Author's response to reviews

Title: Early feeding of fortified breast milk and in-hospital-growth in very premature infants: a retrospective cohort analysis

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Author's response to reviews: see over
Dear Editor,

We are grateful to have the opportunity to submit a revised version of our manuscript entitled: "Early feeding of fortified breast milk and in-hospital-growth in very premature infants" to be considered for publication in *BMC Pediatrics*.

All Authors have approved this manuscript revision as submitted.

We appreciate the thoughtful and helpful comments of the reviewers and we will respond to all their criticisms.

**David Tudehope:**

*The paper is an important paper in its field and is one of few studies to report very preterm infants rapidly transitioning to full enteral nutrition. However, although babies predominantly receiving fortified human milk grew much better than previously reported they still exhibit a degree of faltering growth at 28 days and at hospital discharge.*

Response: We appreciate the reviewer's appraisal.

1. Insertion of a table of biographic details of 2 study populations >75% and <25% proportion of human milk would enhance reader ship and comprehension
Response: As suggested, we inserted a table with biographic details and further information on important outcomes (table 1). Redundant information was deleted from the results section.

2. Further details of standardised feeding protocol are necessary not just referenced to previous study 8. What was incremental daily increase in feeding volume?

Response: We extended the method section for further details on our feeding protocol as follows:

“Nutrition Policy
A standardized feeding protocol was applied that defined feeding increments, handling of feeding difficulties, and complementary parenteral nutrition. Feeding of expressed breast milk of the infant’s own mother was encouraged. Because donor milk was not available, supplemented breast milk was complemented with preterm formula (Beba preterm formula, Nestlé) if necessary to meet the prescribed enteral feeding volume. The feeding policy in 2006/07 was to start enteral feeds on the first day of life with 10-15ml/kg/d of preterm formula (Beba preterm formula, Nestlé). As soon as possible, preterm formula was replaced by breast milk. Daily feeding advancements were scheduled at increments of 15-20ml/kg/d. Supplementation with a multicomponent fortifier (FM 85®, Nestlé; 1.0-1.5g protein and 18-27kcal per 100ml) was started when enteral feeds reached 150 ml/kg/d.

In contrast, in 2010, enteral feeds were initiated with 20ml/kg/d and advanced by 25-30ml/kg/d. Breast milk fortification was started at a feeding volume of 100ml/kg/d. In cases of fluid restriction (total fluid intake < 150ml/kg/d), the dosage of the multicomponent fortifier was increased up to 7.5% (equal to 1.5g protein and 27kcal per 100 ml) in both periods. At discretion of the attending neonatologist, the dosage of multicomponent fortifier was also augmented in infants showing persistently faltering growth.”

Lines 83 - 100 in the clean copy of R1

3. Further explanation of use of HMF FM85 is necessary. Usually 4 sachets provides 1g protein /100ml milk so did some babies receive 6 sachets per 100ml. What were circumstances when babies received 1.5g protein /100ml [high protein supplementation]?

Response: We added additional information on our unit policy on the use of HMF FM 85. The text now reads as follows:

“…In cases of fluid restriction (total fluid intake < 150ml/kg/d), the dosage of the multicomponent fortifier was increased up to 7.5% (equal to 1.5g protein and 27kcal per 100 ml) in both periods. At discretion of the attending neonatologist, the dosage of multicomponent fortifier was also augmented in infants showing persistently faltering growth.”

Lines 97 – 100 in the clean copy of R1

4. Results would be easier to understand if they too were presented in a table. This could be same table as biographic variables

Response: We appreciate this comment and added major results to the new table 1 comprising biographic details as well.
Minor essential revision

Abstract:

Background and aims:
5. Line 32 - may not meet all nutritional needs

Response: We rephrased the sentence accordingly it now reads as follows:
“Fortified human milk may not meet all nutritional needs of very preterm infants.”
Lines 33 - 34 in the clean copy of R1

6. Line 33- Early transition from complementary parenteral nutrition to full enteral feeds

Response: We modified the sentence as suggested:
“Early transition from complementary parenteral nutrition to full enteral feeds might fur-
ther impair in-hospital growth.”
Lines 34 – 35 in the clean copy of R1

Methods:
7. Line 38- interquartile range preferred to [25th/75th percentile] . Alternatively use term
interquartile range and insert[25th/75th percentile] for first time use only

Response: We inserted the term interquartile range as preferred by the reviewer and
presented data in the text and table accordingly.

