Author’s response to reviews

Title: Reduced Crying in Term Infants Fed High Beta-Palmitate Formula: A Double-Blind, Randomized, Clinical Trial

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Author’s response to reviews: see over
The Editor, BMC Pediatrics

RE: MS: 8173406141172559

Reduced Crying in Term Infants Fed High Beta-Palmitate Formula: A Double-Blind, Randomized, Clinical Trial

Dear Editor,

Thank you and the reviewers for the review of our manuscript “Reduced Crying in Term Infants Fed High Beta-Palmitate Formula: A Double-Blind, Randomized, Clinical Trial” and for the invitation to revise and resubmit. We have elected to respond to the thorough and thoughtful reviews and to submit a revised, improved version of the paper. Changes have been made in the MS in accordance with the comments made by the reviewers and editor. A point-by-point response and a revised version of the MS with changes highlighted are enclosed.

We appreciate the opportunity to resubmit this research and hope that it will now be found suitable for publication in BMC Pediatrics.

Sincerely yours,

Ita Litmanovitz, MD

Corresponding Author
_response to editor's comments:

1. Randomisation is not well described. Authors should provide details of sequence generation, allocation concealment and blinding process (who was blinded, how was blinding done and at what points in the study was blinding done).

A block randomization procedure was used for the subjects' random allocation. Using a computerized automatic randomization system, infants were randomly assigned to receiving HBP formula (forming the study group) or LBP formula (regular infant formula; forming the control group). Formulas were packed in identical and unmarked boxes, with the personnel caring for the infants and mothers being blinded to their content. The study was a double-blind, keeping the parents and doctors blinded during all study.

2. Stool variables measured included color, consistency and frequency but frequency was not stated under methods.

Added as suggested.

3. What were the reasons for attrition?

The sample of non-completers was matched to those who completed the study.

This was added to the MS

The attrition was due to:

- Control group: 5 Dropouts: 3 withdrew consent and 1 for hard stool and 1 for GE reflux
- INFAT group: 5 Dropouts: 4 withdrew consent and 1 for suspected cow milk protein allergy
- Breastfed group: 3 Dropouts: 1 withdrew consent and 2 ceased breastfeeding

If the reviewer wishes, this may be added to the MS.

4. In the tables, the parameters displayed (apart from proportions), were MEAN values and should be so stated in the text.

This is now stated in the text and tables.
5. The authors have not explained the relationship between "crying" and HBP formula intake. Why is crying better in HBP-fed infants? Does it have to do with changes in gastric emptying or stool consistency?

Several possible mechanisms for the relationship between crying and HBP formula intake are now suggested in the revised discussion.

6. It is important to explain in detail the reversal of the proportion of HBP-fed infants and LBP-fed infants with hard stools between the 6th and the 12th weeks.

This is an interesting point. It is well known that stool characteristics may change within the first weeks of life, yet the physiologic reasons for this reversal, as well as the disappearance of hard stools in the breast fed infants (from 5% to 0%), warrants further studies.
Response to Reviewer 1:

Minor essential revisions:

1. Under Results and Conclusions; Page 9; line 4 - The reference to table 2 is wrong. The information is actually in table 1.

   Thank you, corrected.

2. Page 10; line 2: The reference to table 4 is wrong as that table was not included in the manuscript. The information is actually in table 3.

   Thank you, corrected.

3. Table 1: The "harsh" signs in the first column i.e. on maternal age, gestational age and birth weight appear inappropriate.

   Thank you, removed.
Response to Reviewer 2:

1-9. Thank you.
10. ADDITIONAL COMMENTS. I have made some observations and comments in the body of the work. This is to enhance the quality of the work.

Thank you, all suggestions made in the body of the text are now corrected in the revised MS as follows:

Comment [PR1] & Comment [PR2]:
"more comfort " This is subjective. How was this to be determined? "reduced crying, and improved stool consistency " This also need to be qualified. Consistency comparing with what?

The reviewer is correct. We changed the sentence to include only objective measures such as stool frequency and consistency, and reduced crying.

Comment [PR3]: "evening at 6 weeks (88.2% vs. 56.3% and 55.6%, p<0.05) and during the afternoon at 12 weeks"
This is interesting; authors hopefully will develop this. Why this temporal pattern of crying. (Is there a typical temporal pattern of crying in children in this age group?)

This is discussed and highlighted in the revised MS.

Comment [PR4]: Key word "stool"
This needs to be qualified with consistency. As it is it is too wide.

Corrected.

Comment [PR5]: "Crying is a basic, instinctive response governed by basic neuro-chemical mechanisms " Needs a reference

This is now referenced.

Comment [PR6]: This address the comment on PR3 above

Please see [PR3]

Comment [PR7]: "than 3 hours per day"
Is this continuous crying or cumulative crying?

Thank you, this refers to cumulative crying, now stated in the revised MS.
Comment [PR8]: For clarity it is best stated that esterified palmitic acid in position 1 and 3; the sn-2 palmitic acid is also esterified. Therefore the problem is not the esterification but the position.

The reviewer is right. All palmitic acid is esterified. Yet, it is important whether the esterification is at sn-1/3 or sn-2. This is now discussed and simplified in the revised MS.

Comment [PR9]: why high? What is the range of normal?

In human milk, over 70% of the palmitic acid is esterified at sn-2 position.

In contrast, in vegetable oils, usually used for infant formula production, palmitic acid is esterified mainly at the sn-1/3 positions and less than 20% is esterified to sn-2. The study formula (INFAT®) contains 44% of the palmitic acid esterified at the sn-2 position, and therefore referred as "high" compared with standard formulas.

This is now explained in the revised MS.

Comment [PR10]: Obvious …Some congenital metabolic disorders may not have manifested in the first 2 weeks of enrollment

Changed as suggested.

Comment (PR11): why was 44% chosen? Is it the same value as in breast milk?

Please see response to [PR 9].

Comment [PR12]: "Interestingly, although not quite statistically significant, at 12 weeks, none of the parents in the HBP group related the afternoon crying to abdominal discomfort, compared to 33% in the LBP group (p=0.068)."

Was this part of the objectives of the study? Wonder why it is being considered. here are other reasons why the children could have cried. Authors may wish to discontinue with this.

We agree with the reviewer. This was removed from the revised MS.
**Comment [PR13]:** It is useful to allude to typical crying patterns of children in this age group.

Typical crying patterns are discussed in the revised MS.

**Comment [PR14]:** It is assumed that all that is stated in this document are ‘facts’

Correct! All are facts! This is corrected.

**Comment [PR15]:** This is not complete reference

Thank you for noticing this. Reference is now completed.