. This article reviewed a total of 1390 patients who were enrolled in 11 RCTs.[8] This study was unique because the diet choice was donated breast milk only compared to formula. This article discussed the lack of human milk as a primary reason many mothers choose formula.[8] This

study compared the results of donated breast milk to formula on preterm infants. The meta-analysis selected RCTs that included preterm infants with a gestational age of less than 37 weeks, or with a birth weight less than 2500 g infants as participants.[8] The control group consisted of formula-fed infants and the experimental group was the donated breast milk individuals. Studies with incomplete data and without full RCT information were excluded from this analysis.[8]

The results of the dichotomous data were presented as a risk ratio with a 95% confidence interval.[8] The heterogeneity of the studies was evaluated with I^2 and X^2 tests.[8] The data used was considered statistically significant with a p score <0.05. The birth weight of the infants in the 11 RCTs chosen was either less than 1500 g or less than 1000 g.[8] Fortifiers were added to the donated breast milk in four of the studies.[8] The sterilization method of the donated breast milk was not described in one of the studies, the milk was pasteurized in the rest of the RCTs.[8]

The meta-analysis showed a reduction in the incidence of NEC in the infants that had donated breast milk.[8] The RR was 0.67, 95% CI (0.48-0.93), and p-value was 0.02, in the donated breast milk group.[8] The heterogeneity was low with I^2 at 40% and p-value=0.15. Further subgroup analysis was performed comparing multi-center and single-center groups. The multi-center groups showed a significantly reduced incidence of NEC, compared to the single-center groups.[8]

Chinnappan et al[9]: The study conducted was an open-label, randomized noninferiority trial that compared the fortification of breast milk with preterm formula powder vs human milk fortifier in preterm neonates. This trial enrolled 123 neonates born at or less than 34 weeks of gestation.[9] The preterm formula fortification group had a sample size of 59 and the human milk fortifier had a sample size of 63.[9] The mean difference and relative risk had a 95% CI.[9] The

incidence of NEC was a secondary outcome for this study and was recorded per occurrence with its standard definition from AIIMS protocols in Neonatology.[9] The median age of enrollment was 7 and 8 days old. The mean weight enrollment was 1038 g in the formula-fortified group and 1074 g in the human milk-fortified group.[9] Both groups had similar maternal characteristics. Three neonates in the human milk-fortified group developed NEC stage II or more, which equals 5% of the group.[9] The formula fortification group had zero neonates develop NEC stage II or more. The difference found was not ruled significant, and the CI did not apply to this outcome.[9]

DISCUSSION

The studies of Altobelli et al[7], Lapidaire et al[1], and Li et al[8] supported breastfeeding to reduce the risk of developing NEC in neonates. The Chinnappan et al[9] study results did not support these results. The Chinnappan et al[9] results had the smallest sample size of 123 neonates which were not ruled significant, and CI was not applicable. Although the results differed from the rest of the articles in this study, they were insignificant.

Altobelli et al[7] and Lapidaire et al[1] studies noted both were conducted before fortifiers were added to the human milk. This allowed for baseline data using natural breast milk without any additions. Lapidaire et al[1] data was collected from research nurses which decreases discrepancy with results. Li et al[8] studies incorporated donor breast milk, further supporting the benefits of human milk.

Altobelli et al[7] articles had several limitations to their study. One limitation of this review was the consideration of mothers' breast milk and donor's breast milk under one entity. Another limitation of this study was the pasteurization of milk can reduce microbial contamination, which can alter the results. Altobelli et al[7] described the heterogenicity in the articles reviewed,

they emphasized that even within one state or country there can be significantly different socio-cultural differences that can play into the results. Altobelli et al[7] and Li et al[8] used relative risk reduction, a single statistic to analyze their results, which could overestimate positive results.

A limitation of the Lapidaire et al[1] study is the combination of infection and NEC into one category. Along with this, the study included confirmed and non-confirmed cases of NEC.[1] This could greatly alter the results of which neonate had the correct data for NEC. The Li et al[8] studies used donated breast milk with added fortifiers. The Chinnappan et al[9] study had a significantly lower sample size than the rest of the studies, used fortification, and the NEC data did not yield significant.

Altobelli et al[7], Lapidaire et al[1], and Li et al[8] studies had large sample sizes and showed a reduction in the risk of NEC with breastfed neonates. The articles reviewed in this study varied between mothers' breast milk, donor's breast milk, and added fortifiers. Li et al[8] and Chinnappan et al[9] had the NEC data as a secondary outcome. Altobelli et al[7] and Lapidaire et al[1] had several limitations to their studies. The articles reviewed had different variations in their studies requiring further research to replicate these results.

Medical professionals should assess the mother's intention to breastfeed early in pregnancy to help mothers overcome barriers and misconceptions that may come along with breastfeeding. Prenatal counseling has been shown to solve breastfeeding problems postpartum and increase self-efficacy.[10] If discussed early in prenatal care with expecting mothers, they can obtain the proper education on breastfeeding, counseling on the intricate process, and guidance to overcome their obstacles. Proper education and adequate support from medical professionals have improved the number of women who initiated breastfeeding their newborns.[11]

The CDC 2022 report card for breastfeeding highlights that constant support can help families reach their breastfeeding goals.[12] These support systems include maternity care practices, state-paid family leave laws, early care, and education policies.[12] State-to-state early care licensing requires comfortable accommodations for mothers wanting to breastfeed on-site. The paid family and medical leave (PMFL) helps the family financially with the arrival of a newborn.[12] The lack of paid maternity leave was a major barrier to breastfeeding for mothers, and the PMFL insurance program will help this barrier.[12]The current state is constantly improving for breastfeeding with the implemented support systems and making mothers feel like this source of nutrition is feasible and comfortable.

Future research needs to compare the data of breastfed versus formula-fed neonates and evaluate the NEC risk as the primary outcome, with and without additions to breast milk, to gain more data. The supported systems in place for mothers and families will help them complete their breastfeeding goals. Readers should continue to promote breastfeeding based on the CDC recommendations and the research on reducing NEC.

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