8 Line 47 – insert p value 0.07

Response: We rephrased the sentence; the p-value of 0.017 is included. It now reads as
follows:
“Standard deviation score for weight from birth to day 28 decreased more in infants with
a cumulative human milk intake >75% of all enteral feeds (-0.64(-1.08-0.34)) compared to
those with <25% human milk intake (-0.41(-0.7-0.17); p=0.017).”
Lines 43 - 46 in the clean copy of R1

9. Lines 47-49 - there is a double negative in this sentence .Change line 11 to ... intake,
either at d 28 or at discharge

Response: We shortened the sentence as follows:
“In contrast, we observed no significant difference for HC growth.”
Lines 47 – 48 in the clean copy of R1

Introduction:
10 -Line 63-64 – delete cumulative human milk intake [described as .With this excluded
meaning is just as clear.

Response: We rephrased the sentence as follows:
“We consequently investigated the relationship between the proportion of cumulative total enteral feeding volume administered as breast milk and early postnatal growth in a cohort of very preterm infants after early transition to full enteral feeds.”

Lines 64 – 66 in clean copy of R1

**Patients and Methods:**

11. What techniques were used for weighing and measuring HC? Which birth weight and HC charts were used? What is LMS growth?

Response: We complemented the text as follows:

> From birth to discharge, weight was measured daily with electronic scales and frontooccipital head circumference (HC) weekly with a measuring tape. Standard deviation scores (SDS) for weight and HC were computed using LMSgrowth (version 2.14; www.healthforall-children.co.uk). The reference population was the British 1990 growth reference [9, 10] fitted by maximum penalized likelihood as described before [10]. To account for the impact of intrauterine growth restriction, SDS-differences (SDSdischarge – SDSbirth) and (SDSd28 - SDSbirth) were calculated to illustrate in-hospital postnatal growth.

Lines 109 – 115 in clean copy of R1

**Results:**

12. Presumably babies who’s proportion of human milk was>75% had mothers who produced EBM earlier but did they reach full enteral feeding more rapidly?

Response: There was no difference in time to full enteral feeds (see new table 1).

**Discretionary Revision**

**Introduction:**

13. Line 60- it is not clear what is meant by consecutive in this context .Consider substituting with a different word

Response: We rephrased the sentence as follows:

> “This is most probably caused by intra- and interindividual variability of human milk composition resulting in deficits in macro- and micronutrient supply in some infants [7].”

Lines 60 – 62 in clean copy of R1

**Patients and Methods**

14. Line 75 – Please confirm that study population had to be both gestational age<32 weeks plus birth weight <1500g not either or . There is no recognised term for gestational age<32 weeks plus birth weight <1500g .I would prefer to call them very preterm infants rather than VLBI. Add non- consecutive 3 year study 2006,2007 and 2010

Response: Yes study population was actually both gestational age <32 weeks and birth weight <1500 g. We agree with the reviewer that there is no recognized term for this population and changed the term VLBI to very preterm infant in the text as preferred by the reviewer.

We rephrased the 1st sentence of the method section as follows:
“This retrospective, non-consecutive three year cohort analysis was performed at Tuebingen University Children’s Hospital.”
Lines 69 – 70 in clean copy of R1
(The years 2006, 2007 and 2010 are referred to later in the method section describing the patient population.)

Results:
15-Line 125 - insert p value
Response: We added the p-value as suggested, the sentence now reads as follows:
“The incidence of necrotizing enterocolitis was 3.6% in the group receiving > 75% human milk and 5% in the group receiving < 25% human milk (difference not significant, p=0.33).”
Lines 140 – 142 in clean copy of R1

Discussion:
16- Line 135 - add significant drop in SDS for weight and non-significant drop in HC
Response: We rephrased the sentence as suggested:
“Following early transition to full enteral feeds with predominantly fortified human milk, we observed a significant drop in SDS for weight and a non-significant trend towards lower HC during the first four postnatal weeks, with the majority of infants returning to their growth trajectories until discharge (fig. 1).”
Lines 151 – 154 in clean copy of R1

17-Line 136- to their growth trajectories
Response: We rephrased the sentence accordingly it now reads as follows:
“…with the majority of infants returning to their growth trajectories until discharge (fig. 1)”
Lines 163 – 164 in clean copy of R1

18-Line 138- 140 - new results should be in results section not discussion for first time
Response: We agree with the reviewer. The above mentioned results were (Original version) and are (R1) mentioned for the first time in the result section (see lines 132- 134 in clean copy of R1:
"SDS-difference for weight from birth to d28 was significantly more negative with >75% cumulative human milk intake in comparison to the group receiving <25% human milk (Fig. 1, p=0.017))

19-Line 145- remove remarkably
20-Line 147- both at d 28 and at discharge
Response: We rephrased the sentence accordingly:
“In contrast to the observed differences in weight gain, no significant difference was observed in head circumference growth with different proportions of cumulative human milk intake, both, at d 28 and at discharge.”

