

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Apr 18, 2019
To: "Hernan Gomez, MD" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-547

RE: Manuscript Number ONG-19-547

Blood Lead Levels of Females of Child Bearing Age in Flint Michigan and the Water Crisis

Dear Dr. Gomez, MD:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Dear Dr. Gomez,

Thank you for submitting your manuscript "Blood Lead Levels of Females of Child Bearing Age in Flint Michigan and the Water Crisis" for consideration in the Green Journal. This is overall a well done study that addresses a persistently controversial issue in the State of Michigan.

The following are comments I have concerning your study:

- 1) The statistical methodologies seem appropriate for the study. It would be nice to see an actual summary of the data points of maternal blood lead levels and/or a comparison of the arithmetic mean and the geometric means of the lead levels. As well, the mixed linear regression analysis seems appropriate.
- 2) I do not think umbilical cord blood data post exposure and the modeling data for umbilical cord blood levels is worth having in this study. It is not a part of the objectives of the study, and it implies that there is also no fetal/neonatal effects of the lead exposure without any real "pre-exposure and during exposure" data as was analyzed in the females of childbearing age population.
- 3) Even though not explicitly stated, the study seems to imply that there were no maternal/fetal/neonatal/reproductive effects due to lead levels in the water in Flint. This is probably true given the lead levels presented in the manuscript, but again there is no actual outcomes data to support this conjecture. In this same vein, we also do not have blood lead levels in patients with adverse outcomes in the Flint areas studied.
- 4) Finally, the multiple acronyms stated in the abstract are not re-defined in the body of the actual manuscript.

Reviewer #2: I think this study can contribute to information that informs monitoring in flint as well as sparks interest in further investigation of exactly how lead levels affect pregnancy outcomes.

I do have some concerns and questions that I think should be more explicitly stated in the paper, however:

Why choose the geometric mean as a marker?

Were pregnancy outcomes of these women of CBA looked at? I would be interested to know that information as well.

Does MI/Flint routinely test for lead in pregnant women?

Also why use all women of childbearing age? Why not only look at pregnant women? Is this CBA surrogate an appropriate proxy for pregnant women? Is there something about pregnant physiology that changes levels of lead, or dangerous levels of lead? Although women of CBA can be pregnant, they cannot experience adverse pregnancy outcomes without being in that physiologic state.

It is not clear from the paper why cord BLL were calculated or validated. From what is talked about in the manuscript it seems that pregnant female BLL are what is used when comparing rates of SAB, preterm labor, etc. Why bother calculating cord BLL? how does this contribute? What are dangerous cord BLL seen in previous research?

Is there a possibility that lower levels are still dangerous (seems unlikely if you base previous studies), or that there is an unidentified factor that is contributing?

I think a clearly stated thesis would help answer some of these questions for me. I am working on the assumption that you aim to show that this working paper is not in line with what your objective data is suggesting given previously published dangerous lead levels to reassure the community that while terrible and inexcusable, lead levels are not at a level likely to cause drastic increases in poor ob outcomes.

Specifically:

Introduction:

I think the introduction can be shortened. I would somewhere in the beginning explicitly state expected lead levels

not sure 111-113 is necessary and would condense 115-122 into just that first sentence.

128-129 I am assuming these are the BLL of the pregnant spouse although I found this sentence a little confusing

135-138 This is a key sentence in addition to your last paragraph in setting the stage for your presentation of results and argument as to why those results are important

Methods:

I would mention a strength is this hospital is NPO with pts of low SES which arguably would be most vulnerable with highest lead levels- ans still the values were much lower than the previously described "danger zones."

What were the water sources of these patients? Do we have any way of knowing?

I would discuss why we think levels post may have dropped off? Awareness of crisis? Drinking more bottled water?

162- can the heavy metal panel values and just lead level values be directly compared? Is this significant/worth mentioning?

184 again not sure why we are looking at cord BLL

Outcome measures:

246-267 again i feel like this could be condensed. I also think structurally if they are significant enough to be under 2 different headers, than the info should be in 2 tables and not 1 (everything is all in table 3). But if you condense than removal the 260 header and keep all in table 3.

264-267 I had difficulty understanding this sentence the way it was written- would restructure sentence.

271 -missing figure #

269- again what is the purpose of the cord blood modeling? in terms of supporting your research and its implications

Discussion:

306-311 This is useful information, but I'm not sure why it is being presented here

324-336 This paragraph reads more like background than discussion

356-360 this was said earlier and i think can be removed from this section unless you expand upon why controlling was important and who this population represents and how that is relevant to your data.

Reviewer #3: The authors present data and blood lead levels (BLL) in women during the Flint water crisis. This is a very germane topic as teratogens such as lead can cause substantial issues during gestation if at high levels in maternal blood. I think this is an overall well written work with a clear and well executed hypothesis.

Lines 111-113: Please use a different example than Charles Dickens- this makes this work seem immature; it could be removed altogether.

Lines 166-167: Please expand on this issue: If you did not have access to the medical records, how can you be sure that these patients did not have a history of lead exposure previous?

Lines 184-189: How did you pick this rubric to use to determine maternal or serum lead levels? Is their data to support his approach. This needs to be further elucidated as it is central to the conclusions being drawn.

Line 209 Why do AA women have higher baseline lead levels than whites? Is this environmental or is their some genetic issue here?

Please add a statistical assessment of how you decided to run your data the way that you did.

Lines 210-214: It is interesting that the BLL was actually lower during the water issue. Do you think that the water was therefore contaminated prior to this? This has profound implications for the community and needs to be elucidated further.

The discussion is overall well written and not over reaching. I do think more should be written about the inherent weaknesses of this paper.

Reviewer #4: This study examines blood lead levels in women between the ages of 12 and 50 living around Flint Michigan. Although this is interesting and important data that needs to be known - it is so highly specific to one situation that it doesn't really add to the general knowledge base of the practicing Ob/Gyn. In addition - the methodology - which extrapolates predicted cord BLLs only holds if there are no other individual factors that change lead pharmacodynamics. In this dataset, little is known about where women drink water (in home, at work, percent bottled). Given that the researchers based their analysis on where women live - it is reasonably possible that home zip code does not accurately classify source of water intake. This misclassification bias would tend to obscure true differences and reduce power to determine true differences between populations. It would be helpful if actual fetal death rates could be captured and depressing that as a country our public health infrastructure does not support this kind of critical tracking. The primary outcome of interest should not be GM BLL but the proportion of women with elevated BLL levels. This analysis is suggestive that there was an increase in women with elevated levels. No statistical testing appears to be performed on these rates using Poisson distribution testing. The denominator is not given in Table 3- but I suspect that the results would be highly statistically significant if the data was provided to allow calculation. The analysis of GM BLL and the subsequent prediction work on cord blood levels is only marginally relevant. Without direct testing of cord levels - I think it would be enough to infer that women with normal BLL would not put a fetus at risk. In the study of cord BLL - rates of elevated lead levels are not presented, and again mean BLL is not a useful outcome. The range suggests that no levels were elevated - however I am not certain that these are full ranges or if they are just interquartile range. This should be stated explicitly.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 97-103: Should cite GM(95% CI), not as SEM to convey to readers more sense of the variability of the lead levels. This is particularly an issue since the POST cohort is much larger than the others and hence its SEM much smaller. Also, although the average levels did not significantly increase from PRE to DURING, the levels POST were significantly, albeit slightly lower than the PRE or DURING levels.

lines 106-107: Should read "in the literature associated with fetal loss ...", rather than "to result in "

lines 246-259: Again, should format the GM with their 95% CIs, not the SEM. Should make clear to the reader the 95% CI cited represent the CIs for the differences. In fact, since the actual GMs are already in Tables, could simply cite the difference, then its 95% CI for the difference in this section of text. Also, when the difference is NS, there is no need to cite the p value to 3 significant figures, could either omit (since the CIs include 0) and therefore the p-value is redundant, or simply state that the difference was not statistically significant.

Table 2: Should include some measure of variability for age, eg, SD if appropriate metric for the age distribution.

Table 3: Should clarify that OUTSIDE Geometric mean refers to area outside of Flint. Should cite as GM (95% CI), not as SEM. For the number of values ≥ 5 $\mu\text{g}/\text{dL}$, should include (95% CI) for those proportions and should show in Results that the rates are not significantly different pre, during and post. Should also acknowledge that the sample sizes for the pre and during and the rates of BLL ≥ 5 $\mu\text{g}/\text{dL}$ are so infrequent that there is little power to ensure that there were 0 instances of BLL exceeding those levels among the Flint population PRE or DURING (For rates of 0/91 or 0/84, the upper boundary on the 95th% CI is $\sim 4\%$). Should include the Total (N) designation of Table 2 for Table 3.

Table 4: Should cite blood cord levels as mean (95% CI), rather than as mean \pm SD, to be consistent with previous tables.

Fig 1: The legend cites calculated GM, while the figure y-axis label states mean BLL. Need to clarify. Should re-format as mean (95% CIs), not mean \pm SEM. Also, the legend could be clearer re: the meaning of the *s.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- We do not require that initial submissions adhere to the Green Journal publication requirements. Articles for which a revision is requested however, do require that the revised submission adhere to all Green Journal formatting requirements. We strongly recommend that you read the Instructions for Authors to be able to present your revised submission in a format that is likely to allow for a prompt final decision. It is available as a PDF download from the login page for EditorialManager. It has information for formatting, required elements, word limits, reference style and other necessary items.

- Please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell out all abbreviations on first use. It is reasonable to not use abbreviations for words that are seldom used in the paper. We try to limit "unique" abbreviations so that readers don't have to frequently refer back to the first notation of the abbreviation to remember its meaning. We realize that this may affect word count but believe it makes it easier in most cases for the reader. So for instance, CBA, FRW, and BLL and GM will not be acceptable.

- You don't mention anything in your objective about predicting fetal levels. Is that an objective of your study? If so, it should be included. Please indicate primary and secondary outcomes.

- You will see that your introduction needs to be shortened quite a bit and a lot of this moved to your discussion section. However, please do provide some background in introduction for the following

1. Absorption of lead from food, water sources--are these the most common exposures in adults? Is it efficient? (ie, what I'm trying to ask, is there typically a linear association between water levels and blood levels?)
2. Persistent: Once ingested and absorbed, how long does lead persist naturally without treatment if source is eliminated?
3. Placental transfer

Briefly, indicate that there are conflicting data about association of maternal blood levels and pregnancy complications, including miscarriage, preterm labor, stillbirth. Then give the background about the article estimating the pregnancy related problems in Flint as the reason for your study.

- Before you start using specific blood lead levels, could you please give us normal values in adult women?

- please substitute causal language for associative language. Its not the blood lead level that is the issue (ie, its not a lead level of 62 vs 68) its elevated blood levels, correct?

- for clarity would you consider editing the sentence starting on 127 to something like....."....pregnancy outcomes by Nogaki in 1957, who reported an 84.6% spontaneous abortion rate in the spouses of ... Did this mean of all pregnancies in spouses (Partners?) of these lead work, 84,6% ended in SAB or did the find that among these mean, 84.6% of their partners had an SAB? Really different things and needs to be clear.

- 84.6%
- what did this study find?
- please give authors' names here (Grossman and Slusky)
- your introduction is about 2x as long as it should be as much of this should be in discussion. You could condense the information about different studies down quite a bit here in introduction.
- I'm not clear in your methods section about why these lead levels were obtained prior to the water switch. Are these cross-sectional lead levels (ie, any patient who met your inclusion criteria who had a blood level obtained during the prespecified time periods and may have had only 1 blood level obtained?) or were they serial measurements (same woman's values pre, post and during?). Its important particularly in the pre-switch period to know why these tests were done. Presumably its because the clinician felt that the patients was at increased risk for having an elevated blood lead level (and perhaps why you didn't find a difference in the pre vs during levels). It perhaps would be a cleaner study to have taken stored blood from reproductive age women in the same area and test it for the pre-levels.
- what do you mean by "single source"?
- controlled or specified? IF controlled, what did you control?
- how far outside Flint?
- Do you mean it was the reference lab for the area? Does it measure other lab tests disproportionately? Or do you mean the medical center provides the care for the majority of low SES people in the area AND has its own lab that measures lead levels SO does most of the lead testing in the area?
- Is this important to the outcome of the study? (Ie, that in one time frame the lead levels were parts of a panel and later they were drawn as single lab tests?) Do the results differ? Are you reporting on any of the other components of the panel? If not, you can exclude this information (Panel vs single)
- On line 159 you said the medical center did the analysis. Here, you say it's a send-out test. Which is it? They can't both be true.
- delete highlighted
- you will see when you read the instructions for authors that we don't use subheadings like here on line 176-177
- perhaps well -known to you , but news to me and I suspect most Ob GYN's. Can you provide a bit of information about this? Levels go up in Winter and Down in Summer? Vice versa?
- Perhaps more clear to state that "the fetal blood level of lead ranges from 55-92% of the maternal levels [give reference]
- why not just randomly pick one of the values for these 18 women?
- for women with first time deliveries". What do you mean for "First time deliveries"? Were these women having their first baby ever or their first at this hospital?
- this information needs to be references in your objectives for your study as well.
- The predicted cord blood levels seem predicated on the kinetics, distribution and blood levels in all women (the group studied in Table 2) would be transferable if all those women hypothetically were pregnant. Wouldn't it be simpler to just use the data (Table 4) from the actual maternal values. Not sure what the point was, besides making the samples larger.
- can you provide the level of maternal care at your hospital (LoMC)--its a specific level based on ACOG standards. This should go up around line 156.
- What is the relevance of including information about women outside of Flint? Were they also in an area in which there were concerns about increase exposure to lead in the drinking water? How far outside Flint are you talking about?
- What are the CI's referring to?
- what is extremely high?
- please change from "post-partum" to "at delivery"

- As noted earlier, its unclear what your estimated blood lead levels add. You have measured levels...those are more relevant.
- Fertility rate=The Total Fertility Rate (TFR) is the average number of children that would be born alive to a woman during her lifetime if she were to pass through her childbearing years having births according to the current schedule of age-specific fertility rates.
- Not "late fetal death". The term is stillbirth
- Since you've not provided the rate of stillbirth here, saying that that the rate of miscarriage is far higher since it occurs in 10-20% doesn't really make sense. A reasonable number of stillbirth is about 6/1000 live births.
- I am guessing this is the author of the non peer reviewed working paper referenced in your introduction, but you never gave a name. Please make this clearer. You could make this paragraph clearer by saying some like this:
The spontaneous abortion rate is estimated to be 10-20% in recognized pregnancies.
- This is not a very rigorous report as it is based on patient self-report. As well, limiting it to parous women makes it non-generalizable. I think it is reasonable to just stick with the 10-20%.
- Important to state here that the drop in fertility rates they focused on was after the switch but before the advisory went out about the lead exposures, so they were suggesting that something about the lead exposure and NOT behaviors after the lead exposures were none that might be mediating this change.
- Please call this something more specific here and where introduced in Introduction."working paper" isn't a specific thing that I know of Perhaps just by the authors' names? Is this a graduate students' thesis?
- They do note in the article that this calculation is a bit unstable and only added a 0.1/1000 live birth increase in stillbirth rate. Likely just noise. I would focus on that.
- true that these may be non comparable data, but in general, the birth rates are higher in lower SES communities, so this doesn't help your argument as it would be working in the opposite direction than what was seen
- While perhaps true, not part of the scope of your paper to be commenting on use of "gray literature". It may have been the impetus for your work.
- You've already said all of this (lines 348-360) elsewhere so its not necessary here.

2. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- a. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
- b. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."
*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

- Lines 169-181: Please cite your Clinical Toxicology article "Analysis of blood lead levels of young children in Flint, Michigan before and during the 18-month switch to Flint River water" here, and note that you have described these methods previously.

6. Please submit a completed STROBE checklist with your revision.

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

7. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

8. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

10. Précis, Abstract, and Body Text: Please avoid using causal language. Your findings should be framed as "associations."

11. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

12. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

13. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. Figures

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

17. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>) Please contact the publication office if you have any questions.

HURLEY

May 22, 2019

Nancy C. Chescheir, MD

Editor-In-Chief, Obstetrics & Gynecology

Ms. No. ONG-19-547 Blood Lead Levels of Females of Child Bearing Age in Flint Michigan and the Water Crisis

Dear Dr. Chescheir,

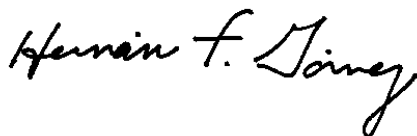
Thank you for giving us an opportunity to send a revised version of our manuscript designed to satisfactorily address comments from the Reviewers. As requested, I have included in this cover letter the comments made by the Reviewers (and the Editor) followed by our response. I believe the criticisms have allowed for an improved and tighter manuscript.

The authors anticipate the findings of this paper will be of interest to the readership of Obstetrics & Gynecology. I am the lead author and affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. The study was approved by the Institutional Review Board of the Hurley Medical Center where the data was obtained.

The authors fully support transparency and wish to select "OPT-IN" (if accepted) for publication — please publish my response letter and subsequent email correspondence related to author queries.

