Reviewer’s report

Title: Transcriptome-wide analysis of changes in the fetal placenta associated with prenatal arsenic exposure in the New Hampshire Birth Cohort Study

Version: 0 Date: 15 Aug 2019

Reviewer: Tiffany Sanchez

Reviewer's report:

This is an interesting study that seeks to better understand potential mechanisms of the adverse effects of arsenic on birth weight by using RNAseq from fetal placental samples to identify genes whose expression are affected by arsenic exposure. The major limitation of the study, which the authors rightfully acknowledge, is that RNA sequencing was performed on separately on males and female placentas so one cannot rule out that differential findings between males and females are related to experimental variation rather than true sex-differences.

Title

1) I suggest condensing the title so that it's easier to read quickly and reflects the overall scope of the project

Abstract

2) Please include the number of participants/fetal placentas included in this study.

3) In the abstract, it is unclear why results are only presented as sex-stratified.

Intro

4) Page 5, Lines 9-10. Other than arsenic exposure, how did the 46 infants compare to the other infants in the cohort?

Methods

5) Page 6, line 4. What is meant by the use of "subcohort" in the sentence beginning: "Out of the NHBCS subcohort of 312,"
6) Page 6, line 6. Can you please provide more context for the range of arsenic exposure in this cohort and define the range for being in the "high" and "low" arsenic exposure groups.

7) When used as a continuous measure, urinary As is usually right skewed. For the highly exposed groups, since the standard deviation is much larger than the mean, it appears that the distribution is likely still highly right skewed. Please provide the median and interquartile ranges for each of the groups instead of mean and SD so that readers will get a better idea of the distributions of exposure?

8) Page 7, line 1-2. Please include detection limits for each arsenic species and also include how many samples were below the detection limit.

9) Page 7, line 3-4. For samples that were below the detection limit but above zero, what happened after samples were flagged?

Results

10) Page 10, line 4-7. Please explain why results were validated using qPCR only for female samples. Was this a post hoc analysis? Were the new tissues samples from an adjacent location near the original subsection of the placenta?

11) Table 1. It would be helpful to included how many DE genes were included in each gene set as a column.

12) Table 1 and 2. Remove underscores so that the gene set names are easier to read.

13) Table 2. Several U-As and birthweight FDR p-values are listed as 0, but this is likely not the true p-value, please use exact p-values.

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published
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