Author's response to reviews

Title: Comparing the growth of preterm infants through the gestational period of 37 to 50 weeks with the reference fetus

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Version: 3 Date: 11 January 2013

Author's response to reviews: see over
Response to Reviewers
We wish to thank each of the reviewers for their time, expertise, and assistance.

Comparing the growth of preterm infants through the gestational period of 37 to 50 weeks with the reference fetus and term infant

Version: 1 Date: 29 October 2012
Reviewer: Shripada Rao
Reviewer's report:
The authors have compared the postnatal physical growth of a large sample of preterm infants (born at 23-31 weeks gestation; between 2001 and 2010) to the new (to be published) Fetal-Infant growth reference charts (Fenton 2012). They also have identified secular trends in the postnatal growth of preterm infants by comparing the data from study population to those born between 1994 and 1995 (NICHD).
Their main findings were
a. The median weight growth curves of the preterm infants remained between the 3rd and the 50th percentiles of the FIGR from birth through 10 weeks post term.
b. Immediately after birth, preterm infants grew more slowly than the fetus
c. Preterm infants grew more rapidly than the fetus between 37-40 weeks PCA.
d. Preterm infants born in 2001-2010 had better growth velocities compared to those born in 1994-1995.

Major essential revisions:
1. Certain paragraphs in the manuscript will need to be reworded to make it easily understandable to clinicians. Eg: Introduction, paragraph 5: “The objective of this study was to observe weight gain patterns of preterm Infants and to compare this growth with a meta-analysis estimate of fetal and infant growth, to inform the revision of the Fenton growth chart”. The meaning of this sentence is unclear to me. “To inform the revision of the Fenton growth chart” needs to be deleted from this sentence.
Response: Thank you very much for your helpful review. This suggestion has been followed.

2. Introduction, paragraph 5: “We expected the growth during the initial postnatal period to be inferior compared to the fetus, and the period between 37 and 40 weeks to be superior since the growth of preterm infants is not constrained by the placenta at this latter age”. This is the author’s hypothesis and hence does not fit well here in the objectives section. Also the sentence is a bit difficult to understand at this stage of the manuscript.
Response: Based on your comment and Dr. Sauer’s, we have omitted the hypothesis.

3. Methods, first paragraph: “For the purposes of comparison for this study, a fetal-infant growth reference (FIGR) was generated based on a systematic review of the literature”. If the FIGR was generated for the purposes of this study, the authors will need to give more details of the FIGR. If not they could say we compared the postnatal growth of preterm infants born in three North American units to the “to be published FIGR” and quote ref 21 and describe briefly the updated FIGR.
Response: Thank you for this helpful suggestion.

4. Methods section, second paragraph:
Please add details of feeding practices of these units (enteral and parenteral, such as dose and type of amino-acids and lipids, rate of increment, enteral feeding, fortification etc).

Response: Good idea, now included as Table 2.

5. Results, first paragraph:
“The infants in the oldest gestational age category had a high rate of small size for gestational age and a low rate of being large for gestational age, likely since the entrance criteria for post-discharge follow-up in Calgary favoured infants less than 1250 grams at birth”.
The authors need to point out the limitations of the retrospective nature of their study in the discussion.

Response: Done

6. Results, paragraph 2:
“The median weight growth curves of the preterm infants in this study superimposed on the FIGR curves generally placed between the 3rd and the 50th percentiles (Figure 1)”. The authors could discuss the possible reasons behind the fact that even though growth velocities were better than FIGR, still the postnatal weights were below the 50 centiles of the FIGR.

Response: Recognizing that the Figure showing the median growth of each cohort is not clear how it summarizes the growth patterns of the individual babies, we have now included these individual patterns as a new Figure 1, and the median curves are now Figure 2. We were surprised to see the median curves to be so similar between the 3 cohorts.

7. Tables:
Table 2: Please mention stage of NEC. I suppose they were stage 2 NEC.
Please give the definition of bronchopulmonary dysplasia
Table 3 missing. I think there are only four tables and they need to be rearranged.
Table 4: Weight z--scores and percent of “study” infants weighting less than the 10th percentile.
Table 5: The plus minus symbols need to be carefully observed and rewritten where needed. Eg: while comparing the growth velocity between 40-50weeks with the FIGR, the study infants had higher growth velocities than FIGR, but the differences are written with a minus symbol. They should carry a plus symbol. While comparing the growth velocity between 40-50 weeks with the WHO growth standards, the study infants had slower velocity compared to fetal infant estimate, but the differences are not written with a minus symbol.