The manuscript is not under consideration elsewhere and will not be submitted elsewhere unless a final negative decision is made by the Editors of Obstetrics & Gynecology. I am the corresponding author, who along with the other authors wish to assure you that we do not have any conflicts of interests to disclose.

Respectfully Yours,



Hernán F. Gómez, MD (lead and corresponding author)



REVIEWER COMMENTS:

Reviewer #1:

Dear Dr. Gomez,

Thank you for submitting your manuscript "Blood Lead Levels of Females of Child Bearing Age in Flint Michigan and the Water Crisis" for consideration in the Green Journal. This is overall a well-done study that addresses a persistently controversial issue in the State of Michigan.

The following are comments I have concerning your study:

Reviewer 1: 1) The statistical methodologies seem appropriate for the study. It would be nice to see an actual summary of the data points of maternal blood lead levels and/or a comparison of the arithmetic mean and the geometric means of the lead levels. As well, the mixed linear regression analysis seems appropriate.

Response: "The authors agree and have modified Table 3 (now Table 2) to contain arithmetic means, as well geometric means, to allow for comparison. Table 2 will thus allow the readership to compare visually the arithmetic and geometric means."

Reviewer 1: 2) I do not think umbilical cord blood data post exposure and the modeling data for umbilical cord blood levels is worth having in this study. It is not a part of the objectives of the study, and it implies that there is also no fetal/neonatal effects of the lead exposure without any real "pre-exposure and during exposure" data as was analyzed in the females of childbearing age population.

Response: "The authors reviewed these data and agree that little is added to the study with the modeling. Therefore the umbilical cord data post exposure and the modeling data for umbilical cord data have been eliminated from the manuscript."

Reviewer 1: 3) Even though not explicitly stated, the study seems to imply that there were no maternal/fetal/neonatal/reproductive effects due to lead levels in the water in Flint. This is probably true given the lead levels presented in the manuscript, but again there is no actual outcomes data to support this conjecture. In this same vein, we also do not have blood lead levels in patients with adverse outcomes in the Flint areas studied.

Response: "The authors agree with the reviewer that it is probably true there were no maternal/fetal/neonatal/reproductive effects due to lead levels in the water in Flint. We note, there are no blood lead level data for actual pregnant patients available for analysis before or during the Flint River water exposure. Thus, the reviewer is correct that there are no outcomes data to directly support the conjecture. This is a limitation of the study. Given readers of The

Green Journal may have the same question/observation we added wording to address this limitation.”

Additional Response: To address this limitation we added the following sentence in the discussion section (page 12, paragraph 2, line 306):

“The main limitation in this investigation is that females of child bearing age were studied as a comparable surrogate to pregnant females. Neither blood lead levels nor actual outcomes data from pregnant females before or during the Flint water exposure are available for analysis.”

Reviewer 1: 4) Finally, the multiple acronyms stated in the abstract are not re-defined in the body of the actual manuscript.

Response: “In order to conform to journal standards and to eliminate the need to re-define acronyms in the body of the manuscript, the multiple acronyms have been eliminated and the words are now fully spelled out. We believe this will also make it easier for the reader”

Reviewer #2:

I think this study can contribute to information that informs monitoring in flint as well as sparks interest in further investigation of exactly how lead levels affect pregnancy outcomes.

I do have some concerns and questions that I think should be more explicitly stated in the paper, however:

Why choose the geometric mean as a marker?

Response: “In the revision, we provide arithmetic means data in Table 2 to allow the readership to review these data. We have also added an explanation of why geometric means were utilized since the readership may have the same question. We opted to utilize geometric mean blood lead levels to evaluate blood lead levels instead of arithmetic means because we aimed to utilize the same methodology as The Centers for Disease Control and Prevention.”

Additional Response: In addition to providing arithmetic mean data to the readership, we added wording to address the use of geometric means in this study in the section labeled “Statistical Analysis of Blood Lead Levels” (page 7, paragraph 1, line 187):

“We opted to utilize geometric mean data to evaluate blood lead levels because this is the preferred measurement used by the Centers for Disease Control to analyze population exposure to environmental toxins in blood; providing a better estimate of central tendency for data that are distributed with a long tail at the upper end of the distribution (18). The Centers for Disease Control utilized national estimates of geometric means based on data from the National Health and Nutrition Survey to determine the current Centers for Disease Control blood lead reference value of 5.0 µg/dL (9).”

Reviewer 2: Were pregnancy outcomes of these women of CBA looked at? I would be interested to know that information as well.

Response: “Of the N = 84 Flint women of child bearing age tested DURING the Flint River water switch period, four were pregnant. Three had term deliveries, and one had a miscarriage at 8.5 weeks. These are not sufficient numbers to allow for formal comparison to other timeframes (PRE or POST).”

Reviewer 2: Does MI/Flint routinely test for lead in pregnant women?

Response: “Hurley Medical Center, the regions ACOG Level III (Subspecialty Care) facility, began testing blood lead testing routinely in pregnant women in the delivery room beginning in January 2016 (three months after the water was switched back to the original Great Lakes water source). Routine testing did not occur before or during the period of use of Flint River water.”

Reviewer 2: Also why use all women of childbearing age? Why not only look at pregnant women?

Response: The number of pregnant women tested (n = 4) was not sufficient to allow for formal study.

Reviewer 2: Is this CBA surrogate an appropriate proxy for pregnant women? Is there something about pregnant physiology that changes levels of lead, or dangerous levels of lead? Although women of CBA can be pregnant, they cannot experience adverse pregnancy outcomes without being in that physiologic state.

Response: “The whole blood lead levels of pregnant women are determined primarily by their blood lead levels just prior to pregnancy and tend to decrease slightly during pregnancy because of the increase in plasma volume. For example, in a study of 128 “healthy” pregnant Chinese women conducted during 2007-2008, mean BLLs were 5.95 ± 2.27 , 5.51 ± 1.93 , 5.57 ± 1.85 , and 6.88 ± 1.90 $\mu\text{g/dL}$ during the first, second, and third trimesters and postpartum, respectively. In this study the mean BLL of 120 non-pregnant women (controls) was 6.87 ± 2.29 $\mu\text{g/dL}$ (36).”

(36) Y Jiang, H Wang, J Chen, G Zhang, L Chen, W Dai, W Zhou, H Yang, and H Shi:
Blood lead levels during different trimesters of pregnancy and possible influencing factors in Chengdu, China. Biol Trace Element Res, 144: 27-35, 2011.

Additional Response: The reviewer adds an important question that the authors believe the readership may have as well. Therefore, we have added the following wording to the discussion section (page 12, paragraph 2, line 311):

“Blood lead levels of pregnant women are determined primarily by their blood lead levels just prior to pregnancy and tend to decrease slightly during pregnancy because of the increase in plasma volume (36).”

Reviewer 2: It is not clear from the paper why cord BLL were calculated or validated. From what is talked about in the manuscript it seems that pregnant female BLL are what is used when comparing rates of SAB, preterm labor, etc. Why bother calculating cord BLL? how does this contribute? What are dangerous cord BLL seen in previous research?

Response: “The authors reviewed these data and agree that little is contributed to the study with the calculated cord blood lead levels. Therefore, calculated cord blood lead levels and mention of cord levels have been eliminated from the manuscript.”

Reviewer 2: Is there a possibility that lower levels are still dangerous (seems unlikely if you base previous studies), or that there is an unidentified factor that is contributing?

Response: “Based on our literature review, there is no measurable effect in pregnancies with maternal lead levels below 5 µg/dL—thus we agree that adverse outcomes at the lower levels we found are unlikely. The authors agree that an unmeasured or unidentified factor in Flint River water that may (in theory) have been present.”

Additional Response: We added wording to acknowledge the possibility of an unknown factor in the discussion section (page 13, paragraph 1, line 316):

“Our investigation focused on a single measurable variable — blood lead, however other as yet unidentified environmental substances in the Flint River may have a potential effect on pregnancy outcome.”

Reviewer 2: I think a clearly stated thesis would help answer some of these questions for me. I am working on the assumption that you aim to show that this working paper is not in line with what your objective data is suggesting given previously published dangerous lead levels to reassure the community that while terrible and inexcusable, lead levels are not at a level likely to cause drastic increases in poor ob outcomes.

Response: “The reviewer is correct that an aim is to demonstrate (using the best available objective data) that while lead exposure in drinking water is unacceptable, blood lead levels were not at a level to result in poor OB outcomes.”

Additional Response: We added the following hypothesis in the introduction section (page 5, paragraph 1, line 143):

“Our hypothesis is that although increased exposure to lead from drinking water was possible during the water switch, blood lead concentrations of reproductive-age women living in Flint were below levels associated with adverse obstetric outcomes.

