Reviewer’s report

Title: The Role of Nutrition in Promoting Growth in Preterm Infants with Bronchopulmonary Dysplasia: a Prospective Non Randomized Interventional Cohort Study

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Reviewer: Arieh Riskin

Reviewer’s report:

General comments (major compulsory revisions):

This study’s hypothesis was that feeding high enteral energy intake to preterm infants with BPD would improve postnatal growth. The researchers have shown that the infants with mild, moderate and severe BPD in the intervention group, fed either individually tailored fortified breast milk and/or preterm formula (with additional extra carbohydrates – Duocal - and fat – MCT oil), had better weight gain velocity (but not of length or head circumference) and fewer of them presented with postnatal growth retardation compared to the historic control group, fed either breast milk routinely fortified according to the HMF manufacturer’s instructions and/or preterm formula.

Although adequate protein intake, there were no differences in protein intake between the groups, which raises a concern when it comes to premature infants growth in general, and infants with BPD specifically, as high caloric intake alone may lead to disproportionate weight gain compared to linear growth (Olsen et al. J Pediatr 2009;154: 486-91) with risk of change in body composition in favor of fat accumulation as opposed to lean body mass growth (Cooke and Griffin Ped Res 2010;67(6):660-4). No other nutrient differences, or lack of differences, are mentioned, although they should have been mentioned as well (e.g. calcium, phosphorus and vitamin D, which are so important for bone mineralization and linear growth). The enriched enteral nutrition of infants with BPD should comprise of higher energy (caloric) intake (preferably as fat and less carbohydrates within relatively low fluid intake), but this although very important is not sufficient, as these infants may also need more protein, minerals, and many more important nutrients (vitamins, trace elements, etc’) (Biniwale and Ehrenkranz Semin Perinatol 2006;30:200-8; Dani and Poggi, J Matern Fetal Neonatal Med 2012;25(Suppl):37-40). The authors should detail whether the infants in the intervention group got any other nutrient supplementation other than energy, or if they did not, refer to it, as should have been done regarding the equal protein intake that was mentioned but not fully discussed. Even if there were no differences other than caloric intake, the authors should convince us that this is should suffice. As far as I look at the limited data they provided the only difference between the intervention and the historic control groups at 36 weeks post menstrual age was in weight gain, but not in length which is a better measure of linear growth, and not in head circumference which is related to neuro-developmental outcome. Maybe the authors can provide other
anthropometric measures like skin fold or fat accumulation measures or measures of lean body mass, biochemical measures like urea (BUN), pre-albumin, calcium, phosphor and alkaline phosphatase, or measures of bone density to support their hypothesis that increased energy intake alone was sufficient. Alternatively, even respiratory data regarding better pulmonary function, shorter duration of support or supplemental oxygen requirement or decreased need of BPD medications could have helped. Actually the intervention group had a significantly higher proportion of infants on diuretics (Table 1), whether it is incidental finding or outcome measure, it should definitely have been further discussed.

In summary, the authors should provide us with more data to support their nutritional rationale, and to prove that their outcome was better than mere extra weight gain that might lead to fat accumulation without improved linear growth or other improved nutritional or disease outcomes. Extra data and analysis is needed to support this study and conclusions. If this could not be available at least a thorough discussion about these study limitations should be provided leading to the inevitable conclusion that the findings are thus more limited, and support but do not add much to the previous knowledge from the studies already done using this strategy, as the authors mention in the Discussion section (page 9, especially References 16-17).

Abstract (minor essential revisions):

In the Results paragraph please provide units for the quantitative results (e.g. days for mean duration of PN; Kcal/Kg/day for mean enteral energy intake; g/Kg/day for enteral protein intake and so on).

Background (discretionary revisions):

As discussed above, I would have addressed other increased nutritional needs of infants with BPD and not just increased energy intake.

Methods (discretionary revisions):

Could the authors provide data regarding the proportions of infants on fortified breast milk only, formula only or mixed feedings? It could be of interest in relation to the results, especially if these proportions were different between the intervention and control groups.

Results (minor essential revisions):

The term growth velocity should be avoided in this section as well as in the other sections and the Abstract. The researchers were measuring weight gain velocity as they define it on page 7 lines 140-142. The term growth velocity is confusing and may lead the reader to wrong conclusions as to the growth outcomes of this study which were only extra weight gain without any improvement in other growth measures, as discussed above in my general comments.

Discussion (major compulsory revisions):

The discussion needs to be re-written to reflect the issues that were raised in the general comments above. Study limitations should be addressed accordingly.
I would have avoided the categorical statement that “protein needs of infants developing BPD appear to be similar to those not affected by BPD” (page 9, line 191). Even Dani and Poggi (Dani and Poggi, J Matern Fetal Neonatal Med 2012;25(Suppl):37-40) who originally used this statement state that this assumption is currently appropriate because there is not much data available, but also mention that there are few other studies suggesting that these infants’ protein needs might be increased because of many causes, as discussed there.

Minor essential revisions:
Line 189 on page 9 “… that infants with BPD appear to require …” (not appears)
Line 200 on page 9 reference is [16] (not 17 as printed by mistake).
Line 206 on page 9 reference is [17] (not 18 as printed by mistake).

Tables (discretionary revisions):
Many publications nowadays prefer to provide all p-values in the tables (even those that are not statistically significant for the readers to judge).
In table 1 for 1’ and 5’ Apgar scores one decimal is sufficient, as originally these score are given even without any decimal.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests