Reviewer’s report

Title: Association of urinary concentrations of early pregnancy phthalate metabolites and bisphenol A with length of gestation

Version: 0 Date: 31 Mar 2019

Reviewer: Jennifer Adibi

Reviewer's report:

This is an analysis, using a cohort of 221 women for whom they collected repeat urine samples from the period of pre to post implantation. These data are novel and the analysis was well done overall. They measured phthalate levels, urinary levels of hCG, and duration of pregnancy. Previously, there have been reports of inverse associations of urinary phthalate levels and the duration of labor, and one report of higher phthalate levels being associated with longer gestation. This was an opportunity to assess this relationship based on exposure levels pre-conception, at time zero of implantation, and up to 5 weeks of pregnancy. A strength is use of Cox proportional hazards models to model duration of pregnancy as an outcome. The early period in which they measured exposure is the time period of embryogenesis, formation of the placenta and the gestational sac. In these early stages, there is no direct communication between maternal blood and embryo/placenta. That which they measured as phthalate exposure using these urinary biomarkers might reflect long-term chronic exposure of the uterine and ovarian tissue, and the oocytes to phthalates, contemporaneous levels in the uterine glands, or general xenobiotic metabolism as an indicator of general uterine/pregnancy health. Given the latter, it is not surprising that they had null effects of the monoester phthalates and only detected associations with MEHHP and MCPP, which are products of secondary and tertiary metabolism of the monoesters. One indication of this is the seeming opposite direction of association of MnBP and MCPP with outcomes. MCPP is considered a metabolite of DnBP/MnBP. I would further suggest that authors create a molar sum of the DEHP metabolites (MEHHP, MEOHP, MECPP) and calculate the association with outcomes. If the association is the same as that of MEHP, then we can infer that these metabolites represent the same thing i.e. DEHP exposure. If the association differs, then we can infer that those metabolites represent something different than DEHP exposure, and may be confounded by metabolism differences between women.

Comments:

* The rationale behind the censoring by medical intervention is not clear to me. Was this considered as an intermediary variable which is why it is included in the analysis? Should it
be a separate outcome assuming phthalates may have contributed to risk of intervention? What were the medical interventions?

* I read the methods several times and don't understand how the imputation to fill in the missing values for medical intervention related to the overall analysis of phthalates and duration of gestation. Please make this clearer;

* It would be helpful to share the results with regards to correlations in phthalate levels over this time period. Authors mention a range, but could they show the correlations in a table or in a figure?

* Did they have information on the sex of the baby at birth? HCG levels differ by sex of the baby as early as 3 weeks gestation so they may also see sex differences in these associations. Maybe they could impute fetal sex based on hCG?

* Underadjustment is better than overadjustment but it still might be important to adjust for maternal age if it reduces the standard error in the phthalate estimate. I agree that it would be likely confounder. The other ones would be maternal weight/BMI, race, smoking status, and infertility treatment.

* In their previous paper, this group of authors report the association of phthalates with change in hCG levels over time. How does that finding relate this finding, either conceptually or statistically/analytically?

* Authors might consider some type of strategy to 1) adjust for confounding by phthalate metabolism/excretion, and 2) consider a summary measure of the phthalates.

* The first paragraph of the Discussion section discusses the results of previously published reports. That seems odd. Usually, that paragraph starts with the primary findings and then offers an interpretation with regard to previous findings.

* Did you learn something different by having pre vs. post implantation phthalate measures? Can you offer a summary or interpretation of that comparison?

* Given the dynamic nature of these associations relative to time, could you include a figure or set of figures with time as the x-axis?

* How did the Cox models compare to a regression model with gestational age regressed on phthalates and interacted on time?
* Were pre and post implantation phthalate levels correlated?

* In previous papers, these authors studied DES exposure in utero in relation to these endpoints. How was that variable treated here? How do they conceptualize DES in this model?

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