Author’s response to reviews

Title: Growth of extremely low birth weight infants at a tertiary hospital in a middle-income country.

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Author’s response to reviews:

If the following concerns can be addressed successfully in a revision, then I believe the paper should be published in BMC Pediatrics.

Methods

1. Could the authors explain why they decided to restrict the inclusion of patients to those born between Jan/15 and Mar/17? Given that one of the study limitations mentioned by the authors is the sample size, it would be important to explain why the rest of the data in REDCAP was not included in this analysis.

Before January 2015 the record keeping department at Charlotte Maxeke Johannesburg Academic Hospital did not include the daily infant feeding charts in the computerized filing system. This precluded the use of data before January 2015. This study was designed to follow up the infants up to 12 months corrected age hence data beyond March 2017 was excluded at the time of proposal submission. However, only a few infants returned at 12 months corrected age for follow up. Therefore, this latter part of the study could not be conducted.

2. Were there data available for length and head circumference at birth and discharge? It would improve the paper if those two figures (and the mean delta Z-scores for the 92 infants) could be included in the description of these infants.

Whilst birth length and birth head circumference are available, at discharge this data is not available.
3. The definitions of "good growth" and "poor growth" according to the selected cut-offs for time to regain weight and weight velocity should be moved to the statistical analysis section.

This has been done in section 2.6.

4. The list of statistical tests used does not specify what groups are being compared. This is particularly important for the associations between complications of prematurity and poor growth.

5. Are all quoted p-values for two-sided tests?

Yes.

6. If possible, provide a justification for statistically testing a difference between the observed mean weight values in the study and the expected weight value of the Fenton Chart, a smoothed growth curve generated to be a reference. It is not a commonly reported analysis, and in this study p-values are not necessary to show the more than clear separation of the curves over time. Still, if the authors decide to keep the tests in the manuscript, they should explain how the weekly weights were compared to the expected value of the Fenton charts, how the "various intervals of post-menstrual age" were selected for the different comparisons, how the values were aggregated within each time interval, and give a reference to the paper that provides the values (N, mean, SD from the Fenton chart) that were used for the statistical testing (assuming the t-test was the preferred test).

We have removed the statistical analysis testing the difference between the observed mean weight and Fenton Growth Chart over selected time intervals.

Results

7. For the 42 infants with "missing records" that were excluded from analysis, was any information available? Any potential bias by not including them?

These infants did not daily infant feeding charts in their computerized records file.

8. It is not mentioned in the text how many infants out of the 92 included in analysis were discharged before 36 postmenstrual weeks, and at what average postmenstrual age they were sent home.

This information has been added in section 5.
9. Was there any information available about breastfeeding for the patients in the study? How many infants were exclusively/predominantly breastfed at hospital discharge?

This information has been added in table 2.

10. Please report all p-values to the third decimal place.

This has been corrected

11. The description of the sample characteristics should include the number of infants in the "poor growth" and the "good growth" groups (both in the text and in Table 1).

This information has now been added in Table 4 and section 3.2 and 3.4

12. The section that describes the difference in weight Z-score from birth to 36 postmenstrual weeks could be made clearer.

The mean birth weight Z-score should be reported in the main text (not only in Table 1).

The mean delta Z-score for weight from birth to 36 postmenstrual weeks is reported to be -2.1 (SD 1.0), which was a statistically significant difference (p-value <0.01); however, all delta Z-scores in Table 3 are positive, which seems contradictory.

Birth Z-score has been added in section 3.2. Table 4 has been corrected.

13. In the section describing results from the weight comparison against reference charts (page 10), the text should specify that the "50th centile line" refers to the Fenton Growth Chart.

This is now specified (section 3.2)

14. The section that describes the associations between complications of prematurity and poor growth needs improving.

The results should specify that the comparison was done between the group classified as "poor growth" and the group classified as "good growth" (if that is the case as Table 4 suggests); the term "poor growth parameters" is unclear on whether weight velocity and time to regain birth weight were evaluated separately.

Sections 2.6 and 3.4 have been amended.
Discussion

15. The authors affirm that the postnatal growth of ELBW infants should approximate the intrauterine growth rate. This is a concept that has been challenged in the last few years (1), and the mention of the evidence, or lack of it, to back up this basic assumption, particularly in ELBW infants, could enrich the discussion.

