Author's response to reviews

Title: Growth in VLBW infants fed predominantly fortified maternal and donor human milk diets: a prospective cohort study

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Author's response to reviews: see over
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RE: Growth in VLBW Infants Fed Predominantly Fortified Maternal and Donor Human Milk Diets: A Prospective Cohort Study

Authors: Colaizy, TT; Morriss, FHM; Carlson, SC

Dear Editorial Board of BMC Pediatrics:

We would like to thank you for your thorough review of our manuscript. Drs. O’Connor and Tuttle have provided thoughtful critiques that have aided us in strengthening our study. Below you will find a point by point response to their reviews.

Reviewer #1: Dr. O’Connor

Major Compulsory Revisions:

1. The authors examine the z-scores at birth and then again at discharge. Lots can happen in terms of trajectory of growth in-between. Can it be assumed that the z-scores are lowest at discharge or were they lower at some point during the in-hospital course and improved somewhat by discharge? Some thoughtful discussion of this should be included in the paper.
   - We do not have sufficient data to compute z-scores at other times during the hospitalization, and thus cannot use our data to answer this question. We do not assume that the z-score at discharge is the lowest during hospitalization. Two sentences have been added to the last paragraph of the discussion in the limitations section, page 15.

2. Authors should expand on limitations of the study to include the following if they can't be included in this submission: (1) no measure of linear growth included in these analyses and implications of this short-coming; (2) no measure of “actual” total milk volume/total caloric intake to achieve growth presented and implications of this short coming; (3) expand on why observational nature of study could be a limitation.
   - 1- Unfortunately, during the time period of the study, routine length measurements were not obtained in this population. Therefore, we could not assess the effects of human milk on length gain. We freely acknowledge that this is a limitation of our study. Weight gain does not tell the entire story, as it does not estimate lean body mass gain on its own. Georgieff and colleagues have recently shown that poor linear growth rates are associated with poor 24 month cognitive outcomes in former VLBW infants, and that length z-score for gestational age at hospital discharge was lower than weight z-score. This information has been added to the manuscript in the last paragraph of the discussion, page 15.
2. Our data collection also did not include this information, and this has been noted as a limitation on page 15.

3. A more thorough discussion of the potential impact of the observational study design was added to the last paragraph in the discussion, page 14.

3. Revise the overall conclusion to the paper so that the conclusions follow what the data from the study show.
   - The conclusions were significantly revised to reflect the study results. See page 15.

4. In terms of selection of the study sample versus other studies reviewed in the paper, did these earlier studies also exclude infants that expired or were transferred? If different, implications?
   - Our study sample was comparable to those of the previous studies reviewed in the paper’s discussion:
     - Dusick et al [1] (ref #14 in manuscript) studied VLBW infants in the NRN at 36 weeks’ corrected gestational age, therefore any infants dying prior to that time period were excluded.
     - Lemons et al [2] (ref #20 in manuscript), also studied NRN survivors at 36 weeks’ corrected gestational age.
     - Schanler et al [3] (ref # 2 in manuscript) studied 108 infants between 26 and 30 weeks’ gestation at birth, 4 of whom died, none of whom were transferred. Infants who died were not included in the growth outcome data, which were reported for hospital discharge.
     - O’Connor et al [4] (ref #11 in manuscript) also studied infants who survived to discharge, since this analysis was part of a randomized trial which lasted to 12 months’ corrected age. The report of this trial notes that infants were excluded from analysis after enrollment in the case of death.
     - Sullivan et al [5], (ref # 3 in manuscript) also excluded infants who died or were transferred prior to discharge.
     
     As we studied a similar population to those investigators whose studies we discussed, with similar treatment of death and transfer prior to discharge, we do not feel any adjustments in the manuscript are needed.

5. Add in a sentence or two describing pasteurized donor milk
   - These sentences have been added under Methods: Study Population, page 5.