Response: Thank you for these suggestions and for noticing the minus symbol error. These things are now corrected. We have replaced BPD with the two common definitions, use of O2 to 36 weeks and to 28 days, to be as clear as possible. We apologize for the Table numbering error.

8. Figures: All figures need title, legend and a brief interpretation. At present, it is not clear what the percentiles on FIGR are, Is it 97, 50 and 10? Legend for figure 1: Median growth patterns of the 24 (dot), 27 (dash), and 30 (dash dot) week preterm infants superimposed on the Fetal-Infant Growth Reference, “which was based on a 6 country meta-analysis of intrauterine growth (22 to 40 weeks) and the World Health Organization Growth Standard (40 to 50 weeks)” can be deleted. Same for figure 4 legend.

Response: Thank you for the other suggestions, which we have completed.

Minor essential revisions:
1. Page 4, second paragraph: line 3: daily weight for first 21 “days”
Response: Done
2. In some places it has been labelled as 7 country meta-analysis
Response: Done

Discretionary revisions:
1. Out of interest, does the FIGR need to have separate charts for males and females? This is purely for my understanding of the subject rather than suggestion to the authors. The WHO 2006 has separate charts for males and females.

**Response:** We plan to do some more analyses regarding the effect of sex, small size for gestational age, morbidities, and nutrition support but elected to keep this paper focused on the overall growth patterns.

2. Methods section, second paragraph:
   “These neonatal units have provided early nutrition support (parenteral nutrition started on the birth day or day one of life for most of these infants) since 2005”. It will be interesting to see if the cohort of infants born between 2005 and 2010 had better growth velocities compared to the cohort before 2005. The authors may want to consider it for future if not for this publication.

**Response:** We will consider this good idea for future publications.

3. Tables: Instead of calling it as “6 country meta-analysis”, it is better called as FIGR-2012.

**Response:** Done, except as the FIGR-2013 as it is now a new year.

**Reviewer:** Pieter Sauer

**Reviewer’s report:**

In this paper the authors present data on weight gain of infants cared for in Calgary, Regina and san Diego. They compare their data with growth curves developed by the first author, but not yet published. The authors conclude that the infants do not follow the dip in growth that is found in the present growth curves and secondly that these infants show a better weight gain compared to cohorts a decade ago. Although this topic is interesting, I have a number of concerns.

1. It is unclear to me what is the hypothesis or question raised in this paper, what do the authors want to answer?

**Response:** Thank you for your careful review and questions. We have omitted our hypothesis and hopefully clarified our objective.

2. In this paper weight gain is considered equal to growth, while real growth is gain in length and head circumference, but those data are not provided.

**Response:** We have changed the word “growth” to weight gain as appropriate.

3. Weight gain is compared with curves constructed by the first author but not-yet= published, so not to evaluate.

**Response:** We submitted the papers together. So that this paper can stand alone, we have noted the “to-be-published” status and included the reference to the companion paper.

4. The authors seem to neglect that present I.U. and E.U curves are based on cross sectional data, these apply not to longitudinal growth data. It is known for a long time that the "dip" found around 37-40 weeks in curves is artificial, due to the cross sectional data.

**Response:** We agree with you that some of the dramatically slowed velocity seen in older intrauterine data (for example Alexander 1996 where the 90th percentile 32 week weight was 3200 grams, while in comparison the FIGR 90th percentile 32 week weights were 2220 for girls and 2300 for boys) was likely due to misclassification of some term infants as preterm infants, as was noted by Kramer et al 2001. However, all studies that met our strict inclusion criteria to be included in the FIGR meta-analysis demonstrated the flattening of velocity close to term, especially at the upper centiles. This effect persisted even though these studies were all based primarily on gestational age confirmed by either ultrasound or neonatologist assessment.

5. In the title the reference fetus is mentioned, but there is no comparison with the reference fetus.
Response: We are proposing that the FIGR is an estimate of the weight pattern of the reference fetus.