We have now expanded the discussion to include this.

16. Even more relevant is the discussion of choice of reference chart for monitoring postnatal growth. The authors chose the Fenton weight chart, which is a tool that has been previously recommended for this purpose, but has certain limitations that may need to be acknowledged (i.e. data/methods used for the construction of the charts, population selection, etc.). In this study, the majority of ELBW infants showed inadequate linear growth. It would be interesting to see if the same conclusions are reached by estimating the delta Z-score using a different tool, given that it has been shown that the instrument may determine the inference of a comparison (2). Reporting the Z-scores estimated with other charts (particularly those adopted internationally) would increase the comparability of evidence with other studies.

Intergrowth 21st Project growth standards have been added to the article

17. Please provide some context to the studies mentioned in the discussion. For example, the term "uncomplicated hospital" used for the paper from Dejhalla et al could be improved; it would be more relevant to provide information of the type of setting, number of participants, type of participants in the study, etc.

This has been done in the Discussion

18. Section 5 on study limitations should be extended to include the strengths of the study.

Strengths have been added

Some stylistic and formatting changes are suggested below.

Abstract.

19. Page 2; Methods. Please prefer the word "association" to the word "effect" to avoid inferring causality.

This has been corrected
20. Page 2; Methods. Remove the word "normal" to define the number of days to regain birth weight used as criterion for defining good growth parameters.

This had been corrected.

21. Page 2; Results. Suboptimal nutritional intake is listed as a factor associated with poor growth parameters, but the main text only presents associations with weight velocity.

This has been corrected.

Methods.

22. Page 7. Please provide full terms for the NCPAP and RDS acronyms.

Full terms have been provided

23. Make sure that all acronyms are defined in the first appearance of the term in the text.

This has been done.

Results.

24. Table 1. Why is the first column of the table providing daily requirements? Was this information used for the estimation of caloric intake?

Daily requirements were quoted so that the results can be interpreted in this context. The title of the table has been renamed to make it more appropriate for the contents.

25. Table 2. Being gender a binary outcome, the frequency of only one sex can be presented (making more efficient use of the space in the table); all acronyms used in the table should be explained in a footnote; all numerical values in the table should be reported with the same decimal precision; make sure that there is a space between the first number and the opening bracket for all cells presenting numerical data; remove duplicated headings (i.e. the word "variables"); the term "sampled infants" used in the title of the table could be improved.

Only the frequency of females has been presented. All non-integers have been corrected to 1 decimal place. The title has been changed to “characteristics of sample population”
26. Table 3. Should specify that mean weight velocity was calculated from the date birth was regained to 36 postmenstrual weeks in a footnote.

This has now been specified

27. Table 4. The table is confusing, and casts doubts on how the association tests for the complications of prematurity were carried out. All neonatal characteristics are binary (yes/no) variables. It is not entirely clear in the paper, but the poor and good growth groups seem to be mutually exclusive groups with N=25 for "good growth" and N=67 for "poor growth". For this kind of tabular data, correlation analysis is not the correct statistical test to perform. This table needs to be modified to reflect adequate comparisons, explaining in a footnote what test the p-values correspond to, and reporting percentages and p-values in a standard manner.

The statistical test performed has been specified, p values expressed to the third decimal place and correlational analysis replaced by odds ratio.

28. Figures 1 and 2. Should specify if the weekly weight is presented with confidence intervals (at what level), standard deviations, or standard errors. The symbol legend should specify that the 50th centile corresponds to the Fenton Growth Charts. It would be informative to also plot the 10th centile of Fenton's Growth chart. The number of weight values averaged at each gestational week for the study curve should be presented at the bottom of the plot. Please capitalise the word "weight" in the title of the y-axis.

This has been done. Intergrowth 21st Project growth centiles lines have also been added. Postmenstrual weeks with less than 5 patients have also been excluded from the graphs.

29. Legends for figures 1 and 2. The word "next" could be changed to a word that reflects the two curves are overlapping, not one beside the other. It is not correct to refer to values of the Fenton Growth Chart as another group to compare against.

