OBSTETRICS & GYNECOLOGY

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- 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.*

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

Date: Jul 18, 2019
To: "Ellen H. Lee" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-845

RE: Manuscript Number ONG-19-845

Maternal Zika virus infection: evaluating the risk of small-for-gestational-age and preterm birth

Dear Dr. Lee:

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 Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Authors report on the outcomes of liveborn singleton infants with confirmed and probable ZIKV compared to those with no infection using a population based study based in NY City from 2016. The study supports an association between ZIKV infection and fetal growth restriction.

Main issues:

1- Well designed and well conducted study that provides important evidence to support the association between ZIKV and fetal growth restriction! While it might be well powered for the main questions utilizing the main group, any conclusion derived from sub-group analyses (e.g. differences based on trimester of exposure) should be taken with cautions!

Specific issues:

1- Introduction: well written

2- Methods: Please identify the primary outcome of the study! Please also provide the power based on the sample size to detect a clinically significant difference in the primary outcome!

3- Results, tables, and figures:
a. Table 1, please consider adding the unadjusted OR for all included variables!
b. Table 3 and 4: please consider different design for the tables to be easier to read!

4- Discussion:
a. Please limit the strong conclusions to the main group of the study (n=250); all conclusions from subgroup analyses should be highlighted as hypothesis generating due to smaller samples.
b. Please add some discussion about proposed recommendations for surveillance that can help in clinical practice and if there is any change needed for the current guidelines based on the finding of this study

Reviewer #2: Zika burst into the news several years ago with a flurry of reports that created some disquiet, particularly among exposed pregnant women. Although a number of case series have since been published, that have started to clarify the course and consequences of the infection in pregnancy, questions remain. These investigators have taken advantage of a very large data set to try to solidify some of the initial impressions of the consequences of obstetrical infection for the neonate. The paper has much to recommend it, though a few clarifications would be useful. Specifically:

1. Their information was obtained largely from birth certificates, giving them access to a broad but somewhat shallow and often unreliable data set. They acknowledge this to a small extent in their limitations section (citing cigarette use as an example of unreliable data). I would just say that many covariates might be similarly limited, because even things such as medical complications are not uniformly defined nor obtained by all institutions.

2. BMI is an important covariate. They used pre-pregnancy BMI, rather than delivery BMI. In the first instance pre-pregnancy BMI is notoriously unreliable with clinicians often seeing women weighing 200 pounds at 6 weeks gestation, who say that their pre-pregnancy weight was 150. In addition, weight gain also contributes to size, so weight at delivery might be a more telling metric.

3. I wasn't clear about the manner in which women were segregated into two groups—exposure in the first trimester or additional exposure in the second and third trimester. Wouldn't some women have had exposure only later in pregnancy (e.g., lived in an endemic starting at 16 weeks, and came to the US later in pregnancy? I may be confused because the definition of timing given on line 120, and the definition given on line 197 differ slightly.

4. Although the conclusion that birthweight at term was significantly different is true, it might be worth contextualizing it by noting that a 64 gram difference is clinically insignificant.

5. In regard to a 64 gram difference, it might be useful to change the gestational age grouping "term" which encompasses several weeks, to a specific week of gestation (e.g., 38 vs. 40). The weight gain per week is more than the 64 gram difference they found between groups, so if one group delivers a week earlier, that would explain the difference.

6. It might be worth assessing differences between pregnancies whose infection was diagnosed based on antigen, from those based on antibody alone.

7. Could the authors speculate as why only 5.2% of women had babies in the lowest 10th percentile of birth weight?

8. Were iatrogenic and spontaneous preterm births assessed separately?
While addressing these issues may be helpful, they are peccadillos, not fatal flaws. The authors have made an important contribution to our understanding

Reviewer #3:

Table 1: Should include stats testing to evaluate any differences in baseline characteristics.