Reviewer 2: Specifically: Introduction:

I think the introduction can be shortened. I would somewhere in the beginning explicitly state expected lead levels

Response: “The authors understand that the introduction can be significantly shortened. We have followed the suggestions outlined below to tighten the manuscript.”

Additional Response: Regarding expected lead levels, the authors added the current blood lead level data from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey for environmental toxins for 2019 in the manuscript (page 4, paragraph 1, line 130):

“The current geometric mean lead level, 0.735 µg/dL, in all females nationally is far lower, and is 0.920 µg/dL for all adults age 20 years and older (9).”

Reviewer 2: not sure 111-113 is necessary and would condense 115-122 into just that first sentence.

Response: “The original lines 111-113 have been eliminated from the manuscript. Detailed description of the historical publications noted in lines 115-122 have also been removed so that the introduction may be tighter and meet The Green Journal formatting guidelines.”

Additional Response: The opening sentence in the revised manuscript introduction now begins (page 4, paragraph 1, line 111):

“Lead is a reproductive toxicant and high blood lead concentrations in pregnant women have been reported to cause spontaneous abortions, stillbirths, and preterm deliveries (1).”

Reviewer 2: 128-129 I am assuming these are the BLL of the pregnant spouse although I found this sentence a little confusing

Response: “The sentence *is* somewhat confusing. The Nogaki (1957) study in question is cited numerous times in the literature. However, since women in the study were not directly tested for blood lead concentrations, the authors decided to remove this reference.”

Reviewer 2: 135-138 This is a key sentence in addition to your last paragraph in setting the stage for your presentation of results and argument as to why those results are important

Response: The authors agree with this assessment and have left intact the key message of the sentence in the revised introduction regarding blood lead levels of 5 µg/dL.

Reviewer 2: Methods:

I would mention a strength is this hospital is NPO with pts of low SES which arguably would be most vulnerable with highest lead levels- and still the values were much lower than the previously described "danger zones."

Response: “The reviewer is correct that Hurley Medical Center is a not-for-profit organization serving patients of lower socioeconomic status. And the reviewer is further correct in his assessment that these patients are arguably most vulnerable to higher lead levels.”

Additional Response: We have added the following describing the above to the methods section (page 5, paragraph 2, line 154):

“Hurley Medical Center is a public non-profit hospital providing ACOG Level III maternal care to the majority of patients of lower socioeconomic status in the region. Patients of lower socioeconomic status are more vulnerable to having higher blood lead concentrations.”

Reviewer 2: What were the water sources of these patients? Do we have any way of knowing?

Response: “Patients addresses were geocoded to allow for probable access to household water serviced by the Flint Water Authority. The authors agree that the possibility that other sources of water may have been available should be addressed in the discussion.”

Additional Response: We have added the following describing the above to the discussion section (page 12, paragraph 1, line 303):

“These citizens may have had other sources of water such as school, university tap water, bottled water, or places of employment; all of which may or may not be within the Flint boundary.”

Reviewer 2: I would discuss why we think levels post may have dropped off? Awareness of crisis? Drinking more bottled water?

Response: “The authors agree that we should discuss possibilities for the modest, but statistically significant decline in blood lead levels. Possibilities include the public health warnings and subsequent avoidance of tap water”

Additional Response: We have added the following wording regarding the blood lead level decrease noted in the POST timeframe (page 10, paragraph 2, line 254):

“There was a modest but significant decrease in blood lead levels when comparing the DURING versus POST Flint River water exposure periods along with a substantial 4000% increase in the number of females of child bearing age tested after public awareness of lead contaminated water was widespread in Flint.”

Additional Response: We further addressed the very real possibility that water avoidance of tap water may have occurred (page 12, paragraph 1, line 292):

“Evidence for a water avoidance phenomenon may be found in the statistics from the City of Flint’s financial reports, that document a sharp decline in total water consumption after the Flint River water switch; and before the water advisory regarding lead was issued in late September 2015 (17,35). The centum cubic feet of residential water consumption dropped from 2013 through 2015 as follows: 2013 = 9,470,315; 2014 = 8,114,852; and 2015 = 2,857,898 centum cubic feet. This is a decline of nearly 70% of residential water consumption in Flint from 2013 to 2015 (17,35).”

Reviewer 2: 162- can the heavy metal panel values and just lead level values be directly compared? Is this significant/worth mentioning?

Response: “The heavy metal panels were all unremarkable and these concentrations were not significantly correlated with blood lead values.”

Reviewer 2: 184 again not sure why we are looking at cord BLL

Response: “Portions of the manuscript looking at modeling or cord blood lead levels have been edited out.”

Reviewer 2: Outcome measures:

246-267 again i feel like this could be condensed. I also think structurally if they are significant enough to be under 2 different headers, than the info should be in 2 tables and not 1 (everything is all in table 3). But if you condense than removal the 260 header and keep all in table 3.

Response: “The authors agree, and as a result the line 260 header has been removed, we have condensed this section, and utilized Table 3 (Table 2 in the revised manuscript) as suggested.”

Reviewer 2: 264-267 I had difficulty understanding this sentence the way it was written- would restructure sentence.

Response: “In response we have restructured the sentence found in Lines 264-267 aiming for clarity.”

Additional Response: The sentence in question has been rewritten and condensed as follows in the revised manuscript (page 9, paragraph 2, line 240):

“Within Flint during the POST Flint River water period, thirteen females of 3,546 tested (0.37%) had BLLs ≥ 5.0 $\mu\text{g/dL}$; while in those living outside Flint, seven of 3,678 of females (0.19%) had BLLs ≥ 5.0 $\mu\text{g/dL}$.”

Reviewer 2: 271 -missing figure #

Response: This portion of the manuscript, outlining results of predicted margins of cord levels, has been edited out of the manuscript.

Reviewer 2: 269- again what is the purpose of the cord blood modeling? in terms of supporting your research and its implications

Response: This portion of the manuscript, outlining results of predicted margins of cord levels, has been edited out of the manuscript. In addition, all references to cord blood or cord blood modeling are no longer part of the paper.

Reviewer 2: Discussion:

306-311 This is useful information, but I'm not sure why it is being presented here

Response: The authors agree the information contained in lines 306-311 is not integral to the manuscript — the lines have been removed.

Reviewer 2: 324-336 This paragraph reads more like background than discussion

Response: “A key impetus to this investigation has been the rather unfortunate message to the Flint community (and nationally) that lead exposure resulted in negative OB outcomes. As such the authors hope to leave part of this section intact. Upon review of lines 306-336, we note that this section may be condensed by eliminating lines 306-327.”

Additional Response: Lines 306-327 has been edited out of the document. The following is eliminated:

~~“Recognized fetal losses generally fall into two categories, spontaneous abortions and losses after 20 weeks (late fetal deaths/ stillbirths). Losses from spontaneous abortions are far higher since an estimated 10 to 20% of recognized pregnancies end in miscarriage. Cohain (2017) reports spontaneous abortion rates of 27% among 53,479 parous women.”~~

Reviewer 2: 356-360 this was said earlier and i think can be removed from this section unless you expand upon why controlling was important and who this population represents and how that is relevant to your data.

Response: “We agree that lines 356-360 are a bit redundant. We have thus removed these lines from the manuscript.”

Reviewer 3:

The authors present data and blood lead levels (BLL) in women during the Flint water crisis. This is a very germane topic as teratogens such as lead can cause substantial issues during gestation if at high levels in maternal blood. I think this is an overall well written work with a clear and well executed hypothesis.

Reviewer 3: Lines 111-113: Please use a different example than Charles Dickens- this makes this work seem immature; it could be removed altogether.

Response: “We agree that lines 111-113 are unnecessary. The lines have been edited out of the manuscript.”

Reviewer 3: Lines 166-167: Please expand on this issue: If you did not have access to the medical records, how can you be sure that these patients did not have a history of lead exposure previous?

Response: “The authors note this point would be appropriately addressed as a limitation in the investigation.”

Additional Response: We have added the following wording in the discussion section (page 12, paragraph 2, line 313):

“Access to medical records, which may have given us insight to exposure history, was limited and any previous short-term or long-term exposure to an unknown lead source would have had the potential to result in an upward bias in subsequent blood lead levels in the subjects studied.”

Reviewer 3: Lines 184-189; How did you pick this rubric to use to determine maternal or serum lead levels? Is their data to support his approach. This needs to be further elucidated as it is central to the conclusions being drawn.

Response: “This section and all sections having to do with modeling have been removed from the manuscript.”

Reviewer 3: Line 209 Why do AA women have higher baseline lead levels than whites? Is this environmental or is there some genetic issue here?

Response: “It is thought that African American females have higher baseline lead levels due to greater environmental exposure to lead.”