6. the authors do not provide data to show that weight gain in their cohort is better compared to cohorts a decade ago, so no conclusion in this direction can be made.
Response: We have now conducted a more in-depth comparison of the growth patterns of these two studies (Table 6), although our conclusions must be limited because of differences between the studies, in the proportions of SGA infants, and the use of different references to determine size for gestational age. We decided to compare the average curves (instead of the previous use of our median curves) of our study cohorts with the NICHD study, since the NICHD reported the average curves. Since the NICHD paper did not report a measure of variation from the NICHD cohorts, it is not possible to compare the weight gain (g/kg/d) results statistically. We were able to compare the age when birthweight was regained. We hope this analysis helps.

7. the weight z-score of the infants at 37, 40 and 50 weeks show that 35-65% of the infants have a weight < 10 perc, compared to 11% at birth, indicating a rather poor weight gain.
Response: We agree and are not claiming that these infants were ideal in terms of nutrition support or growth.

Reviewer: David Tudehope
Reviewer's report:
Major Compulsory Revisions
1 Authors previously submitted a paper on A revised Fenton growth chart for preterm infants "developed from a meta-analysis of many charts and used charts from 6 countries to prepare FIGR." Readers need to understand the genesis of this chart and are given too little information in this paper. Even though it involves data from 6 countries chart is a growth reference not a growth standard and involves cross sectional birth weight data. Which countries?
Response: Thank you for your careful review and questions. The countries: Germany, Italy, USA, Canada, Australia, and Scotland. The reference to the development paper is included and we have added more information about the FIGR.

What centiles are represented on Figure 3?
Response: Figure 3 (now Figure 4) represents the differences between the median current preterm infant cohorts and the FIGR, and thus a way to demonstrate the difference between the preterm weight gain velocity from the calculated Median weight gain velocity of the FIGR. We hope our legend is clearer now.

From what gestation was WHO data added?
Response: We used the WHO data from birth to 10 weeks after term.

2 Title of this paper is misleading - "reference fetus from 37-50" weeks doesn't make sense. Surely title needs reference fetus and infant not just reference fetus as chart involves WHO data from ?40 weeks.
Response: Good point, thank you.

3 There is no table 3 submitted. Legend for figures provides insufficient description
Figure 1&4 – centiles of FIGR curves not provided Figure 2 – why does dot curve [23-25 weeks] start at 28 weeks rather than 25 weeks? Figures 3 – once again why does dot curve start at 28 weeks if it begins 2 weeks after birth? Figure 4 – presumably red dots are NICHD and blue dashes are 3 NICUs in Canada and USA but is unclear and also unclear for 24,27 and 30 week cohorts
Response: For Figures 2 & 3 (now 3 & 4), we thought the early low velocity was distracting (especially since it bounced around as the data was combined between 3 individual weeks (e.g. as the 24 week infants were added to the 24 week cohort of the 23 weekers, the mean weight increased, not due to
growth of the 23 week infants), but have now included the low velocity beginning now one week greater
than the category label. For Figure 4 (now 5) we have tried to make it clearer which cohorts are the
NICHD and which are the current study.

Minor Essential Revisions.
1 The challenge of providing a chart to plot post-natal growth [longitudinal ] of preterm infants has also
been taken up by INTERGROWTH, which is not referenced in this paper. INTERGROWTH are
collecting longitudinal data of highly selected preterm infants from 23-36 weeks to plot a growth
standard[prescriptive curve ] .This alternative approach should be acknowledged in introduction and/or
discussion
Response: Done.

2 It is correct to state that preterm infants 23-31 weeks gestation managed in 3 NICUs in Canada and
USA had early nutritional support with TPN on day 1 of life. However, later nutritional support or
aggressive nutritional support [Ziegler’s terminology] was lacking e.g minimal enteral feeding starting on
days 2.7-7.4 days, enteral feeds 6.6-16.7 days and full feeds 17-34 days are not consistent with current
nutritional standards. Data from table 2 on Fortified breast milk are unclear. Does this mean % of
babies who received any fortified breastmilk [mothers or donor] or the % of breastmilk fed infants who’s
breast milk was fortified?
Response: Good points, thank you. We agree that these babies did not receive care that would be
described as ideal. We have added this point into the discussion. We have clarified that fortified
breastmilk refers to the percent of babies on fortified breastmilk as the majority of their feedings while in
hospital, and included more information on their feedings.

3 Data on size for gestational age [only SGA] based on FIGR are included on table 4 [not referenced]
Response: Now referenced.

4 The better reference for readers to understand the genesis for fetal growth in /Kg/d is provided by
Response: We have now included this reference.

Respectfully submitted,

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