Reviewer's report

Title: Biomonitoring of Bisphenol A Level in Maternal and Umbilical Cord Blood Relevant to Birth Outcomes and Adipokine Expression

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Reviewer: Lynn Goldman

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The paper presents levels of prenatal bisphenol A (BPA) in prenatally sampled maternal blood in relation to umbilical cord blood serum levels of BPA, leptin and adiponectin (measured via ELISA), and low birthweight and small-for-gestational age birth for male and female infants. Exposure to BPA was assessed via measurement of free BPA in maternal blood at some time unspecified prenatally and in umbilical cord blood by HPLC/UV detector.

There were much lower levels of BPA in cord blood than in maternal blood, and a negative association between maternal and fetal BPA. The paper reports that among males, but not females, maternal exposure to BPA was associated with increased risk of low birthweight and SGA births and increased rates of levels of leptin and adiponectin consistent with "adverse action".

The paper presents interesting results on an issue that is of great currency of the moment. However it is not yet suitable for publication and requires major revision.

Major Compulsory Revisions:

1. Background: In the review of the animal literature the authors need to clearly identify dosing routes since oral routes are more likely to be relevant to human internal doses. Also, more care need to be taken in describing internal doses; what is the evidence that BPA 'accumulates' in adipose tissue?

2. Recruitment and sampling methods need to be better described. When was the study conducted? Was there IRB approval? How were subjects were identified and recruited? How were women approached and what was the response rate? What information was collected on the questionnaire and what steps were taken to make sure that the questionnaire was properly administered? At what point during pregnancy were maternal samples collected? How were data including blood samples collected? Were precautions used to assure that sample containers were not contaminated with BPA?

3. Laboratory methods need to be better described. Measure of low levels of BPA in serum can be confounded by background levels of BPA in laboratories and in laboratory equipment. The paper needs to describe the QA/QC procedures used by the laboratory. The situation with regards to non-detects (ND) samples also needs to be described. How many of the results were
non-detects? How were non-detects handled in data analysis?

4. Statistical methods: What was the approach to modeling and selection of control variables for multiple regression analyses? Did the investigators assess potential effects, effect-modification and/or confounding by factors known to impact LBW and SGA, most notably maternal smoking, parity and socioeconomic status?

5. Results: The paper reports that there is a relationship between BPA exposure and all four outcomes in male infants. These findings could have been significantly influenced by just a few infants and it is important to make sure that such results aren’t driven by just a few influential points. Two of the outcomes (LBW and leptin) show elevated odds ratios for both the 2nd and 4th but not 3rd quartiles of BPA whereas SGA and adiponectin show an elevated OR in the 4th quartile only. The former relationships are interpreted as “u-shaped” dose response curves in the discussion. However, the lowest dose level is not a “zero” or control level like in animal studies but actually is the “low dose” level. If there were a u-shaped dose response the response would be higher at these lower doses than at intermediate dose levels. These dose response curves more resemble a seesaw relationship than a u-shaped curve. In any case the data for females was interpreted inconsistently. All of the results for females were interpreted as null findings however the pattern of odds ratios for SGA is similar to the pattern among males for LBW which are interpreted significant relationships.

6. Results: If the BPA blood analyses are valid the ratio between maternal and fetal levels may be the most important finding. However it is unsettling that, as stated in the discussion, there “was no significant correlation” between maternal and fetal levels. Were the samples taken at disparate points in time? Also, discussion cites a study reporting that 27% of BPA crosses the placenta. If so, why are the levels in this study so much lower? This needs to be discussed.

7. Discussion: Please discuss the findings in the light of the fact that there is a very short biological half-life of serum BPA the issue of timing of sample collection and relevance of a single exposure level at a single point in time to longer term outcomes (like LBW, SGA, leptin and adiponectin) should be discussed.

8. If information on smoking, socioeconomic status and parity was not available this is a major limitation of this study and needs to be discussed.

Minor Essential Revisions:

1. Please describe how were the “adverse action” cut points for adiponectin and leptin determined?

2. Results: Table 3 needs to include the numbers of infant/mother pairs included in each of the 4 groups for the outcomes in the multiple regression analysis.

3. Discussion: The discussion goes into numerous issues (e.g. breast
development and brain differentiation) that are not directly related to the study hypotheses and study findings. The discussion needs to be focused on fetal growth and metabolism.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.