Additional Response: Given the readership may have a similar question, we added the following wording to the revised document (page 8, paragraph 1, line 201):

“This disparity is thought to reflect the cumulative effect of differential age-related environmental exposure to lead [20]”

Reviewer 3: Please add a statistical assessment of how you decided to run your data the way that you did.

Response: “A statistical assessment of how he decided to run the data in the manner done was requested from our statistician.”

Additional Response: We have added the following wording to the Statistical Analysis section of the manuscript (page 7, paragraph 2, line 194):

“Geometric mean blood lead levels were compared across the three 18-month periods and within and outside the boundary of Flint by means of a mixed effects linear regression model with a Gaussian conditional distribution and a log link function. Since geometric mean blood lead levels are very right-skewed, this model can account for the skew and allow calculation of arithmetic means.”

Reviewer 3: Lines 210-214: It is interesting that the BLL was actually lower during the water issue. Do you think that the water was therefore contaminated prior to this? This has profound implications for the community and needs to be elucidated further.

Response: “The authors note that the geometric mean (and arithmetic) mean lead levels were lower in the DURING period (compared to PRE), but the difference is very minute with a geometric mean decrease of 0.04 µg/dL. This difference did not reach statistical significance and thus speculation about this observation needs to be done rather cautiously. However, the reviewer brings up a rather intriguing point – the lead concentration in Flint water before the water switch is an unknown variable – we have thus added this as a limitation (page 13, paragraph 1). We do know that fairly profound water avoidance behaviors began shortly after the Flint River water switch – likely due to color changes and odor of the water – and this may have blunted the lead exposure in drinking water overall. Striking evidence of water avoidance behavior is noted in the publicly available annual City of Flint financial report (see below).”

Additional Response: In order to address the lack of an increase in the DURING period (in relation to PRE) we have added the following wording in the discussion (page 12, paragraph 1, line 300):

“We suggest that the lack of an increase in blood lead concentrations in females studied during the Flint River water switch may have been the result of avoidance of using Flint River water in food preparation or direct consumption due to the disagreeable appearance and odor of the water. These citizens may have had other sources of water such as school, university tap water, bottled water, or places of employment; all of which may or may not be within the Flint boundary.”

Reviewer 3: The discussion is overall well written and not over reaching. I do think more should be written about the inherent weaknesses of this paper.

Response: “The authors are certainly appreciative of the sentiment in the first sentence above. Critiques from this reviewer (and others) have allowed for a more robust discussion of inherent weaknesses of the manuscript.”

Additional Response: In order to further expand on inherent weaknesses of the manuscript we have added the following wording in the discussion. (page 12, paragraph 2, line 306):

“The main limitation in this investigation is that females of child bearing age were studied as a comparable surrogate to pregnant females. Neither blood lead levels nor actual outcomes data from pregnant females before or during the Flint water exposure are available for analysis. There are no specific guidelines from the Centers for Disease Control for blood lead testing in pregnant females. Blood lead levels in non-pregnant females of child bearing age are nonetheless a comparable surrogate to those found in pregnant females. Blood lead levels of pregnant women are determined primarily by their blood lead levels just prior to pregnancy and tend to decrease slightly during pregnancy because of the increase in plasma volume (36). Access to medical records, which may have given us insight to exposure history, was limited and any previous short-term or long-term exposure to an unknown lead source would have had the potential to result in an upward bias in subsequent blood lead levels in the subjects studied. Our investigation focused on a single measurable variable — blood lead, however other as yet unidentified environmental substances in the Flint River may have a potential effect on pregnancy outcome. This study is subject to selection bias in testing higher-risk patients in the

PRE and DURING time periods which did not exist in the POST exposure period. Finally, the lead concentration in Flint water before the water switch is an unknown variable.”

Reviewer 4:

This study examines blood lead levels in women between the ages of 12 and 50 living around Flint Michigan. Although this is interesting and important data that needs to be known - it is so highly specific to one situation that it doesn't really add to the general knowledge base of the practicing Ob/Gyn.

Response: The authors agree that data is specific to a rather unusual situation, one that reached national consciousness as the greatest environmental disaster of the 21st century. And again, as a disaster that has been reported through news outlets nationally to have had a substantial negative impact on pregnancy outcomes. The authors submit that an objective study using the best available evidence may help to reassure a population exposed to the unfortunate water switch. We also suspect that this timely study and review of lead exposure may benefit practitioners in other communities where residents are at risk for lead exposure.

Reviewer 4: In addition - the methodology - which extrapolates predicted cord BLLs only holds if there are no other individual factors that change lead pharmacodynamics.

Response: “We agree that the methodology and data which extrapolates blood lead levels may be problematic. Therefore, we have eliminated the cord blood lead data from the manuscript.”

Reviewer 4: In this dataset, little is known about where women drink water (in home, at work, percent bottled). Given that the researchers based their analysis on where women live - it is reasonably possible that home zip code does not accurately classify source of water intake. This misclassification bias would tend to obscure true differences and reduce power to determine true differences between populations.

Response: “We agree with the reviewer that refusal to drink from the tap, or drinking bottled water, or water from work/ school all may have played a critical role in the mean blood lead levels of the various time periods examined. We welcome the postulation that these and other sources of drinking water may have served to keep the blood lead concentrations in females unchanged during the period of the Flint River water exposure.”

Additional Response: We have added wording regarding the possibility of utilization of alternative water sources to the discussion (page 12, paragraph 1, line 300):

“We suggest that the lack of an increase in blood lead concentrations in females studied during the Flint River water switch may have been the result of avoidance of using Flint River water in food preparation or direct consumption due to the disagreeable appearance and odor. These patients may have had other sources of water such as school, university tap water, bottled water, or places of employment; all of which may or may not be within the Flint boundary.”

Reviewer 4: It would be helpful if actual fetal death rates could be captured and depressing that as a country our public health infrastructure does not support this kind of critical tracking.

Response: “The authors agree that actual fetal death rates would have been helpful and that it is rather unfortunate the current public infrastructure does not support this critical tracking.”

Reviewer 4: The primary outcome of interest should not be GM BLL but the proportion of women with elevated BLL levels. This analysis is suggestive that there was an increase in women with elevated levels.

Response: “The authors agree that an analysis of woman with elevated levels would be of interest. An analysis of the proportion of women with elevated blood lead levels will not be feasible given that there are virtually no subjects tested PRE nor DURING the Flint River water source change that tested at or above a level that might be considered to be elevated (5 µg/dL, the threshold level found to result in increased risk of spontaneous abortions and coincidentally the CDC reference value).”

Additional Response: Given members of the readership might have the impression there was an increase in women with elevated levels we added the following wording in the discussion (page 10, paragraph 2, line 250):

“In this investigation examining females of child bearing age both inside and outside Flint, all those tested before and during the Flint River water exposure had geometric mean blood lead levels well below the Centers for Disease Control reference value of 5 µg/dL. Not one level was greater than 1.6 µg/dL and the majority had a level of 0.5 µg/dL (limit of detection) or lower.”

Reviewer 4: No statistical testing appears to be performed on these rates using Poisson distribution testing. The denominator is not given in Table 3- but I suspect that the results would be highly statistically significant if the data was provided to allow calculation.

Response: “The authors (and the statistician) are not clear what is meant by denominator in this context. We agree that Poisson distribution is appropriate for count data (such as the number of re-admissions). At times these models involve an offset/ exposure, such as if the outcome is “number of surgeries with complications,” a surgeon with more surgeries would naturally have a higher number of complications, so one can set his/ her offset as total number of surgeries which essentially acts like a denominator for their complication rate. However, there is no natural analog here. We felt a Poisson modeling strategy was not optimal due to geometric mean blood lead levels taking on continuous values. We have adjusted our analysis to fit a generalized mixed model with a conditional Gaussian distribution and a log link function which is more appropriate for right-skewed data similar to a Poisson model, but unlike a Poisson model does not assume the outcome to be counts.”

Reviewer 4: The analysis of GM BLL and the subsequent prediction work on cord blood levels is only marginally relevant. Without direct testing of cord levels - I think it would be enough to infer that women with normal BLL would not put a fetus at risk.

Response: “The authors agree with the assessment that modeling using geometric mean blood lead levels and subsequent predictions on cord blood levels may be eliminated and that it would be enough to infer that women with blood lead levels would not put a fetus at risk. This portion of the manuscript has been deleted.”

Reviewer 4: In the study of cord BLL - rates of elevated lead levels are not presented, and again mean BLL is not a useful outcome. The range suggests that no levels were elevated - however I am not certain that these are full ranges or if they are just interquartile range. This should be stated explicitly.

Response: “In response to this comment (and comments of other reviewers), all portions of the text which involved the modeling and study of cord blood lead levels have been edited out of the document.”

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Statistical Editor: lines 97-103: Should cite GM (95% CI), not as SEM to convey to readers more sense of the variability of the lead levels. This is particularly an issue since the POST cohort is much larger than the others and hence its SEM much smaller. Also, although the average levels did not significantly increase from PRE to DURING, the levels POST were significantly, albeit slightly lower than the PRE or DURING levels.

Response: “The data is now cited as GM (95% CI), no longer as SEM to better convey to readers more a sense of the data variability, as described above.”

Statistical Editor: lines 106-107: Should read "in the literature associated with fetal loss ...", rather than "to result in "

Response: “Wording has been altered in Line 106 (abstract) to read “in the literature associated with fetal loss ...”

Statistical Editor: lines 246-259: Again, should format the GM with their 95% CIs, not the SEM. Should make clear to the reader the 95% CI cited represent the CIs for the differences. In fact, since the actual GMs are already in Tables, could simply cite the difference, then its 95% CI for the difference in this section of text.

Response: “The data in lines 246-259 is now cited as geometric mean with their 95% CIs, not the SEM. Wording has been added to the portion of the manuscript to make clear to the reader the 95% CI cited represent the CIs for the differences.”

Statistical Editor: Also, when the difference is NS, there is no need to cite the p value to 3 significant figures, could either omit (since the CIs include 0) and therefore the p-value is redundant, or simply state that the difference was not statistically significant.

Response: “The text has been written to state that the difference was not statistically significant, and the NS p values were omitted.”

Statistical Editor: Table 2: Should include some measure of variability for age, eg, SD if appropriate metric for the age distribution.

Response: “Measure of variability for age (SD) has been added to Table 2 (Table 1 in the revised manuscript).”

Statistical Editor: Table 3: Should clarify that OUTSIDE Geometric mean refers to area outside of Flint. Should cite as GM (95% CI), not as SEM.

Response: “Table 3 (Table 2 in the revised manuscript) was modified to clearly state that OUTSIDE geometric mean refers to the area outside of Flint. SEM was removed and replaced with geometric mean (95% CI).”

Statistical Editor: For the number of values ≥ 5 $\mu\text{g/dL}$, should include (95% CI) for those proportions and should show in Results that the rates are not significantly different pre, during and post.

Response: “Table 3 (Table 2 in the revision) has been modified to include percentages of values ≥ 5 $\mu\text{g/dL}$ with the inclusion of (95% CI).”

Additional Response: After consulting with our statistician who confirmed no significant differences in the rates ≥ 5 $\mu\text{g/dL}$, we added the following wording in the results section (page 9, paragraph 2, line 243):

“The percentages of blood lead levels ≥ 5 $\mu\text{g/dL}$ PRE, DURING, and POST are not significantly different.”

Statistical Editor: Should also acknowledge that the sample sizes for the pre and during and the rates of BLL ≥ 5 $\mu\text{g/dL}$ are so infrequent that there is little power to ensure that there were 0 instances of BLL exceeding those levels among the Flint population PRE or DURING (For rates of 0/91 or 0/84, the upper boundary on the 95th% CI is $\sim 4\%$).

Response: “We added wording to acknowledge the lack of power regarding the proportion of blood lead levels ≥ 5 $\mu\text{g/dL}$.”

Additional Response: we added the following wording in the results section (page 9, paragraph 2, line 244):

“The sample sizes for PRE and DURING are low, and the occurrence of blood lead levels ≥ 5.0 $\mu\text{g/dL}$ are so infrequent that there is little power to ensure there were no instances of elevated blood lead levels among the entire Flint population during the PRE or DURING time frames.”

Statistical Editor: Should include the Total (N) designation of Table 2 for Table 3.

Response: “The Total (N) designation of Table 2 (now Table 1) is included in the revised Table 3 (now Table 2).”

Statistical Editor: Table 4: Should cite blood cord levels as mean (95% CI), rather than as mean \pm SD, to be consistent with previous tables.

Response: “The portion of the study involving cord blood lead levels has been removed from the study in response to other commentaries. As a result, Table 4 is edited completely out of the manuscript.”

Statistical Editor: Fig 1: The legend cites calculated GM, while the figure y-axis label states mean BLL. Need to clarify. Should re-format as mean (95% CIs), not mean \pm SEM. Also, the legend could be clearer re: the meaning of the *s.

Response: “We have modified the figure legend and figure y-axis so both state geometric mean. In addition, the graph has been re-formatted as geometric mean (95% CIs), not SEM. The legend has been clarified regarding the meaning of the *s (we added: * = significance ($P < .05$) during v. post exposure).”

EDITOR COMMENTS:

Editor Comment: Line 87 - Please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell out all abbreviations on first use. It is reasonable to not use abbreviations for words that are seldom used in the paper. We try to limit “unique” abbreviations so that readers don’t have to frequently refer back to the first notation of the abbreviation to remember its meaning. We realize that this may affect word count but believe it makes it easier in most cases for the reader. So for instance, CBA, FRW, and BLL and GM will not be acceptable.

Response: “The abbreviations listed above (and others) have been eliminated and the words spelled out to conform to journal standards and make it easier for the reader”

Editor Comment: Line 87 - We do not require that initial submissions adhere to the Green Journal publication requirements. Articles for which a revision is requested however, do require that the revised submission adhere to all Green Journal formatting requirements. We strongly recommend that you read the Instructions for Authors to be able to present your revised submission in a format that is likely to allow for a prompt final decision. It is available as a PDF download from the login page for EditorialManager. It has information for formatting, required elements, word limits, reference style and other necessary items.

Response: “The Instructions for Authors has been reviewed for adherence to the Green Journal publication requirements.”

Editor Comment: Line 96 - You don't mention anything in your objective about predicting fetal levels. Is that an objective of your study? If so, it should be included. Please indicate primary and secondary outcomes.

Response: “The portion of the manuscript involving predicting fetal levels, cord blood modeling and so forth has been edited out of the study (as recommended by reviewers).”

Editor Comment: Line 22 - You will see that your introduction needs to be shortened quite a bit and alot of this moved to your discussion section.

Response: “Most of the literature review of blood lead levels and fetal outcome in the introduction has been moved to the discussion section—thus shortening the introduction considerably.”

Editor Comment: Line 122 - However, please do provide some background in introduction for the following:

1. Absorption of lead from food, water sources--are these the most common exposures in adults? Is it efficient? (ie, what I'm trying to ask, is there typically a linear association between water levels and blood levels?)
2. Persistent: Once ingested and absorbed, how long does lead persist naturally without treatment if source is eliminated?
3. Placental transfer

Response: “The authors have added background in the introduction for 1) absorption of lead from water as a source (and the association between water lead levels and blood lead levels), 2) the persistence or half-life of lead once ingested and absorbed, and 3) the placental transfer of lead to the fetus.”

Additional Comment: we added the following wording in the revised introduction (page 4, paragraph 1, line 111):

“Lead is a reproductive toxicant and high blood lead concentrations in pregnant women have been reported to cause spontaneous abortions, stillbirths, and preterm deliveries (1). Exposure to metallic lead and lead-containing chemical compounds can occur through inhalation, ingestion, and transplacental routes (2). Ingestion of lead contaminated water is a common source of lead exposure in older homes with drinking water service lines made from lead or containing lead solder (3). The relationship between blood lead levels and lead levels in water reported in different studies varies considerably because water sample collection methods, duration of exposure, and exposure to other sources of lead vary among studies (3). Nonetheless, significant associations between blood and water lead levels have been reported, particularly in sensitive populations such as pregnant women and children. A correlation coefficient of 0.59 between blood lead levels and composite water lead concentrations was found in one study (4). Once absorbed, the elimination half-life of blood lead is estimated to be 28-36 days (5). The

placenta provides little protection to the fetus from maternal blood lead with the ratio between umbilical cord and maternal blood lead concentrations estimated to be 0.92 (6).”

Editor Comment: Line 122 - Briefly, indicate that there are conflicting data about association of maternal blood levels and pregnancy complications, including miscarriage, preterm labor, stillbirth. Then give the background about the article estimating the pregnancy related problems in Flint as the reason for your study.

Response: “The lengthy portion of the introduction regarding previous studies has been sharply truncated and largely moved to the discussion section (save one study). And in beginning in line 137 of the revised manuscript we give the background about the Grossman & Slusky paper estimating pregnancy related problems in Flint as the reason for the study.”

Additional Response: We added wording indicating there are conflicting data about the association of maternal blood levels and pregnancy complications (page 4, paragraph 2, line 125):

“Studies of low to moderate level lead exposures have reported mixed findings regarding the association of maternal lead exposure and the risk of pregnancy complications including miscarriage, preterm labor, and stillbirth.”

Editor Comment: Line 123 - please substitute causal language for associative language. Its not the blood lead level that is the issue (ie, its not a lead level of 62 vs 68) its elevated blood levels, correct?

Response: “Certainly blood lead levels as high as 62 or 68 $\mu\text{g/dL}$ would be associated with morbidity— inclusive of an association with increased risk of fetal loss. There is no known safe blood lead level and this exploration of the literature with respect to what levels are associated with poor fetal outcome has been truncated and moved from the introduction to the discussion.”

Editor Comment: Line 123 - Before you start using specific blood lead levels, could you please give us normal values in adult women?

Response: “The CDC utilizes geometric means to report these data in the National Health and Nutrition Survey. Data are available for females (of all ages), and for adults (for both genders); we thus given both of these values in the manuscript.”

Additional Response: We have added the following wording in the revised introduction section (page 4, paragraph 2, line 130):

“The current geometric mean lead level, 0.735 $\mu\text{g/dL}$, in all females nationally is far lower, and is 0.920 $\mu\text{g/dL}$ for all adults age 20 years and older (9).”

Editor Comment: Line 127 - for clarity would you consider editing the sentence starting on 127 to something like....."....pregnancy outcomes by Nogaki in 1957, who reported an 84.6% spontaneous abortion rate in the spouses of ... Did this mean of all pregnancies in spouses

(Partners?) of these lead work, 84,6% ended in SAB or did the find that among these mean, 84.6% of their partners had an SAB? Really different things and needs to be clear. - 84.6% - what did this study find?

Response: “The historical Nogaki 1957 article is by nature confusing since the blood lead levels were obtained in male lead industry workers, not the women studied. It was mainly included for historical reasons and is not integral to the study. The authors have therefore removed this reference and any related wording from the manuscript.”

Editor Comment: Line 134 – what did this study find?

Response: “The investigation showed an odds ratio for spontaneous abortion of 1.8 for every 5 µg/dL increase in maternal blood lead.”

Additional Response: We added the following wording in the introduction section (page 4, paragraph 2, line 127):

“Kosnett (2007) advises pregnant women to avoid occupational or avocational lead exposure that would result in blood lead levels > 5 µg/dL citing an investigation showing an odds ratio for spontaneous abortion of 1.8 for every 5 µg/dL increase in maternal blood lead (7,8).”

Editor Comment: Line 144 - please give authors' names here (Grossman and Slusky)

Response: The names Grossman & Slusky were added to this portion of the manuscript. It now reads (page 5, paragraph 1, line 137):

“Grossman & Slusky used regression analysis to attribute an increase in spontaneous miscarriages, and late fetal deaths to maternal exposure to lead in the drinking water (11).”

Editor Comment: Line 153 - your introduction is about 2x as long as it should be as much of this should be in discussion. You could condense the information about different studies down quite a bit here in introduction.

Response: “The information about different studies has been condensed and largely moved to the discussion section.”

Editor Comment: Line 155 (Methods) - I'm not clear in your methods section about why these lead levels were obtained prior to the water switch. Are these cross-sectional lead levels (ie, any patient who met your inclusion criteria who had a blood level obtained during the prespecified time periods and may have had only 1 blood level obtained?) or were they serial measurements (same woman's values pre, post and during?).

Response: “The Editor is correct that for the PRE and DURING periods we collected the results of lead levels of any patient who met inclusion criteria for the study during the prespecified time periods. The Editor is also correct that only one blood level was obtained per patient. They were not serial measurements.”

Additional Response: We added the following wording in the methods section (page 5, paragraph 2, line 149):

“This is a retrospective cross-sectional investigation of all available blood lead levels collected from Hurley Medical Center from females of child bearing age (ages 12 through 50) residing within and outside Flint, Michigan during three matched time periods.”

Editor Comment: Line 155 (Methods) - Its importnat particularly in the pre-switch period to know why these tests were done. Presumably its because the clinician felt that the patients was at increased risk for having an elevated blood lead level (and perhaps why you didn't find a difference in the pre vs during levels). It perhaps would be a cleaner study to have taken stored blood from reproductive age women in the same area and test it for the pre-levels.

Response: We did not have direct access to the medical records of primary care physicians to determine the purpose of the various laboratory tests ordered for these subjects. Though we note the tests were not targeted in a fashion to believe the clinicians were specifically concerned about elevated lead levels, rather the blood testing was part of a diffuse battery of testing including “heavy metal panel” (arsenic, lead, and mercury blood concentrations), endocrine panels (commonly thyroid functions studies) and vitamin levels (such as 25-hydroxy vitamin D, and vitamin B-12). This sharply contrasts with the POST timeframe where clinicians specifically ordered blood lead levels as a result of concerns regarding lead contaminated drinking water.”

Editor Comment: Line 156 - what do you mean by "single source"?

Response: “We are referring to subjects in the investigation coming from a single institution (Hurley Medical Center). This term is unnecessary and has been edited out of the manuscript.”

Editor Comment: Line 158 - how far outside Flint?

Response: The females resided outside the Flint boundary line (different water source), but within the same county as Flint.

Additional Response: We edited wording in the methods section (page 5, paragraph 2, line 151):

“Females outside Flint all resided within the same county (Genesee County) but utilized a different residential water source.”

Editor Comment: Line 158 - controlled or specified? IF controlled, what did you control?

Response: “The authors reviewed the wording and do not believe the word “controlled” is helpful in describing methods. The word has been removed.”

Additional Response: We edited wording in the methods section (page 5, paragraph 2, line 149):

“This is a retrospective cross-sectional investigation of all available blood lead levels collected from a single medical center from females of child bearing age (ages 12 through 50) residing within and outside Flint, Michigan during three matched time periods.”

Editor Comment: Line 159 - Do you mean it was the reference lab for the area? Does it measure other lab tests disproportionately? Or do you mean the medical center provides the care for the majority of low SES people in the area AND has its own lab that measures lead levels SO does most of the lead testing in the area?

Response: “Hurley Medical Center provides the care for the majority of people of low socioeconomic status and thus processes most of the lead testing for the region. All blood samples processed go to Warde Medical Laboratory, Ann Arbor, as noted in Line 171.”

Additional Response: Given the redundancy and potential confusion we have edited out the wording in lines 158-159 regarding the Hurley laboratory and added the following wording in the revision (page 5, paragraph 2, line 153):

“The medical center receives most blood samples for lead analysis in patients in the greater Flint region.”

Editor Comment: Line 162 - Is this important to the outcome of the study? (i.e., that in one time frame the lead levels were parts of a panel and later they were drawn as single lab tests?) Do the results differ? Are you reporting on any of the other components of the panel? If not, you can exclude this information (Panel vs single).

Response: “We are not reporting on any of the other components of the panel and have therefore edited out (excluded) this information from the manuscript.”

Editor Comment: Line 171 - On line 159 you said the medical center did the analysis. Here, you say it's a send-out test. Which is it? They can't both be true.

Response: “We clarified the medical center wording on line 159 as they receive blood samples, but do not actually do the analysis. The wording in line 171 (revision line 161) remains regarding Warde Medical Laboratory.”

Editor Comment: Line 175 - delete highlighted

Response: “The highlight has been removed from line 175.”

Editor Comment: Line 176 - you will see when you read the instructions for authors that we don't use subheadings like here on line 176-177

Response: “We reviewed the instructions for authors and removed the subheadings on lines 176-177.”

Editor Comment: Line 180 - perhaps well-known to you, but news to me and I suspect most Ob GYN's. Can you provide a bit of information about this? Levels go up in Winter and Down in Summer? Vice versa?

Response: Blood lead concentrations are higher in summer months than in winter. This phenomenon has been observed in multiple studies (including one done in Flint) and is thought to be related to environmental factors.

Additional Response: We removed the words “well-known” and added the following sentence in the revised methods section (page 6, paragraph 2, line 167):

“Because blood lead concentrations are higher in the summer months than in the winter (14,15), we compared blood lead levels in females of child bearing age during three 18-month periods selected to match the dates of the Flint River water exposure to control for the seasonal variability of blood lead levels (14,15).”

Editor Comment: Line 184 - Perhaps more clear to state that "the fetal blood level of lead ranges from 55-92% of the maternal levels [give reference]

Response: The manuscript no longer contains an analysis of calculated or predicted cord blood lead concentrations. Therefore, any wording regarding fetal blood levels (such as ranges from 55-92% of mothers) has been removed from the manuscript.

Editor Comment: Line 211 - why not just randomly pick one of the values for these 18 women?

Response: “Statistical treatment was required given it was not 18 women, but rather 18% of the women had repeated measurements in the POST period (N=7224). This is a rather large number of females (18% of 7224 = 1300) with repeated measurements. Given the large number involved a random intercept was deemed necessary in order to eliminate any bias.”