Table 2: The sample sizes are too few to generalize the NS finding of no difference in PTB rates. Given the sample sizes and respective proportions, the power was ~ .25 to discern a difference. Put another way, one would need ~ 6x the sample of maternal ZIKA cases with the same rates of PTB to have sufficient power to conclude that the given proportions supported the NS finding. Alternatively, given the sample sizes and proportions at hand, the maternal ZIKA cases would have to have a PTB rate of > 11.8 %, based on the 80% power etc.
The number of cases of SGA and of PTB were also too few to allow for adjustment with 7 variables. Likely an over fitted model. For the SGA comparison, could use a matching algorithm, since there is a large data set of controls, then evaluate whether the SGA difference is replicated.

Table 3: The differences in (+) vs (-) ZIKA infant test cohorts for rates of SGA and PTB were based on small numbers of cases and the NS findings cannot be generalized, due to low power.

Table 4: These subset comparisons have generally small samples and the NS findings are not generalizable due to low power. With the exception of BW for term infants, the number of cases are too few to allow for adjustment for 7 or 8 variables. Again, could use a matching algorithm to test whether the associations with SGA were corroborated. Should include a column for unadjusted RRs to contrast with aRRs.

Reviewer #4: Summary:
This paper is a retrospective cohort study to evaluate the risk of small for gestational age and preterm birth with Zika virus infection during pregnancy is associated. The authors concluded that maternal Zika virus infection was associated with lower birthweight of term infants and an increased risk of small-for-gestational-age infants, but not with preterm birth in these pregnancies. One strength of this paper is the use of a large sample size to evaluate the association between Zika virus and these outcomes. However, this paper has number of issues that merit comments by the authors:

General comments:
1. One of my biggest concern about the data collection for this study was that mothers self-reported their clinical information, including smoking status 3 months prior to or during pregnancy, parity, and pre-pregnancy body mass index (Page 8, line 135-137). How many women self-reported this information? This can adversely affect the results of the statistical analysis, leading to differential mis-classification and selection bias, because women whose fetuses developed

Zika infection are more likely to remember compared to women whose fetuses did not develop Zika virus infection.

Abstract:

1. Page 5, line 56: Why did the authors prefer to use Poisson regression with a robust error variance (modified Poisson regression) instead of a negative binomial regression for analysis?

2. Page 5, lines 60-62: Was the difference in birth weight between Zika exposed and non-exposed infants of 64 grams statistically significant?

3. Page 5, line 69:….."This supports a putative association between ZIKV infection during pregnancy and fetal growth restriction"...If the authors studied the association between Zika virus infection and SGA/preterm birth, why would they make a conclusion, extrapolating the association between Zika virus infection to fetal growth restriction? In other words, the fact that these fetuses were SGA doesn't necessarily mean there was fetal growth restriction during pregnancy. To buttress my point, if these babies exposed to Zika virus develop microcephalic heads (one of the known complications of Zika virus infection), two components of growth ultrasounds will be abnormal (head circumference and biparietal diameter). Hence, it would be difficult to determine accurate growth evaluations on these babies. The authors should reword this sentence to reflect the conclusions from their study.

Introduction:
The introductory section of this paper was well written and of appropriate length.

Materials and methods:

1. Page 8, Line 126: "…Infants with birthweight <400 or >6000 grams or gestational age <24 or >42 completed weeks were excluded"… How did the authors decide to use 400 grams and 6000 grams? The standard definitions for extremely low birth weight and large for gestational age are 1000 grams and 5000 grams respectively.

2. Page 8, lines 144-145: "…maternal age, parity, race/ethnicity, education, neighborhood poverty, pre-pregnancy BMI, and infant sex"… How did the authors select these potential predictors/confounders to include in their Poisson model? In the adjusted Poisson model(s), did the authors include all potential predictors/confounders, or did they eliminate predictive factors that were not statistically significant? If yes, which factors were eliminated?

