Reviewer's report

Title: How well do blood folate concentrations predict dietary folate intakes in a sample of Canadian lactating women post-folic acid fortification of the food supply: An observational study.

Version: 1 Date: 7 May 2007

Reviewer: Paul F Jacques

Reviewer's report:

General

The purpose of the manuscript is not clear. More importantly, the sample may not be appropriate for any general examination of folic acid supplementation in a population exposed to folic acid fortification because the baseline folate status of this sample was very high. The population is appropriate to consider the importance of supplementation to maintain adequate folate status during lactation, but it is not clear if this was the question that the authors intended to examine.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Page 5, lines 6-19: I am somewhat confused by the proposed rational for undertaking this project. It seems that the authors are hypothesizing that the correlation between markers of folate status and folate intake will be stronger in the post-folic acid fortification period. The basis for this hypothesis seems to be the fact that pre-fortification associations between RBC folate and dietary intake were low and the correlations were improved after inclusion of women taking folic acid supplements. There are two possible explanations for this increase in the correlation that are unrelated to fortification. First, it is well known that you can increase the correlation of for two relationships of the same strength (i.e., slope) if you increase the range of the exposure (i.e., the variance), if the relationship remains linear across the extended range. By including supplement consumers in their previous analyses, the authors must have greatly extended the range of folate intakes so that even without any affect on the slope of the relation between intake and RBC levels, the correlation would have increased. Second, there is likely to be a much greater measurement error associated with dietary folate than there is with supplemental folic acid. Thus, by adding supplement consumers to the analyses, the overall quality of the folate exposure information is improved, which would again strengthen the correlation coefficient. Therefore, as for the authors' hypothesis, one could argue that the fortification of enriched cereal grain products should increase the range and variance of the folate intake, which would increase the correlation. However, it is uncertain whether the relationship would remain linear at very high folate intakes. Moreover, since the quality of folic acid from enriched cereal-grain products is as yet somewhat uncertain and may be of poorer quality than that of supplement consumers, one might also expect that the post-fortification correlations may not increase, and may even decrease if the error in folic acid intake from the fortified foods overwhelms the folic acid intake from supplements. The bottom line is that the raison d'être for this manuscript is unclear.

Page 6, line 13: Many of the readers may realize that the majority of the women enrolled in this study had been exposed to very high folic acid intakes for months before enrollment, as they were enrolled at 36 weeks gestation. However, this point is not clearly made until the page 15, lines 3-5. Essentially all of the women, even those in the placebo group, had RBC folate levels >906 nmol/L at 4 weeks into the study. There was little evidence of inadequate folate status in this sample. Moreover, the folate status appeared decline through the course of the study for the women on placebo. Based on the numbers in table 1, it appears that there was a significant reduction in RBC folate status, between weeks 4 and 16, a point not mentioned by the authors in the results. Although there is little that the authors can do to remove the limitations associated with the very good folate nutriture of the study sample, the authors do not adequately address the potential consequences of this on their study sample. This sample may not be the ideal sample in which to address the relation between dietary folate intake and blood folate levels in the post-folic acid fortification era.

Page 10, lines 12-23 and Page 11, lines 1-2: The results and the data presented in Tables 2 and 3 are inconsistent with what one might expect based on the study design. I would have expected that the correlations with the RBC and plasma folate concentrations would have strengthened over time as the effect of the folic acid supplementation during pregnancy on folate status diminished. However, that is not the
case in Table 2. And in Table 3, we see the opposite of what I would expect. That is, the correct classification of RBC folate based on intakes diminished, rather than improving, over time.

Page 11, lines 3-10: Figure 1 provides the most interesting result of this study. It strongly implies that there is little benefit in terms of RBC folate concentrations from intakes above approximately 151 micrograms per day of synthetic folate intake. The authors imply that there is added benefit at intakes of 411 and above, but they have not demonstrated this statistically. This could be a function of statistical power, but then the >475 micrograms per day group has a mean essentially identical to the 151-410 micrograms per day group. This result might be somewhat confounded by the mixture of folic acid and 5-MTHF supplements, and by the high folate status due to prior fortification with large doses of folic acid.

Page 11, lines 12-13: Given the limitations of their study, the authors’ statement regarding the relation between folate intake and blood folate is far too strong. At a minimum, it should have appropriate caveats regarding the select nature of their study sample and the potential biases introduced by the prior supplement use by these women. Also this statement seems to be turned on its head. Ultimately the important consideration is folate status, not our ability to predict intake from markers of status (unless of course we are using biomarkers as a validation of our dietary assessment methods, which does not appear to be the case in the present study).

Page 13, lines 18-22: The authors’ discussion and conclusions in this paragraph are more appropriate to their data and analyses. If the purpose of this manuscript was to describe the appropriate levels of supplementation for lactating women exposed to fortification to maintain appropriate RBC folate levels, many of my above arguments would be nullified.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Page 8. lines 18-21: the authors note that they included the type of treatment as a covariate in some of their models. However, folic acid and 5-MTHF are handled quite differently post-absorption. This difference in metabolism may not be functional under conditions of low folic acid intake, but under conditions of higher folic acid intake, may be important. For example, there is evidence of a high prevalence of individuals with circulating unmetabolized folic acid levels since fortification was implemented. Did the authors consider treating the different forms of supplemental folate as a modifier of the association between intake and blood levels? One could hypothesize that the relation would be stronger in those women assigned to the 5-MTHF supplement.

Page 11, lines 15-19: I cannot argue with the authors’ statement that women planning a pregnancy should continue to consume a folic acid supplement. We don’t have sufficient evidence to advise otherwise. However, the authors’ logic supporting this statement, that the association between supplements and NTD risk is stronger than that observed between RBC levels and NTD risk, is very weak. The former association was examined in unfortified populations. Although it would be unethical to undertake a trial even in a fortified population, I would imagine that such a trial would provide a fairly weak association between supplementation and NTD risk. In the post-fortification era, RBC levels might well be a better predictor of NTD risk than supplement use.

Page 12, lines 12-15: There is some evidence to suggest that the actual folic acid intakes from fortified foods is greater than the anticipated intakes, in part based on overages. Were the data that the authors use to calculate folic acid intakes from fortification based on calculated estimates or measured folic acid values in the fortified foods?

Page 15, line 5: I believe that the average life span of red cells is ~120 days. If that is true, many of the red cells may still reflect the folate levels associated with the high dose folic acid supplementation during pregnancy at 16 weeks. The average life span is less important to this argument than is the distribution of the lifespan of red cells.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major
compulsory revisions

Level of interest: An article of limited interest

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.