6. Page 6 (end of Nutritional Intake and Growth Variables Section): Substantiate the statement, “Negative change in weight z score from birth to discharge represents growth failure less than the in-utero growth rate, whereas positive change represents a greater than the predicted growth rate.” With a small deviations in z-score, the weight gain/kg can still be positive...would this still be considered “growth failure”?
   - Thank you for raising this issue. This sentence was intended only to explain what a negative and positive change in z-score indicate, for readers not familiar with z-scores. I agree that the published in-utero growth curves for fetuses do not match the Fenton growth curves of VLBW infants. Therefore, this sentence has been revised to read, “Negative change in weight z-score from birth to discharge represents growth less than the predicted growth rate, whereas positive change represents a growth rate greater than the predicted growth rate.” Page 6.
Dr. O’Connor

Minor Essential Revisions:

1. Abstract: The sentence, “Protein supplementation beyond standard human milk fortifier was related to human milk intake” didn’t mean much to me until after I read the paper.

   - We agree, this is not clear in the abstract. It was edited to add “protein and caloric supplementation…”, to clarify. See page 2.

2. Define maternal milk and human milk at the beginning of the paper—i.e. what is mothers’ own milk alone versus both mothers’ own milk and pasteurized donor milk.

   - This has been defined in the background, third paragraph, top of page 4.

3. Third paragraph of the background, “A recent study…”. Cohort of infants followed 10 years ago.

   - This is a good point, 10 years is not recent. This word has been removed and replaced with ‘later’, see bottom of page 3, 3rd paragraph of background

4. Page 7, was human milk fortifier added once infants were tolerating between 25 to 40 ml of milk per day or was this 25 to 40 ml/kg per day?

   - Fortifier was added when infants were tolerating 25 – 40 ml of milk per day, not ml/kg/day. This range was chosen because 25 ml per day is the soonest that maternal milk can be fortified with the products used in this trial without wastage. One packet of powdered bovine HMF is added to each 25 ml of human milk per manufacturer directions. A sentence explaining this was added to page 7 for clarification, as the concern raised by Dr. O’Connor is likely to occur to other readers.


   - A sentence explaining this has been added to page 12, 2nd paragraph.

6. Page 12 last paragraph: Comment on whether spot checking milk validly represents overall protein content of milk expressed. Provide citation.

   - The discussion of adjustable and targeted fortification, which included the statement that Dr. O’Connor requested a comment on was removed from the manuscript on the advice of the second reviewer, so this revision was not required.

Dr. O’Connor

Discretionary Revision:

1. My understanding may be antiquated, but should you be starting a sentence with a numeral; shouldn’t numbers normally be written out?

   - This was edited, page 8, results, 1st paragraph. As writing out two hundred twenty four was deemed clunky, that sentence was edited so that it did not start with a number.

2. For the background statement, I would set up so it better defines the problem or issue and then follow this with an objectives statement.

   - We chose not to modify the background.
3. Clinical Variables. I would just say you collected supplemental oxygen at discharge and delete the end of the sentence...as a measure of chronic lung disease.
   • This change was made on page 5, under Clinical Variables.

4. Discussion page 10 2nd paragraph: Probably no need to use shortform NRN. Not used enough to warrant.
   • This was not changed, as NRN is used twice after the initial definition and using the long form would make the sentences hard to read.

5. Table 1: Footnote. Define day of life as Day zero.
   • We elected not to make this change.

Reviewer #2: Dr. Tuttle
Minor Essential Revisions:

1. Study described as prospective cohort study. Later in the article, description of two distinct time periods pre and post introduction of donor milk availability described. This suggests that babies who received the smaller percentages of human milk care may not have been cared for concurrently with babies who received higher percentages of human milk and raises the question about the type of study.
   • Thank you for this observation. We chose to study the transition period between preterm formula and donor human milk use in our unit, to assess the effects on growth of increasing amounts of human milk use in the <1251g preterm infants. In the first six months of the study period chosen, no donor milk was used, and therefore preterm formula was used more frequently. However, predominantly preterm formula diets were rare in our population during the entire study period. Out of 171 subjects, only 47 received <50% human milk, with only 5 receiving no human milk. To address this concern, we have substantially revised the last paragraph of the Background, page 4.

2. Study goals defined as comparison of in hospital growth in patients being fortified donor milk, v. fortified maternal milk, v. formula. However, the main data analysis was change in wt z score stratified by percentage of human milk received, . There was then a sub group analysis in the >75% human milk intake group based on type of human milk received. The goals and primary outcome measures need to be aligned.
   • The last paragraph of the Background, page 4, has been substantially revised so that it better matches the study outcomes described in the methods section. Thank you for this clarification.