3. Page 9, line 151: Please change "restricting" to 'restricted'.

4. Page 9, line 152: Please change "comparing" to 'compared'.

5. Please show a power analysis so that reviewers and authors will know if the authors were adequately powered to show statistically significant findings.

Results:

1. Page 10, lines 178-180: Why do you think that women with and without ZIKV infection during pregnancy differed with respect to self-reported age, race/ethnicity, geographic area of birth, education, neighborhood poverty, and pre-pregnancy BMI (Table 1)? What effect would this difference have on your results?

2. Page 10, lines 196-197: "……For 28 (11.4%) of these women, exposure occurred in the first trimester only, while the remaining 217 women had exposure during the second and/or third trimester….." This suggests that more fetuses were exposed to Zika virus infection during the 2nd and 3rd trimesters, when fetal organ development is near complete. It this pattern typical of Zika virus exposure? How might more exposure in the 2nd/3rd trimester compared to 1st trimester affect your results?

3. One major concern remains if the authors found any association between Zika virus during pregnancy and SGA. I would think that comparing babies of mothers who tested positive Zika virus infection would be the best way to determine if Zika virus during pregnancy is associated with SGA (i.e infected versus uninfected babies). On Page 10, lines 185-187, The authors state that "…..twenty-eight (11.2%) women with ZIKV infection during pregnancy and 5961 (5.2%) women without ZIKV infection gave birth to an SGA infant; after adjustment, the risk of SGA was 1.8 times higher for women with ZIKV infection during pregnancy (95% CI, 1.3 to 2.6)….." However, on the same page 10, lines 192-195, the authors state that "…..Of the 250 infants born to women with ZIKV infection during pregnancy…..we found no association between congenital ZIKV infection and birthweight, SGA, or preterm birth…" This is very confusing and needs to be clarified - whether there was or wasn't an association between Zika virus infection and SGA.

Discussion:

4. This raises the same concern I had as stated above. The authors state on Page 11, lines 213-214 that…."women with ZIKV infection during pregnancy gave birth to infants who were more likely to be SGA when born at term compared with women with no ZIKV infection during pregnancy….". However, on Page 12, lines 231-232, the authors again stated that…."we found that among infants born to women with ZIKV infection during pregnancy, the prevalence of SGA was no

different among infants with and without laboratory evidence of congenital infection. This needs to be clarified.

Conclusion:
The conclusion is apt, and reflects the hypothesis and findings from the paper.

EDITORIAL OFFICE COMMENTS:

1. 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. 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 point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. 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.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. 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.

4. 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); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Conundrums articles should not exceed 6 pages (1,500 words); Questioning Clinical Practice articles should not exceed 6 pages (1,500 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.

5. 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).

6. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

7. 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.

8. 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.

9. 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.

10. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For p-values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

11. 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.

12. The Journal's Production Editor had the following to say about the figures in your manuscript:

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.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

13. 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/ifauth.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.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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 Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

Nancy C. Chescheir, MD
Editor-in-Chief
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024

August 19, 2019

Dear Dr Chescheir:

Thank you for the opportunity to revise and resubmit our manuscript entitled, “Zika virus infection during pregnancy: evaluating the risk of small-for-gestational-age and preterm delivery” for further consideration as an Original Research article in Obstetrics & Gynecology.

We were grateful for the thoughtful and constructive comments we received from the four reviewers, and would like to highlight the key changes we have made to address these.

To address the concerns raised about confounding control and the number of variables in our models, we have restricted our primary analysis to only include women who identified as Hispanic, non-Hispanic Black, or Other race/ethnicity (i.e., non-Hispanic White women are excluded) and to non-smokers. As there were no non-Hispanic White women or smokers in the group with ZIKV infection during pregnancy, this restricted analysis retains all women with our exposure of interest, ZIKV infection during pregnancy. The groups now have a more comparable distribution of baseline characteristics, and we adjust for fewer covariates in our models. Our finding of an association between ZIKV infection during pregnancy and risk of having a small-for-gestational-age infant is unchanged in this revised analysis.

