Reviewer’s report

Title: Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy

Version: 1 Date: 09 Oct 2018

Reviewer: Kristina Whitworth

Reviewer’s report:

Title: Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy

This paper examines the association of a suite of PFAS compounds, measured in cord blood, and HDP among the mother. The authors implement a novel statistical technique to deal with the correlation among the different PFAS species measured in this group of women. While this paper adds to the evidence regarding this association and the study investigation has merit, the authors have not fully considered the existing literature, and there are several methodologic considerations that should be clarified.

Major Comments:

1. The authors indicate that international studies (plural) provide a prevalence of HDP ranging from 5-8%, but only give a single citation, which is quite outdated. I suggest reviewing more up to date citations (e.g., Hutcheon JA et al. Best Pract Res Clin Obstet Gynaecol, 2011; 25(4), 391-403, and Duley L. Semin Perinatol, 2009; 33 (3), 130-7), which indicate the prevalence of HDP may be up to 10%. Further, the Chinese report cited by the authors provides a prevalence of 5.2% which, while within the range of other studies, is on the low end.

2. Only a single original article from Canada in 2005 is provided as a reference for the statement of multiple PFAS exposure pathways (page 4, line 51-53). This is inappropriate given the robust literature on this topic. Further, exposure pathways in China are likely to be different than in Canada. At a minimum, a more thorough citation for this statement is needed.

3. No mention is made in the introduction (page 5, lines 11-40) of the potential impact of varying exposure levels on inconsistent results of the three previous studies, nor of potential differences due to timing (i.e., given that concentrations are declining in many parts of the world). How does exposure differ between the US-based C8 population, MoBA, and Chinese populations?

4. It's unclear from the methods, but were women recruited at the time of birth? If yes, then this is a cross-sectional study, not a prospective cohort study. Perhaps the parent study
was intended as a prospective cohort and these women and their children are currently being followed, but the present analysis is cross-sectional, using only the baseline data.

5. Please provide the LODs for PFOSA, PFHPA, PFOS, PFNA, and PFHxS.

6. What was the justification for the inclusion of age, education, and pre-pregnancy BMI as a priori confounders?

7. Why were other covariates (e.g., smoking, parity, socioeconomic status, occupation, etc.) not explored as potential confounders? Given toxicokinetics, parity in particular has been shown as a very important variable when examining associations of PFAS and pregnancy outcomes.

8. The discussion section of the manuscript seems to indicate that a primary motivation for this analysis was the very limited information on health effects of PFBS; if this is the case, it should have been made clearer in the introduction.

9. There is no discussion in the manuscript regarding the present study's results compared to previous studies, including some comparison of exposure levels.

10. The sentence on page 13, line 67, starting with 'a direct causal association…' should be omitted. No study will provide "direct causal evidence". This sentence is unnecessary and irrelevant.

11. On page 15, line 109, the word 'causation' should be changed to 'association'.

12. On page 15, the authors indicate that studies provide evidence that PFAS are 'by and large consistent across pregnancy'. But, only a single study from the DNBC is cited. Moreover, contrary to what the authors indicate, while Fei et al report high correlation between PFOS and PFOA concentrations in 1st and 2nd trimester samples, they also indicated that on average, concentrations decreased. Given urine as a major route of elimination, it is likely that PFAS concentrations decrease across pregnancy as the GFR increases - this is actually supported by the findings in Fei et al. as well as by Fromme 2010 [pmid: 20722433], Monroy 2008 [pmid 18649879], and recent PBPK modelling (see Loccisano et al, pmid 23151209] of PFOA and PFOS. In addition to revising the statement, they should provide some indication on how the presumed decrease in concentrations across pregnancy may impact their results.

13. 'confirm the causal relationship' should be omitted from the conclusion. As the authors indicate, the association they observed may be spurious given preeclampsia may impact the toxicokinetics of PFAS - this possibility should also be further discussed.

Minor Comments:
1. Hypertensive disorders of pregnancy is plural, thus the first sentence in the introduction (page 1, line 3) should be revised accordingly.

2. HDP includes several separate diagnoses but there is no background regarding whether these have different or similar etiology.

3. Importantly, though the two US studies of PFAS and HDP are from populations with high PFOA concentrations, they experience background concentrations of PFOS and other PFAS; this should be noted.

4. When discussing associations (page 5, lines 10-40), it would be helpful to provide some indication of the magnitude of associations, rather than just saying 'weak', 'modest', 'positive' or 'inverse'.

5. Medians, GMs, SDs, and ranges are not used to describe "basic characteristics of subjects" (page 7, lines 38-44).

6. I believe the authors mean 'a priori' rather than 'a prior' on page 8, line 48.

7. In the methods, the authors indicate that detailed methods for measuring PFBS were already described…does this imply that these methods differ from those used to measure the other PFAS?

8. Given this study is among a Chinese cohort, it's unclear of the relevance of the statement (page 12, line 50) regarding the phase out of PFOA and PFOS.

9. The first sentence in the discussion is missing some context. The authors state that "our study used elastic net regression models to select a subset of PFAS components"…but it should indicate that they used elastic net to select the subset of PFAS components most strongly related to HDP.

10. The authors spend a lot of space in the discussion laying out the potential biologic mechanism of PFBS on preeclampsia, which is nice, but I suggest providing a more concise overview of this information.

11. There are font differences in Table 2.

12. There is no legend for the figure.

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal