Reviewer’s report

Title: Urinary phthalate metabolites in relation to serum anti-Müllerian hormone and inhibin B levels among women from a fertility center: a retrospective analysis

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Reviewer: Haotian Wu

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Comments for: Urinary phthalate metabolites in relation to serum anti-Müllerian hormone and inhibin B levels among women from a fertility center: a retrospective analysis

Summary: The main objective of the study was to quantitatively examine the associations of urinary phthalate metabolite levels with serum anti-Müllerian hormone (AMH) and inhibin B (INHB) levels. The authors report on associations of urinary MEHP and MEOHP with serum INHB, concluding that it adds to the growing evidence that certain phthalate species lead to diminished ovarian reserve. Overall, the manuscript was well written and the analysis seems acceptable, though there are some lingering questions that need to be addressed prior to publication. Most importantly, the authors should better clarify 1) the discrepant results observed for AMH vs. INHB and 2) potential impact(s) of the sample collection timeline (outcome measured 4 months prior to exposure).

Major Comments

* Why were the unadjusted urinary phthalate concentrations, as opposed to the creatinine-adjusted concentrations, categorized into quartiles? One imagine that creatinine-adjusted concentrations likely better reflect true exposure levels.

* The authors should clarify why the spline models were fitted using unadjusted urinary MEOHP levels as opposed to the creatinine-adjusted levels? From the quartile results, the non-linear relationship is not obvious as estimates do not meaningfully differ between quartiles. It would be very helpful if authors clarified their analysis and thought process behind this.

* The authors should have an expanded discussion of temporal relationship as the exposure (phthalates) appear to be measured up to 4 months after the outcome. A couple of potential issues arise from this and needs to be discussed:

   Phthalate exposures might be a reflection of prior knowledge (reverse-causation)

   A single urine sample might have some capacity to represent exposure over a few months preceding sample collection, but the urine sample is taken 4 months after the serum outcome measures. Therefore, the measured phthalate concentrations in urine needs to be reflective of a period of time longer than a few months for temporality to be established.
In lines 241-247, the authors cited the fact that AMH is produced by small growing follicles as opposed to non-growing primordial follicles as a central reason why it led to a null finding. However, this does not explain why there was a difference between AMH and INHB as INHB is similarly produced from small growing follicles (line 113). The authors should clarify this, as well as any other potential reasons for differences in AMH vs. INHB results.

* Please provide any QA/QC results for all measured biomarkers (phthalates, AMH, INHB).

Minor Comments

* Figure 1 - Please label green vs. red lines.
* All abbreviations in tables should be clarified in the footnotes.
* IQR is erroneously labelled as "IOR" in Table 1.
* While MOP had a low rate of detection, instead of ignoring it completely, it would be interesting to see it analyzed as a dichotomous exposure (>LOD and <LOD) to take advantage of the available data. It would have comparable, if not better, power than comparisons of any two quartiles.
* Lines 169-170 - given that in linear regression analyses, the addition of covariates will likely not lead to a loss of power, the authors should consider adding ethnicity and current smoking as covariates in the model and compare the resulting estimates to the models presented in the manuscript.

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