All tables and figures in the revised manuscript have been amended from the original to reflect the analyses in this restricted cohort. The manuscript contains tracked changes to indicate where the text has been revised. Please find below a point-by-point response to each reviewer comment.

All authors have approved of and agreed to re-submit this revised version of the manuscript.

I affirm that I have read the Instructions for Authors, and opt-in to publication of my point-by-point response letter.

We are again grateful for your review.

Yours sincerely,

Hannah Cooper, MBChB
[redacted]

On behalf of:
Ellen H. Lee, MD
[redacted]

REVIEWER COMMENTS:

Reviewer #1: Authors report on the outcomes of liveborn singleton infants with confirmed and probable ZIKV compared to those with no infection using a population based study based in NY City from 2016. The study supports an association between ZIKV infection and fetal growth restriction.

Main issues:

1- Well designed and well conducted study that provides important evidence to support the association between ZIKV and fetal growth restriction! While it might be well powered for the main questions utilizing the main group, any conclusion derived from sub-group analyses (e.g. differences based on trimester of exposure) should be taken with cautions!

Specific issues:

1- Introduction: well written

2- Methods: Please identify the primary outcome of the study! Please also provide the power based on the sample size to detect a clinically significant difference in the primary outcome!

The primary outcomes for our study are incidence of SGA, incidence of preterm birth and birth weight of term infants. Our primary analysis compares these outcomes for women with and without our primary exposure of interest, ZIKV infection during pregnancy.

For the secondary analysis, we again compare the outcomes of SGA, preterm birth and birth weight but restrict the analysis to the subgroup of infants born to women with ZIKV infection during pregnancy. For this secondary analysis, the exposure of interest is laboratory evidence of ZIKV infection in the infant. Therefore, the secondary analysis compares birthweight, incidence of SGA, and incidence of preterm birth for infants with and without positive ZIKV testing. We have flagged more clearly our secondary analysis in the text (see line 187).

Although we appreciate the reviewer's concerns about the power of our primary analyses, we advocate for the use of confidence intervals and p-values as the best reflection of the study's power, once it has been conducted. We have found support for this approach in the statistical literature, as in the Hoenig and Heisey publication cited here.[1] Additionally, we would like to note that a power calculation can provide information on a statistically significant difference but not a clinically

significant difference.[2] Therefore, we respectfully decline the reviewer's suggestion to provide power calculations.

Given reviewers' comments, however, we have reconsidered whether our results are adequately powered, and we agree that our analysis of preterm birth is underpowered, and several sub-analyses do not have sufficient power. Consequently, we have changed our analyses as follows:

- Presented confidence intervals instead of p values in all tables of results so the precision of each effect estimate can provide information regarding the power of each analysis
- Removed the analyses by trimester of exposure because of the low power for these sub-analyses in addition to the lack of precision of trimester of exposure data as a proxy for timing of ZIKV infection
- Removed statistical testing from the comparison of infants who tested positive for ZIKV in the neonatal period to those who had negative testing, given the small sample size and small number of events

1. Hoenig JM, Heisey DM. The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis. The American Statistician 2001; 55 (https://www.vims.edu/people/hoenig_jm/pubs/hoenig2.pdf)
2. Wasserstein, R. L., & Lazar, N. A. (2016). The ASA's statement on p-values: context, process, and purpose. *The American Statistician*, *70*(2), 129-133.

3- Results, tables, and figures:

a. Table 1, please consider adding the unadjusted OR for all included variables!

We thank the reviewer for this suggestion. Although we appreciate the suggestion and understand how it may be desirable for some readers, we were guided in our decision not to present statistical testing in Table 1 by the 2016 statement from the American Statistical Association (ASA) on p values,[1] and a reflection on this guidance by Farland *et al*.[2] in the journal *Human Reproduction*. Respectfully, we do not believe statistical testing adds useful information regarding the baseline differences between our two groups for this manuscript, and would like to encourage the reader to compare the data presented in the 2 columns themselves.

1. Wasserstein, R. L., & Lazar, N. A. (2016). The ASA's statement on p-values: context, process, and purpose. *The American Statistician*, *70*(2), 129-133.
2. Farland, L. V., et al. (2016) P-values and reproductive health: what can clinical researchers learn from the American Statistical Association? *Human Reproduction*, 31(11), 2406-2410.

b. Table 3 and 4: please consider different design for the tables to be easier to read!

We thank the reviewer for feedback on these tables. We have made several changes to present the data more clearly, including the following:

- Removed p values from all tables
- Simplified Table 3 so it presents results from one subgroup only, infants born to women with ZIKV infection
- Separated Table 4 into two tables (Tables 4 and 5): The revised Table 4 now presents the subgroup analysis comparing women with confirmed ZIKV infection to women without ZIKV infection (in response to comments by Reviewer 2). Table 5 now presents results of sensitivity analyses for the SGA outcome only.

4- Discussion:

a. Please limit the strong conclusions to the main group of the study (n=250); all conclusions from subgroup analyses should be highlighted as hypothesis generating due to smaller samples.

We thank the reviewer for this suggestion. We have removed the analysis of differences in birthweight by trimester of infection in acknowledgement that these findings were based on small numbers and imprecise data. We have edited the discussion regarding the subgroup of infants with positive ZIKV testing to emphasize it is hypothesis-generating (see lines 235-249).

b. Please add some discussion about proposed recommendations for surveillance that can help in clinical practice and if there is any change needed for the current guidelines based on the finding of this study

We do not think our data are sufficient to determine if a change in current guidelines is needed. However, prenatal care providers should understand that even in the absence of a more severe clinical presentation (e.g., congenital Zika syndrome) following maternal ZIKV infection, SGA may be an outcome to anticipate. We have added language regarding this point in the Conclusion paragraph. Surveillance for maternal ZIKV infection currently is complicated by the epidemiology of ZIKV worldwide and limitations of ZIKV diagnostic testing, including cross-reactivity of serologic tests with other flaviviruses. As such, we think recommendations for surveillance would be beyond the scope of this paper.

Reviewer #2: Zika burst into the news several years ago with a flurry of reports that created some disquiet, particularly among exposed pregnant women. Although a number of case series have since been published, that have started to clarify the course and consequences of the infection in pregnancy, questions remain. These investigators have taken advantage of a very large data set to try to solidify some of the initial impressions of the consequences of obstetrical infection for the neonate. The paper has much to recommend it, though a few clarifications would be useful. Specifically:

1. Their information was obtained largely from birth certificates, giving them access to a broad but somewhat shallow and often unreliable data set. They acknowledge this to a small extent in their limitations section (citing cigarette use as an example of unreliable data). I would just say that many covariates might be similarly limited, because even things such as medical complications are not uniformly defined nor obtained by all institutions.

We thank the reviewer for bringing this point to our attention. Investigations by the NYC Vital Statistics group have found that while NYC birth record data may not be sensitive for all measures (e.g., smoking), it is reliable when compared to medical chart review (Joseph Kennedy, personal communication). In light of data reliability concerns, however, we have expanded the section describing the limitations related to birth certificate data, adding the following text:

> Medical co-morbidities and smoking during pregnancy often are poorly documented in birth certificate data,[1,2] potentially explaining the very low estimates of smoking in this cohort. Maternal characteristics and medical condition information obtained from the birth certificate may be inaccurate, therefore models adjusting for these variables may not fully remove confounding.

2. BMI is an important covariate. They used pre-pregnancy BMI, rather than delivery BMI. In the first instance pre-pregnancy BMI is notoriously unreliable with clinicians often seeing women weighing 200 pounds at 6 weeks gestation, who say that their pre-pregnancy weight was 150. In addition, weight gain also contributes to size, so weight at delivery might be a more telling metric.