Editor Comment: Line 224 - this information needs to be references in your objectives for your study as well.

Response: This section (supplemental analysis of maternal blood lead levels) has been removed from the manuscript since it involves calculation of predicted cord blood levels.

Editor Comment: Line 224 - for women with first time deliveries". What do you mean for "First time deliveries"? Were these women having their first baby ever or their first at this hospital?

Response: This section (supplemental analysis of maternal blood lead levels) has been removed from the manuscript since it involves calculation of predicted cord blood levels.

Editor Comment: Line 225 - The predicted cord blood levels seem predicated on the kinetics,

distribution and blood levels in all women (the group studied in Table 2) would be transferable if all those women hypothetically were pregnant. Wouldn't it be simpler to just use the data (Table 4) from the actual maternal values. Not sure what the point was, besides making the samples larger.

Response: This section (supplemental analysis of maternal blood lead levels) has been removed from the manuscript since it involves calculation of predicted cord blood levels.

Editor Comment: Line 229 - can you provide the level of maternal care at your hospital (LoMC)--its a specific level based on ACOG standards. This should go up around line 156.

Response: Hurley Medical Center provides ACOG Level III maternal care; this information was placed around line 156 (revised manuscript - page 5, paragraph 2, line 154).

Additional Response: We added the following sentence in the revised methods section (page 5, paragraph 2, line 154):

“Hurley Medical Center is a public non-profit hospital providing ACOG Level III maternal care to the majority of patients of lower socioeconomic status in the region.”

Editor Comment: Line 234 - What is the relevance of including information about women outside of Flint? Were they also in an area in which there were concerns about increase exposure to lead in the drinking water? How far outside Flint are you talking about?

Response: “The women were just outside the Flint boundary line, but all within the same county (Genesee) —the county information was added to the manuscript. They are in the same area yet would not have been impacted by the Flint River water change. Matching and comparing these women to those inside Flint is relevant to understanding the impact of the water source change to the region.”

Editor Comment: Line 250 - What are the CI's referring to?

Response: The 95% CI represent the CIs for the differences. This was added to the manuscript for clarification.

Editor Comment: Line 299 - what is extremely high?

Response: The authors reviewed words “extremely high” and note the word “extremely” is largely subjective and have elected to remove this word. The word “high” remains (revision line 261), and the authors go on to discuss what is meant by “high” blood lead levels in the same paragraph.

Editor Comment: Line 313 - please change from "post-partum" to "at delivery"

Response: This section of the discussion has been edited out since cord blood modeling is no longer a part of the manuscript.

Editor Comment: Line 317: - As noted earlier, its unclear what your estimated blood lead levels add. You have measured levels...those are more relevant.

Response: “This section of the discussion has been edited out since estimated blood lead levels are no longer a part of the manuscript.”

Editor Comment: Line 328 - Fertility rate=The Total Fertility Rate (TFR) is the average number of children that would be born alive to a woman during her lifetime if she were to pass through her childbearing years having births according to the current schedule of age-specific fertility rates. So, “fertility rates” is not the right term here. Do you mean birth rate?

Response: “We do mean birth rate. The authors are appreciative of the explanation regarding fertility rate = TFR. We now use “birth rate” instead of “fertility rate” in the revised manuscript (page 11, paragraph 2, line 278).”

Editor Comment: Line 329 - Not "late fetal death". The term is stillbirth

Response: “We have replaced “late fetal death” with the term stillbirth (revision line 278).”

Editor Comment: Line 325 - Since you've not provided the rate of stillbirth here, saying that that the rate of miscarriage is far higher since it occurs in 10-20% doesn't really make sense. A reasonable number of stillbirths is about 6/1000 live births.

Response: “Regarding the comments for the rate of miscarriage and rate of stillbirths —The authors appreciate the information provided by the Editor and have modified this passage in the discussion.”

Additional response: To make the paragraph clearer we added the following sentence in the revised discussion section (page 11, paragraph 2, line 275):

“The stillbirth prevalence at the community level is typically less than one percent (32); the spontaneous abortion rate is estimated to be 10-20% in recognized pregnancies (33).”

Editor Comment: Line 327 - I am guessing this is the author of the non peer reviewed working paper referenced in your introduction, but you never gave a name. Please make this clearer. You could make this paragraph clearer by saying some like this: The spontaneous abortion rate is estimated to be 10-20% in recognized pregnancies.

Response: “Regarding the reference cited in line 327, it is not the author of the non-peer reviewed working paper but rather a reference (Cohain 2017) that is not key to the discussion section. The Cohain 2017 reference has been removed. In addition, we have made the paragraph clearer by adding “the spontaneous abortion rate is estimated to be 10-20% in recognized pregnancies” as suggested in revision line 276.”

Editor Comment: Line 327 - This is not a very rigorous report as it is based on patient self-report. As well, limiting it to parous women makes it non-generalizable. I think it is reasonable to just stick with the 10-20%.

Response: “Given it is not a very rigorous report (and limited to parous women) we have opted to remove this reference from the manuscript. We decided to just stick with the 10-20%.”

Editor Comment: Line 328. - Please call this something more specific here and where introduced in Introduction. "working paper" isn't a specific thing that I know of Perhaps just by the authors' names? Is this a graduate students' thesis?

Response: “We agree that the term “working paper” is not a familiar one in the medical community and have therefore substituted “working paper” with the authors names (Grossman & Slusky). This is not a graduate students’ thesis –both authors are faculty members (assistant professors) at their respective institutions.”

Editor Comment: Line 328 - Important to state here that the drop in fertility rates they focused on was after the switch but before the advisory went out about the lead exposures, so they were suggesting that something about the lead exposure and NOT behaviors after the lead exposures were none that might be mediating this change.

Response: “We agree with the observation above regarding the focus of the Grossman & Slusky paper was on a decrease in fertility rates after the water switch (April 24, 2014) but before the advisory regarding lead exposure (issued September 25, 2015). Grossman & Slusky note that reassurance of government officials reduced the scope of an avoidance response to the water crisis.”

Additional response: To make the paragraph clearer we added the following sentence in the discussion section (page 11, paragraph 2, line 288):

“Grossman & Slusky focused on the period beginning with the switch to Flint River water until the City of Flint issued a health advisory 18 months later. They suggest that prior to the health advisory, continual reassurance by officials reduced the scope of an avoidance behavioral response to the water crisis (11).”

Editor Comment: Line 329 - They do note in the article that this calculation is a bit unstable and only added a 0.1/1000 live birth increase in stillbirth rate. Likely just noise. I would focus on that.

Response: “The authors agree that the 58 percent increase of stillbirths in the paper was in fact an increase in stillbirth rate by 0.1 deaths per 1,000 compared to control areas. We also agree that this finding by regression analysis is likely just noise.”

Additional response: we added the following sentences in the revised discussion section (page 11, paragraph 2, line 279):

“The reported 58% increase in fetal death rate is the result of a calculated increase in stillbirth rate of a modest 0.1 deaths per 1000 women aged 15-49. This calculation was based on a regression analysis comparing Flint to 15 large cities in Michigan chosen as “natural controls” (11) since their citizens were not exposed to a water switch during this timeframe.”

Editor Comment: Line 336 - true that these may be non comparable data, but in general, the birth rates are higher in lower SES communities, so this doesn't help your argument as it would be working in the opposite direction than what was seen.

Response: “The lines referring to the communities being non-comparable have been removed from the manuscript.”

Editor Comment: Line 337 - While perhaps true, not part of the scope of your paper to be commenting on use of "gray literature". It may have been the impetus for your work.

Response: “We have removed the comments regarding “working papers” beginning on line 337.”

Editor Comment: Line 348 - You've already said all of this (lines 348-360) elsewhere so its not necessary here.

Response: “The authors agree that Lines 348-360 are not necessary and have deleted these lines from the manuscript.”

CROSSCHECK

Lines 169-181: Please cite your Clinical Toxicology article “Analysis of blood lead levels of young children in Flint, Michigan before and during the 18-month switch to Flint River water” here and note that you have described these methods previously.

Response: We cited the Clinical Toxicology article and added the following sentence in the methods section (**page 6, paragraph 3, line 177**):

“These methods have been described and utilized in a previous investigation (17).”

(17) Gómez HF, Borgialli DA, Sharman M, Shah KK, Scolpino AJ, Oleske JM, Bogden JD. Analysis of blood lead levels of young children in Flint, Michigan before and during the 18-month switch to Flint River water. Clin Toxicol 2019; Mar 14:1-8. doi: 10.1080/15563650.2018.1552003. [Epub ahead of print].