Reviewer’s report

Title: Maternal and Fetal Exposures to Fluoride during Mid-gestation among Pregnant Women in Northern California

Version: 0 Date: 15 Sep 2019

Reviewer: Christine Till

Reviewer's report:

This manuscript is very timely in light of the recent debate on the safety of fluoride exposure in pregnancy. There are a few minor points that require clarification, but overall, this manuscript reads well and makes an important contribution.

1. How were the 49 of the 138 original samples selected? The breakdown of the sample is hard to follow and could be clarified perhaps with a flowchart. Also, please include the range and average week of pregnancy for the women included in the study. (if there is a big range, week of pregnancy should be examined as a covariate because urinary fluoride concentrations can vary by week of pregnancy).

2. The authors should note the equation that was used to adjust for specific gravity.

3. Were the water fluoride levels matched in time to when the women were pregnant? Do the water fluoride levels represent the average over a specific period (month, year)? Timeframe is important given that the recommended optimal level of fluoride was reduced from 1 ppm to 0.7 ppm over the timespan that the sample was recruited (2014-16).

Related to the above point, the authors note in the discussion that:

"for communities with fluoridation levels below federal recommendations, unlike the reports by Smith et al. (Smith et al. 1950), this study and Till's study of Canadian women (Till et al. 2018) found MUF concentrations 2 to 3 times higher than the concentration of fluoride in drinking water."
However, it is not clear whether the sites where water fluoride levels "fall below federal recommendations" are actually non-fluoridated (it is possible for fluoridated sites to have water fluoride readings fluctuate between 0.60-0.70). Or, it is possible that the site has naturally occurring fluoride at concentrations of about 0.60 mg/L. I think the above statement is misleading when comparing across studies because different thresholds were used by each study for grouping the participants (i.e. below and above 0.70 vs. 0.30 mg/L in the current vs. Canadian study, respectively).

4. Please include the LoD for the fluoride measurements. Were any of the values at the LoD?

5. Analyses. Were the distributions for the biological measures of fluoride (serum, urine, amniotic fluid) normal? These outcomes look right-skewed; thus, a log-transformation may be warranted to obtain a more normal distribution for a Pearson correlation.

6. Covariates: the study controls for maternal age, smoking status, and BMI. It would be helpful to explain why these covariates were selected (as opposed to something like race/ethnicity given the racially and ethnically diverse sample and the fact that Black individuals tend to show greater fluorosis, perhaps due to biologic susceptibility, greater fluoride intake, or other factors such as presence of other health conditions, e.g. kidney disease).

7. The discussion may be strengthened by comparing the plasma fluoride findings with those reported in another (more recent) study of pregnant women as in:


8. The consistency between fluoride concentrations in amniotic fluid and maternal serum is interesting. This finding is at odds with the idea of the placenta acting as a selective barrier when fluoride intake is high (>0.4 ppm), but allowing passive diffusion from mother to fetus when fluoride intake is low; See:


9. When referring to the Bashash article as a comparison for mean urine fluoride level (0.91 ppm), it should be noted that this value controls for creatinine rather than SG. This is important because urinary fluoride levels appear higher when adjusting for creatinine vs. SG.

10. Given that the correlation between maternal serum and amniotic fluid (AFF) is stronger (r=0.51) compared with the correlation between maternal urine fluoride and AFF, can the authors comment on whether maternal serum is a better proxy for fetal exposure? Are there any advantages of measuring fluoride in one approach over the other?

11. The discussion could mention some limitations. For example, it did not appear that information was collected on use of fluoridated dental products (or consumption of bottled water) prior to sampling; lack of measuring dietary sources of fluoride (e.g. tea consumption), etc.

12. Last paragraph. Related to the point above about whether sites with water fluoride levels that are in the range of 0.60-0.68 can be called "non-fluoridated". I am not sure I agree with the conclusion that fluoride exposure is increasing in "nonfluoridated" communities if the study includes those that fall near the optimal level. (I see that the same pattern is reported in Table 5 using ≤0.3 ppm as the cut-off, but now the sample size is quite small to be making such a conclusion about a rise in urine fluoride levels).

Minor:

Please include sample size in Table 5.
BMI should be defined at first mention.

Spelling error: Candian should be Canadian on line 38, pg 2 of discussion

I could not find Supplementary Table 1.

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