Although we agree with the reviewer that BMI may be important as it can be associated with poor pregnancy outcomes, we have chosen to use maternal BMI before pregnancy as BMI during pregnancy, and especially at the time of delivery, includes the contribution of fetal and pregnancy tissues, and is thus an indirect measurement of fetal weight and duration of gestation. We strongly believe that including an indirect measurement through delivery BMI would introduce bias. Additionally, a validation study[1] found that, although there is some error and underestimation of pre-pregnancy BMI from birth certificates, it is unlikely to make a substantial difference in research results.

Because BMI is unlikely to be substantially associated with exposure to Zika, adjustment for BMI serves to improve model efficiency rather than adjust for confounding. Therefore, even if errors were more substantial, the use of pre-pregnancy BMI is unlikely to lead to bias in our analysis.

1. Park, S., Sappenfield, W.M., Bish, C. et al. Matern Child Health J (2011) 15: 851. https://doi.org/10.1007/s10995-009-0544-4

3. I wasn't clear about the manner in which women were segregated into two groups—exposure in the first trimester or additional exposure in the second and third trimester. Wouldn't some women have had exposure only later in pregnancy (e.g., lived in an endemic starting at 16 weeks, and came to the US later in pregnancy? I may be confused because the definition of timing given on line 120, and the definition given on line 197 differ slightly.

We recognize the definition of trimester of exposure in our manuscript is confusing. We use trimester of ZIKV exposure as a proxy for trimester of ZIKV infection, given many women in our cohort had asymptomatic ZIKV infection and could not report definitively the timing of their infection. However, as a large proportion of our cohort had exposure to ZIKV that spanned multiple trimesters, these data are imprecise. Given this limitation in the data and the low numbers available for this analysis, we have elected to remove this section from the manuscript as we do not feel it provides useful information with respect to whether timing of infection is associated with SGA, preterm birth and birth weight.

As such, we have removed the definitions that pertain to how the women were segregated into categories based on trimester of exposure.

4. Although the conclusion that birthweight at term was significantly different is true, it might be worth contextualizing it by noting that a 64 gram difference is clinically insignificant.

Thank you for this suggestion. In response to the comment below, we controlled for completed weeks of gestation in our birthweight model and found the difference between the two groups was no longer statistically significant. Our results and conclusions have been revised accordingly.

For our presentation of results from the subgroup of infants born to women with ZIKV infection, we now provide the average weight gain per week after 37 weeks in our data as context for the observed difference:

The proportion of infants born SGA and preterm were similar for infants with positive and negative ZIKV testing, and the difference in mean birthweight was 153 grams, which approximates the average weight gain per week of gestation after 37 weeks for term infants in our cohort.

5. In regard to a 64 gram difference, it might be useful to change the gestational age grouping "term" which encompasses several weeks, to a specific week of gestation (e.g., 38 vs. 40). The weight gain per week is more than the 64 gram difference they found between groups, so if one group delivers a week earlier, that would explain the difference.

We thank the reviewer for bringing this to our attention. We have elected to include completed weeks of gestation in our multivariable model comparing birth weight at term in order to address this concern. We find the difference in birth weight is no longer statistically significant when adjusting for completed weeks of gestation. We have removed the conclusion that ZIKV infection is associated with lower birth weight of term infants from our manuscript.

6. It might be worth assessing differences between pregnancies whose infection was diagnosed based on antigen, from those based on antibody alone.

We thank the reviewer this suggestion. In our study, a diagnosis of ZIKV infection during pregnancy was confirmed if ZIKV RNA was detected in any maternal specimen, or if the infant had any positive ZIKV testing (i.e., detected antibody or viral RNA) immediately after birth. In our cohort, 73 of the 250 women had a confirmed ZIKV infection, and the remaining 177 had a probable infection based on antibody detection.

