

Reviewer Comments/Checklist for Gregory article:

Reviewer #1 (Cindy Smith Greenberg, DNSc, RN, CPNP): Interesting study that adds important information regarding risks for NEC development.

Problem Statement: succinct

Aim: identified

Hypothesis: identified

Literature Review: References are appropriate, most recent cited is 2003.

Consider searching for more recent literature, e.g.:

Mally, P. et al. (2006). Association of necrotizing enterocolitis with elective packed red blood cell transfusions in stable, growing, premature neonates. *American Journal of Perinatology*, 23, 451-458.

Hallstrom, M. et al. (2006). Laboratory parameters predictive of developing necrotizing enterocolitis in infants born before 33 weeks of gestation. *Journal of Pediatric Surgery*, 41, 792-798.

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Theoretical Framework: conceptual framework identified in figure 1, logical flow, appropriate for condition. Nice explanation of the framework, logical link between viewing development of NEC as a matter of adaptation/conservation and variables that nursing can plan interventions to address

Style of Presentation/organization: Generally clearly written; see suggestions under specific comments.

Research Design: Appropriate, procedures are explained.

Data Analysis:

Pg 12, line 15 - clarify the 28 variables used for the Bonferroni correction; from Tables 1 and 2 it is difficult to pick out 28, depending on how you classified them there are either more or less but it is not clear what 28 were used (e.g. in Table 2 p values were reported for 27 variables)

Pg 12, lines 22-23 and Pg 13, lines 2-4 - although all preterm infants were

the sample, there does not seem to be a logical reason why some info was reported and some not (e.g. 92.7% of the total sample was born before 32 weeks - but info on age of those who developed NEC was not reported in text. Or, one would not expect that subjects who did not have NEC would have surgery for the condition, why report surgical management of NEC by percentage of the total sample?); while it is best not to repeat data reported in the tables it would be more pertinent in text to report percentages of those who developed NEC from the total sample since this is the concept of interest.

Specific comments:

Pg 8, lines 14-19 - this paragraph does not fit under the review of the literature; move discussion to the Methods section where you then are presenting your current study, Table 1 presents the points you discuss in this paragraph so can condense the discussion, eliminating much of the elaboration.

In your discussion under Methods please speak to the classification of race - why were there only 2 groups - White, and all other?

Provide legend for abbreviations in Tables.

Make it clear that it is lack of change to fortification of feeding that is the risk factor.

Reviewer #2 (Donna Dowling, RN, PhD): This is a very well written manuscript on a subject not commonly seen in the nursing literature, the evaluation of clinical predictors of a specific medical problem, in this case a problem of premature infants, necrotizing enterocolitis (NEC). I have several suggestions to improve the quality of the manuscript:

1). The purpose of the paper is stated inconsistently. On page 5, line3-4, and page 6, line 17, the purpose of the study is stated as being examination of the relationship between variables related to intestinal inflammation on the incidence of NEC, when in fact the study examines the relationship between specific clinical events that may result in decreased mesenteric blood flow and intestinal inflammation and the development of NEC. You do state this

clearly on pg, 8, line9-11, however this is too late. On page 13, line18-20, you suggest that increase in respiratory support and increase in perfusion support 'represent" inflammation & ischemia—however, these changes in physiological stability represent a wide spectrum of disease processes. Along this line, on page 5, line 6, it is stated that "The study proposes..." while in fact I think you mean the study "assumes".

2). There are some sections (page 5, lines 6-16; 8, lines 14-19) that need citations.

3). The references are very old; the latest is 2003 and some are from the 1970's. While much of the beginning work on NEC started in the 70's, there continues to be a great deal of research being done currently on both the risk factors and management of NEC, for instance the use of probiotics.

There is also new literature concerning the timing of enteral feeding (see Pietz et al, pediatrics, 2007, e164-70). Newer literature needs to be incorporated into the introduction and discussion.

4). Page 12: you set the alpha for the selection of variables for inclusion in the logistic regression at .002. This is a very restrictive and there needs to be an explanation given, Additionally, this restriction resulted in key variables (i.e. breast milk) being left out of the regression even though their p values were significant by standard criteria.

5). On my initial reading of the paper I found that the finding that the lack of fortified breast milk resulted in a 4.4 times increase in NEC to be confusing, as there is strong literature support for the reduction of the incidence of NEC when breast milk is given. Realizing that breast milk alone was left out of the regression analysis made this clearer, and your explanation in the discussion was adequate. My initial confusion was related to the fact that supplementation of breast milk or formula can increase the osmolarity of the feeding which is known to increase the risk of NEC. I was also surprised that you were referring to supplementation that included MCT oil and polyose which are not common, as well as HMF which is almost routine. This needs to be included in the methods section of the paper.

6). Pg. 17, line 13, I don't think that this represents a 'potentially new theory" as it is understood that the incidence of NEC is much lower in stable infants, i.e. those who are on full feedings.

7). pg 18, lines 1-1-4, I don't know of a NICU where such protocols aren't already in place.

8). Pg 19, lines 5-6, this is much too strong of a statement and seems to contradict your discussion that the fortification is related to feeding

progression and as such isn't an independent indicator of risk of NEC

Reviewer #3 (Tracy Yin, PhD, RN): This is a carefully designed, well-conducted retrospective study with clinical significance. The authors used a two to one match to get a sample of over 200. Many possible predictors were explored in the study. The data analyses used in this study were appropriate and the results were presently clearly.

I do have some questions though. The authors mentioned on page 13 that "variables were highly correlated were collapsed accordingly", what is the criteria for "judging highly correlated"? Which variables were combined based on this? In addition, at the results section, the authors entered three enteral feeding variables in the logistic regression model and reported one feeding variable being significant predictor. I thought those variables might have high correlation and multicollinearity needs to be addressed. Even though the authors argued that correlation matrix were assessed prior to the logistic regression and no correlation coefficients bigger than 0.49. I disagree with the authors' claim that this represents little if any relationship at all (page 13, line 15). Often, in this type of research, r around 0.3 or 0.4 does represent a small to medium relationship, model stability need to be concerned. It is better if the authors present a correlation table for the readers.

Some other comments as well. I thought the authors did a nice job highlighting the purpose and significance of their study even without the addition of the conceptual framework. For me, the conceptual framework and Figure one provides little useful information.

CHECKLIST FOR STYLE

References

Update reference list using APA 5th Ed. format. In particular, After the 6th author's name and initial, use et al. to indicate the remaining

authors of the article (i.e., Bell...).

Update in-text citations using APA 5th Ed. Format (The Publication Manual of the American Psychological Association, 5th Edition, pp. 208-209). In particular:

Add in-text citations of the following references to the reference list:
Berseth... 2003

Figures

Other: Please correct spelling of "Develoment" in the figure.