Reviewer’s report

Title: The Association between Maternal Urinary Phthalate Concentrations and Blood Pressure in Pregnancy: The HOME Study

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Reviewer: Ami Zota

Reviewer’s report:

In this manuscript, Werner et al. examine associations between phthalate exposures during the second trimester of pregnancy and various blood pressure and hypertension-related endpoints. The research question is novel and important, and the statistical analysis is well conducted. The sensitivity analyses are an added strength. I have a few recommendations that would further clarify the methods and improve the interpretation of the results.

Major Compulsory Revisions

Introduction
1. The authors begin the introduction by discussing the clinical and public health impact of preeclampsia but it is a bit odd and out of place because their current study was not designed to examine preeclampsia, nor do they specifically look at preeclampsia as a separate outcome. I recommend revising the introduction to emphasize the biologically plausibility of phthalates impact on cardiovascular system including elevated blood pressure. You can also mention placenta-related disorders such as preeclampsia in the introduction and discussion but that should not be the main focus since it was not the main outcome in this paper.

Methods
2. The statistical analysis is generally well conducted and is one of the papers strength as is the availability of repeated measures of both exposure and outcome. The covariates included are generally sound. However, the authors did not include any information on prevalence of hypertension disorders before pregnancy. If the study outcome is pregnancy-induced/gestational hypertension then you need to know the baseline/pre-pregnancy hypertension. Ideally, you would control for pre-pregnancy blood pressure status and/or omit those with chronic hypertension because you are interested in the development of hypertension disorders during pregnancy. This issue is currently a major limitation of the manuscript and needs to be addressed. It would also be important to know if any women were taking hypertension medication and omit them in sensitivity analyses.

3. The authors have modeled phthalate exposure after normalizing for creatinine. This approach is potentially problematic since one could get artificial results if creatinine is associated with the outcome (see Barr et al. EHP 2005). As a sensitivity analysis, you should rerun all models with phthalates modeled as wet
weights and inserting creatinine as a separate covariate.

Discussion

4. The sentence, “A 1-5mm Hg shift upward in diastolic blood pressure across the U.S. population could have large impact on the frequency of the diagnosis of chronic hypertension, gestational hypertension, or preeclampsia.” seems to overstate the significance of the findings. For example, given that the etiology of preeclampsia is poorly understood and likely involves placental factors, I don’t think we know enough to say that this change in diastolic blood pressure “could have a large impact”. Please revise.

5. Paragraph 3 of the discussion needs some refining and editing as it includes everything from a potential biological mechanism to policy implications. In particular the following sentence, “While these results need to be replicated, it is plausible that MBzP may pose a risk to pregnancy early in gestation when the placenta is implanting and maturing” seems out of place without further elaboration (it also needs more citations). Also, since you primarily were looking at hypertension related outcomes, a discussion of placental biology may not be appropriate unless there is a specific pathway or biological mechanism that the authors are referring to.

6. Similarly, the limitations section is well written but the lack of data on pre-pregnancy health status may be a limitation if it is not available. If it is available, it should be incorporated into the analysis.

Minor Essential Revisions

Introduction

1. Also, in the first paragraph, the following sentence needs more references, “More recently endocrine disrupting chemicals, such as phthalates, which can alter the action and metabolism of androgens, cortisol, and thyroid hormones (3-5), have been hypothesized to impact blood pressure and thus may effect gestational blood pressure and preeclampsia risk.” Specifically, who has hypothesized that phthalates may impact blood pressure? Also “effect” in the above sentence should be changed to “affect”.

Methods

2. Participant recruitment: In the conclusion, the authors state that this is a “prospective population-based study”, but this is not accurate language since their population (largely white & higher educated) does not reflect the entire population of pregnant women in Cincinnati, OH. Please change the language in the discussion and perhaps add a sentence to the first paragraph of the methods discussing how participants were recruited.

3. Were there any differences between the women who either disenrolled before delivery (n = 79) and the women who stayed in the study. For example, were those who disenrolled before delivery more high risk pregnancies or lower
Results
4. Please include average age of participants in the first paragraph of results.
5. When you modeled pregnancy-induced hypertensive disease as an outcome, what did you do with the participants who had chronic hypertension (n = 13)?

Discussion
6. In the first sentence, the authors state “we found that urinary MBzP phthalate concentrations in early pregnancy…”; however, since the mean time point of the first measurement was during second trimester and not first trimester, this is actually mid-pregnancy. Please change the wording there and anywhere else in the manuscript with similar language.

7. The authors should include a brief discussion on potential reasons why they observed an association with MBzP but no other phthalates. Could there be residual confounding by other chemicals that co-occur with MBzP in building materials such as vinyl tile. This warrants some discussion.

Discretionary Revisions
1. Since this is an epidemiologic analysis and not an exposure paper, you can omit Table 1. This information has been published in many forms in other papers.

Level of interest: An article of importance in its field

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.