We acknowledge that among the group of women who had a “probable” infection (i.e., diagnosis of ZIKV based on detection of antibody alone), some may have had an infection with another flavivirus as these antibodies can cross-react. We include a sensitivity analysis which restricts analysis to the women with a confirmed infection, and the results of this analysis support our primary findings.

In response to this comment, we have endeavored to draw more attention to the sensitivity analysis in which we address this issue, including dedicating Table 4 to presenting the results of this sensitivity analysis only.

7. Could the authors speculate as why only 5.2% of women had babies in the lowest 10th percentile of birth weight?

INTERGROWTH-21st is a growth standard (as opposed to a growth reference) and as such was developed in a cohort of women selected because they had healthy pregnancies with no risk factors for abnormal fetal growth. Importantly, women with diabetes during pregnancy and with BMI >30 were excluded in this cohort. In our study, around 16% of all women had BMI >30 and 9% had diabetes. We hypothesize that the inclusion of the infants born to these women (i.e., infants who are more likely to be heavier at birth) shifts the population birthweight distribution such that a smaller proportion had weight below the INTERGROWTH-21st 10th percentile cut-off. We have added details about the characteristics of this growth standard to the discussion, see lines 260-267.

In addition, we include a sensitivity analysis using a growth reference derived in a US population. This growth reference classifies 13% of infants in our study overall as SGA.

8. Were iatrogenic and spontaneous preterm births assessed separately?

We thank the reviewer for this suggestion. Although we would like to be able to assess these groups of preterm births separately, the small number of preterm cases among those with ZIKV infection precludes us from conducting this analysis.

While addressing these issues may be helpful, they are peccadillos, not fatal flaws. The authors have made an important contribution to our understanding

Reviewer #3:

Table 1: Should include stats testing to evaluate any differences in baseline characteristics.

We thank the reviewer for this suggestion. Although we appreciate that this has frequently been used in the past, we were guided in our decision not to present statistical testing in Table 1 by the 2016 statement from the American Statistical Association (ASA) on p values[1], and a reflection on this guidance by Farland et al.[2] in the journal *Human Reproduction*. We do not believe statistical testing adds useful information regarding the baseline differences between our two groups.

1. Wasserstein, R. L., & Lazar, N. A. (2016). The ASA's statement on p-values: context, process, and purpose. *The American Statistician*, *70*(2), 129-133.
2. Farland, L. V., et al. (2016) P-values and reproductive health: what can clinical researchers learn from the American Statistical Association? *Human Reproduction*, 31(11), 2406-2410.

Table 2: The sample sizes are too few to generalize the NS finding of no difference in PTB rates. Given the sample sizes and respective proportions, the power was ~ .25 to discern a difference. Put another way, one would need ~ 6x the sample of maternal ZIKA cases with the same rates of PTB to have sufficient power to conclude that the given proportions supported the NS finding. Alternatively, given the sample sizes and proportions at hand, the maternal ZIKA cases would have to have a PTB rate of > 11.8 %, based on the 80% power etc.

The number of cases of SGA and of PTB were also too few to allow for adjustment with 7 variables. Likely an over fitted model. For the SGA comparison, could use a matching algorithm, since there is a large data set of controls, then evaluate whether the SGA difference is replicated.

We thank the reviewer for this thoughtful analysis. In light of these comments, we agree that our analysis of preterm birth is underpowered. We have clarified this in the text as follows:

> There was no association between ZIKV infection during pregnancy and preterm birth in the adjusted model, however, confidence intervals were wide.

We also thank the reviewer for pointing out that the number of variables in the model for small for gestational age is likely too many for the number of events, and thus the models may not fully adjust for the included covariates. We do not believe sparse data has led to overinflated effect estimates in our models, as the adjusted estimates are more conservative than the crude estimates.