3. The target level for protein intake were achieved by use of powdered HMF or formula concentrate, so that the level of fortification of other nutrients was also increased, and the milk more caloric, in addition to having more protein. Given this, the conclusion that the lower growth failure rate is likely due to higher protein intake is not valid as the calorie content of the milk also higher.
   • We have added ‘and calorie’ to every discussion of the increased protein fortification scheme used. See page 10, last paragraph of Results, page 6, under Study Outcomes.
● We have also added a discussion of this phenomenon on page 14, with the sentence beginning, “However, as multi-component…”

4. There is no mention of time to full feedings in each group, just percentage of enteral feeds that were human milk. If it took longer to achieve full feedings and greater time was spent on HA, then would see slower growth velocity. It might also be helpful to see ventilator days as surrogate for level of illness and need for higher calorie intakes.

● In our practice, central line days is synonymous with days of TPN use, and central line days are reported in Table 1. A sentence highlighting this risk factor has been added to the Results section, 1st paragraph, page 9, beginning “Infants receiving <25%…”

● We did not collect time to any other measure of full feeds, such as >120 kcal/kd/day, so that comparison cannot be made, unfortunately.

5. There is no standard definition for adequate growth. Poor growth, inferior growth, slow growth, good growth used descriptively without consistent terminology throughout the publication and at times conflict with the reported outcome of changes in z scores. "...predominately human milk diets in our population resulted in significantly slower growth than diets containing 75% human milk, but earlier discussion states that " our population of VLBW infants fed predominately human milk grew well...". The study infants grew well overall...( p 10) compared to (page 11) "a predominately donor milk diet was associated with higher rates of growth failure", as examples but there are more in the paper.

● We agree that this terminology was used descriptively only, and that no clear definitions were made. Therefore, the Discussion section of manuscript has been edited to decrease confusion by eliminating these descriptive words
  o 1st sentence of the 1st paragraph of the discussion has been changed to, “Our population... experienced low rates of SGA... and average loss of one-half...” from “Our population... grew well overall”. Pg 11.
  o 1st sentence of the 2nd paragraph of the discussion has been changed to, “...grew well overall by the definition of being AGA...”. This was added so that the reader will know the definition of ‘well’ we are using, and that it is not universal.

Discretionary:

1. The writing switched back and forth between VLBW and ELBW and it is confusing. The study population is referred to as VLBW but was limited to pts <1250 grams- VLBW would imply pts up to 1500 g.

● We agree that this can be confusing. All references to ELBW in the paper refer only to other study populations we are describing in the Background and Discussion section, never our own population. Our prospective nutritional database is maintained only for infants with birthweight <1251g, so we were not able to study the full VLBW cohort. We have added, “a subset of” before all uses of VLBW in reference to our own study population, and have edited the Study Population section of the Methods, page 4.
2. page 20, Table 3. There appears to be a mistake in the first column- human milk fortification, highest level used: should this read protein fortification, highest level used?
   - Thank you for identifying this error. It was corrected.

3. page 2, second to last sentence missing of between risk and poor.
   - Thank you for identifying this error. It was corrected.

4. Consider eliminating the discussion about targeted versus individualized fortification as the issue not part of the study design and seems tangential to the article.
   - We agree that this is extraneous, and it has been removed.

5. Consider commenting on why in the sub group analysis, babies in the mixture group had better scores than in the maternal milk group.
   - We added an explanation of the likely reason for this (they actually got a little less human milk overall than the other two subgroups), in the last paragraph of page 12 in the discussion.

6. Consider commenting on any type of processing or storage of mothers own milk used- is it used fresh v. previously frozen, are any measure taken to prevent CMV transmission that would alter the nutritional composition?
   - A sentence was added to page 7, “Maternal milk...” to describe our maternal milk use.

We once again thank the reviewers for a thorough and thoughtful review. We addressed each concern as completely as possible given the constraints of our study, and thank you for the opportunity to do so.

We hope that our paper will be favorably considered for publication in *BMC Pediatrics*.

Sincerely,

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Assistant Professor of Pediatrics
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References:


