Reviewer’s report

Title: Effect of continued folic acid supplementation beyond the first trimester of pregnancy on cognitive performance in the child: a follow-up study from a randomized controlled trial (FASSTT Offspring trial)

Version: 1 Date: 20 Sep 2019

Reviewer: Nancy Potischman

Reviewer's report:

T2 and T3 Folic acid - cognition

This is a well-conceived and executed study of folic acid exposure in the second and third trimesters on offspring cognition compared with exposure only in the first trimester. It will make a large impact in the field due to the clear findings and strong study design. It has many positive attributes and could not be done in many locations where folic acid fortification would influence status to a considerable degree. Despite the small sample size, and marginal response rate, the comparisons with other data outside of their study adds confidence to the findings on cognition. The impact of maternal folic acid status during the pregnancy predicting the outcomes, after adjustment for important early confounding factors, adds to the confidence in the findings. It was interesting to see an effect of breastfeeding and more detail about the length of breastfeeding and perhaps other factors related to this variable would be of interest.

As an outsider to this field on cognition, it would have been helpful to have all reviews of the literature in Background and Discussion be pertinent to the timing in the pregnancy. For example, Page 4 line 72, could the null finding be due to the short duration of folic acid exposure (8 weeks)? Page 14, references 33, 34 are first trimester only - should more be said about reference 35 relevant to timing? A more critical review of this literature would be helpful to the reader.

Specific Comments:

Page 3, line 62 - It would be of interest to know what form of folate was found in the brain. Is it folic acid or a metabolite?

Page 7, Line 153 - is there an impact of having non-fasting samples? If so, this could be mentioned in the discussion.

Table 1 - granted there were fewer people in the Placebo group at the age 3 testing, but this group did seem slightly different than the folic acid group. Is it worth mentioning even if not significant?
Figure 2 - does not add much more than what has been already presented. Is this a common way to evaluate such data so it adds more than what is in the table?

Page 16 - reference 44 - does this study directly address potential adverse effects of unmetabolized FA? There are studies that discuss potential effects, though the evidence of impact is weak. Unmetabolized FA is found in many individuals, even with marginal folate status, it is only found in large amounts at very high levels of folic acid intake and folate status. The authors should consider the wording on this topic carefully, though their discussion of dose and prudent recommendation are appropriate and appreciated.

**Are the methods appropriate and well described?**

If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**

If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**

If not, please explain in your comments to the authors.

Yes

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