Reviewer’s report

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

Version: 0 Date: 22 Jan 2019

Reviewer: Eleonora Staines Urias

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Manuscript Number: BPED-D-18-01115

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

22/01/2019

The above manuscript reports the findings from a retrospective cohort study that aimed to describe the growth of 92 extremely low birth weight (ELBW) infants up to the age of 36 postmenstrual weeks born between 01 January 2015 and 31 March 2017 at the Charlotte Maxeke Johannesburg Academic Hospital in South Africa. Weight velocity and caloric intake were estimated for all infants; postnatal growth was evaluated comparing to the Fenton Growth Charts. The authors differentiated between infants with "good" and infants with "poor" growth, and conducted statistical tests to assess the association of neonatal characteristics and poor growth.

The work in this manuscript represents a valuable contribution to the study of a phenotype that has been infrequently reported in low- and middle-income countries. The study sample is very well characterised in terms of occurrence of adverse clinical outcomes relevant for preterm and ELBW infants, and the evaluation of neonatal nutrition and growth outcomes followed international recommendations for the standardisation of the study of preterm postnatal growth. The paper, however, could be clearer along several lines, improve some presentation aspects, and add relevant topics to the discussion. While a lot of detail is provided about the nutritional evaluation of the study sample, the statistical methods and reporting of results need improvement.

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.

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.

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.

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?

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).

**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?

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.

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

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

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).
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.

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.

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.

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.

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.

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.

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

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.

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.

Methods.

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

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

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?

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.

26. Table 3. Should specify that mean weight velocity was calculated from the date birth was regained to 36 postmenstrual weeks in a footnote.

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.
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.

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.

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).

31. Figure 4. Similar formatting issues like figures 1 and 2. The number of observations averaged at each gestational week should be presented.

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

References


Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
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