Legends reworded

30. Figure 3. The box for the fourth subgroup (bottom) should say "<15" instead of ">15". This figure would be more informative as a table with four columns that shows the mean growth parameters for each of the subgroups, including a row for the N (%) of infants in the subgroup with weight discharge >10th centile. If data on length and head circumference are available, this is where it should be presented as well as the mean weight Z-scores estimated using other charts (i.e. the INTERGROWTH-21st standards for size at birth and preterm postnatal growth).

Figure 3 had been modified into table 3
31. **Figure 4.** Similar formatting issues like figures 1 and 2. The number of observations averaged at each gestational week should be presented.

Figure 4 has been removed because the addition of Intergrowth 21st Project growth standards would require 2 versions of the same graph. Furthermore, essence of the graph is adequately represented without it.

32. **Legend for figure 4.** Please define "poor discharge weight".

Figure 4 is now removed

References


Camilla Menis (Reviewer 2): In this manuscript the authors analyse the pattern of growth of the extremely low birth weight infants and describe the nutritional intakes and the nutritional procedures of their unit. Their aim is also to try to find out the possible improvement in the clinical approach of the preterm babies. This paper is interesting because we still do not have much information about the nutritional management, the growth and the comorbidities of preterm babies in in South Africa in the literature. The results are consistent, and the study has important implications in the clinical practice. However, there are some sections that can be improved.

**Background:**

In the reference n.4 in the paper mentioned the authors concluded that growth deficiency or failure to thrive is a common clinical condition in the follow-up care of LBW infants and that worse cognitive and growth outcomes were observed for those meeting the restrictive case criteria employed in this study. Please change the comparison of ELBW with normal birth weight infants.

This has been corrected
In the reference n.10 it can be better to separate the issues of parenteral and enteral nutrition maybe finding out another reference for the enteral.

Another reference for barriers in enteral feeding has been added.

In the reference n.13 it will be interesting to describe with more details the internationally acceptable standard.

This statement has been reworded to “generally accepted standard” since there is no agreed guidelines specifying minimum growth velocity.

It can be interesting to mention The Intergrowth-21 standards.

These are now included in the article.

Material and Methods:

In the aim of the study the macronutrient intake must be mentioned.

This has been done.

This work used the Fenton's Growth Chart as reference: The Intergrowth-21 standards can be more appropriate for the population assessed.

Intergrowth 21 standards now part of the study.

Please define the Delta Z-score and the calculation made to obtain it.

This has been done.

Please clarify the formula of the daily caloric intake.

We have clarified that the figure 1000 represents the conversion of weight in grams to kilograms. The other parameters are explained.

The complications of prematurity must be defined and supported by adequate references: ROP, Late onset sepsis for example.

This has been done. Definitions of prematurity complexes was based on the Vermont Oxford Network.

The electronic scale must be described.

This has been specified.
The statistical analysis is not solid enough and needs to be modified in the assessment of growth and in the association of growth with complications.

Statistical analysis has been broadened to and now includes associations derived from Intergrowth 21st Project standards.

Results:

The "growth" section needs to be modified: the comment of figure 1 and 2 is not clear and the subsequent part is not solidly supported by the analysis.

The section on growth, figures 1 and 2 have been modified.

In the "nutritional intake…” session two elements are not clear: the percentage "thirty-four infants (37%)" as well as "full enteral feeds was 12.1 days".

This has been clarified.

It can be more appropriate to add a table with the mean macronutrient and caloric intake with the weekly and the 28 days values.

It would be good to add the table, however we tried our best to report in such a way that its would be comparable with other studies, especially the ones we referenced, and also trying to make the paper as reasonably sized as possible.

The session "complications of prematurity" together with the correspondent part of the statistic analysis need to be elaborated.

The session has been expanded to include comparisons and associations derived from Intergrowth 21st Project growth standards and the Table 5 has been adjusted.

Discussion:

It's imperative in the discussion to be more exhaustive in the comparison between the results of this study with the results of the previous studies already published. This must be supported by solid references.

Comparison with previous studies have been expanded and studies referenced put in context.

Conclusion:

The antenatal steroids are not mentioned in all the work and also the need of more CPAP in not correlated with the aim of the study that is focused on nutrition.
Antenatal steroids are now mentioned in the section on Prematurity complications and also in the discussion. The need of more CPAP was put in the study to assess association with growth.