Reviewer’s report

Title: Urinary Trace Metals, Maternal Circulating Angiogenic Biomarkers, and Preeclampsia: A Single-Contaminant and Mixture-Based Approach

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Reviewer: Shohreh Farzan

Reviewer's report:

Bommarito and colleagues have presented a very well-written and nicely designed investigation of the relationship between multiple metals exposures and preeclampsia. While some evidence has suggested that individual metals may be related to preeclampsia risk, little is known about mixed metal exposures or about underlying mechanism. The study has a few limitations (relatively small number of PE cases, potentially limited generalizability due to oversampling for pre-term birth), but the overall results are interesting nonetheless and the investigation of the blood angiogenic markers provides new mechanistic insights. I have a few comments, but overall found the paper to be a thorough statistical investigation, with clearly articulated results, conclusions and limitations.

I was a little surprised to see that the PCA provided PCs that fell into such clear "essential" and "toxic" groupings and I would be interested to see how this method compares to other mixtures analysis methods, such as WQS. WQS would be expected to weight the more significant contributors to the association, which could help clarify some trends or support the observations of the single exposure models. Further, WQS can be specified with a positive or negative constraint, so it would be interesting to see whether the weightings of an additional method mirror the PCs or if it may provide additional information about the relative importance of specific individual or groups of metals.

Only Cr appeared to show consistents association with both PE and angiogenic markers. While a mediation analysis wouldn't make sense for most other metals, given that the authors also observe an association between Cr and PE, as well as with angiogenic biomarker PIGF, it would be interesting to explore whether this marker are potentially mediating the relationship. Further, did the authors examine the relationship between levels/ratio of the angiogenic biomarkers and PE in this population? This information could be potentially informative and could be added as supplemental information.

The authors mention that these metals levels are similar to what has been observed in the general US population, but some brief discussion of expected sources of key metals exposures (particularly for those associated with angiogenic biomarkers and PE) for this population would be a nice addition to the discussion.

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