Lines 161 – 163 in clean copy of R1

Discussion:
21-Line 160 - Future studies are required to show

Response: We rephrased the sentence as suggested by the reviewer
“Future studies are required to show whether this potential protein deficit is best prevented by standardized supplementation with more protein given to all infants fed human milk, or via individual fortification of human milk after milk analysis.”

Lines 174 – 176 in clean copy of R1

22-Line 167- Additionally the cohort included
23-Line 168- who are at the highest risk
24-Line 169- faltering growth is preferred to growth retardation

Response: We changed our phrasing accordingly. The sentences now read as follows:
“Additionally, the cohort included a high proportion of extremely immature infants who are at the highest risk of faltering postnatal growth.”

Lines 181 – 183 in clean copy of R1

Figure :
25-Consider adding the following ; Horizontal line – no difference
DOL is day of life
-x-Median All - could be .....x.....
Box and whiskers is point estimate and interquartile range

Response: We complemented the figure as suggested

Reg S Sauve:

I think most of my suggestions are in the category of discretionary reviews - I would find it better to read this manuscript if there was a table of basic/demographic characteristics and it would be better if they would say why these cohorts were separated in time.

Response: We complemented a table of basic/demographic characteristics (table 1) The initial study (see Ref. 8) aimed at evaluating the effects of different enteral feeding strategies after changing unit policy with regard to enteral feeding advancement. Because there was a transitional period after introducing the new feeding guideline (2008/09) data was collected 2006/07 (old guidelines with slower enteral feeding advancement) and 2010 (after implementation of new guidelines).

To clarify this to the reader we complemented the description of the methods as follows:
“The initial study [8] aimed at evaluating the effect of accelerated enteral feeding advancement on the time to full enteral feeds. As there was a transitional period (2008/09) after implementation of the new feeding guidelines, data was collected for two cohorts: infants born in 2006/07 and in 2010.”

Lines 75 - 78 in the clean copy of R1.

Methods: I have some issues with the Methods section. The population includes two types of infants – those whose birth weight was <1500g and those whose gestational age was <32 weeks. While most probably overlap these two categories, I do not see enough basic descriptors of the population to be sure about that.

Response: We appreciate this concern and added a table (new table 1) with further description of basic variables and main outcomes.

Also, there are three yearlong cohorts born 2006, 2007 and 2010. I know that in their previous study they compared 2006 & 2007 cohorts vs that from 2010 but for this study, why not 3 sequential years?

Response: please see our response to the first comment of this reviewer.

Further the end point of this study is discharge – I am not clear whether the infants were discharged at close to the same chronologic age or whether there were discharge weight criteria etc. It might have been better to follow to a certain age even if that was reached before or following discharge from hospital.

Response: There was no weight or PMA criterion for discharge. To allow for variable postnatal and postmenstrual age at discharge, we chose to compare differences in standard deviations scores (SDS). The comparison of SDS permits a comparison for growth at different postmenstrual / postnatal ages (e.g. at discharge). We added the information on age at discharge into new table 1.

Soundness of data: I think in general the data and data analysis seem good but inadequate descriptions of the population make this difficult to gauge. I am not sure why they omitted data on linear growth.

Response: We hope that table 1 contributes to definite judgement of the soundness of our data. To clarify why linear growth was not reported, we inserted the following comment: “Data on linear growth were not reported due to the poor reliability of length measurements in the routine neonatal intensive care.”

Lines 116 – 117 in the clean copy of R1.

Limitations? There is a sentence re limitations – retrospective observational single center study – but I think there are a few others as mentioned above.

Response: We inserted a sentence:
“The fact that we do not report linear growth data because of potential poor reliability and that non-consecutive years were evaluated may also be perceived as limitation.”

Lines 183 – 185 in the clean copy of R1.

We appreciate your consideration and ask you not to hesitate to contact us if we can provide any additional information.

With kindest regards,
sincerely,

Axel Franz
(Corresponding Author)