Reviewer's report

Title: Lutein-fortified infant formula fed to healthy term infants: evaluation of growth effects and safety in a randomized controlled clinical trial

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Reviewer: Ian J Griffin

Reviewer's report:

The authors have carried out a randomized comparison of two similar formulas – one enriched with lutein, one not. Main outcomes (growth and serum biochemistry) did not differ between the groups.

The study appears to have been carefully conducted and the manuscript is easy to read.

I have a number of questions.

1. (1a) How was the study funded? I presume that the formula company paid for the study, but who designed the study, and who analyzed the data? The formula company is naturally has a stake in the results of the study, and so do the non-company employees who receive funding from the study. This is to be expected, but some discussion of how those conflicts/interests were dealt with should be discussed. Simply saying that “The authors declare that they have no competing interests” is not adequate especially as some of the authors are formula company employees or subcontractors. This does not invalidate them as co-authors, but it does lead to a conflict that must be clearly resolved.

BACKGROUND

2. Human milk may be the best reference for formula composition but it is not “the only”. Human milk content has certainly not guided the amount of minerals and vitamins added to formula, so I question whether “A goal of formula research is to mimic the composition of breast milk”.

3. How was the lutein sourced, and who manufactured it?

METHODS

4. More details of the anthropometric measurements are needed, especially of length measurement. Who did these measurement?

5. Formula intake data and visual acuity data were collected. Why are the results not presented?

6. Was the SD for weight gain (5.3) used in the power calculation seen in the real study population?

DISCUSSION

7. The first paragraph on lutein and vision can be omitted, it duplicates some of the information in the background, and no visual acuity data were presented.
8. Are there any clinical circumstances were lutein supplementation has been shown to improve growth of visual acuity?

CONCLUSION

9. No data is provided to say “fortification of S-26 Gold with lutein … supports infant growth”. Rather the results show that lutein does not interfere with growth.

TABLES

10. These need to be re-formatted. Separate lines are not needed for mean, SD, median, min and max. rather I would suggest one cell for each outcome in each group with Mean±SD (min – max).

11. Likewise a single row can be used for gender formatted as M:F or as %female (or %male). As everyone was asian, thes can be said I the text.

12. Parity and birth order are so similar, I think a single one can be reported.

13. Tables 1 and 2 can be changes so one has the infant/ mother charclearistics, and one has the study disposition.

14. Table 3 – results can be given in the text.

15. What is the exact p-value for the group comparison?

16. Why is a 90% confidence interval given when a 95% CI is more common?

17. Table 4. This table is not helpful as currently presented. I would like to see
   a. The exact “normal” ranges used
   b. The mean±SD (min-max) in each group, and an exact P-value.
   c. Why is “above normal” and “normal” the only data given, what about “below normal”?
   d. An analysis to see if of the distribution was different between groups when characterized by above normal/ normal/ below normal would be helpful, as this is more how results would be considered in a clinical setting.
   e. Of critical importance is who determined what were “normal” ranges were? What information was this based on, and was this decided before or after data the study started? This should be discussed in the text

FIGURES

18. Figure 1: Narrower vertical scales are needed, some measure of the variability of the data as error bars, and points showing outliers whose growth was more or less than 2SD from the population mean are needed.

19. Figure 2. Again, the figures need re-scaling, and outliers should be shown

20. Figues 3&4 were difficult to read. I would suggest that the centiles be shown as broken lines without symbols, and the study data as symbols and solid lines

Major Compulsory Revisions

1a

1b
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