We have elected to address this concern through restriction rather than matching, given the difficulty in matching on so many variables. As there were no non-Hispanic White women or smokers in the group with ZIKV infection during pregnancy, we have restricted the entire analysis to women who identify as Hispanic, non-Hispanic Black or Other race and ethnicity (i.e., non-Hispanic White women are excluded) and to non-smokers. This ensures the groups are more comparable without losing any outcome events in our exposed group.

Our analyses have been updated as follows:

- For the SGA analyses, we now only control for two confounding variables (parity and geographic region of birth) in addition to our variable of interest, ZIKV infection. These variables were selected as their distribution differed substantially by maternal ZIKV infection status and they were strongly associated with the outcome, SGA.

- For the preterm birth analyses, we control for age and geographic region of birth in addition to our variable of interest, ZIKV infection. These variables were selected as their distribution differed substantially by maternal ZIKV infection status and they were strongly associated with the outcome, preterm birth.
- We do not include other potential confounding variables as we acknowledge the number of events in the exposed group means meaningful control for confounding may not be achieved.

These changes are reflected in an updated methods section, see lines 165-185.

Table 3: The differences in (+) vs (-) ZIKA infant test cohorts for rates of SGA and PTB were based on small numbers of cases and the NS findings cannot be generalized, due to low power.

In light of the reviewer's comments, we agree that our analyses in this table are underpowered. Therefore, we have elected to present the number and proportion only, and have not included results of any statistical test. These data may be useful for pooling in a subsequent meta-analysis.

Table 4: These subset comparisons have generally small samples and the NS findings are not generalizable due to low power. With the exception of BW for term infants, the number of cases are too few to allow for adjustment for 7 or 8 variables. Again, could use a matching algorithm to test whether the associations with SGA were corroborated. Should include a column for unadjusted RRs to contrast with aRRs.

We again thank the reviewer for this thoughtful observation and suggestion. We have addressed this by restricting all analyses to a more comparable group of non-White non-smoking women and adjusting for fewer covariates, as described in the response to feedback about Table 2. As stated previously, we have elected to use restriction rather than matching, given the difficulty in matching on so many variables

We have added unadjusted RRs to the revised Tables 4 and 5.

Reviewer #4: Summary:
This paper is a retrospective cohort study to evaluate the risk of small for gestational age and preterm birth with Zika virus infection during pregnancy is associated. The authors concluded that maternal Zika virus infection was associated with lower birthweight of term infants and an increased risk of small-for-gestational-age infants, but not with preterm birth in these pregnancies. One strength of this paper is the use of a large sample size to evaluate the association between Zika virus and these outcomes. However, this paper has number of issues that merit comments by the authors:

General comments:

1. One of my biggest concern about the data collection for this study was that mothers self-reported their clinical information, including smoking status 3 months prior to or during pregnancy, parity, and pre-pregnancy body mass index (Page 8, line 135-137). How many women self-reported this information? This can adversely affect the results of the statistical analysis, leading to differential mis-classification and selection bias, because women whose fetuses developed Zika infection are more likely to remember compared to women whose fetuses did not develop Zika virus infection.

We thank the reviewer for this important point. For NYC birth certificate data, demographic (e.g., age, race, parity) and some exposure (e.g., smoking) information is completed by the mother while clinical information (e.g., hypertensive disorders, BMI) is completed by either a clinician or birth registrar based on information in the medical record. The quality of information from the birth certificate is variable but certain items have been found to be highly reliable. Specifically, in NYC, a set of selected items (e.g., parity, gestational diabetes, delivery route) was found to be generally reliable, with the exception of gestational hypertension and gestational diabetes, for which the birth certificate had low or moderate sensitivity, respectively, but high specificity, when compared to the mother's medical record.[1]

Since most of the clinical information is being reported by clinicians and/or registrars based on the medical record, we believe the likelihood of differential misclassification of these clinical factors is low. Additionally, since these are adjustment variables rather than exposures or outcomes, the impact of misclassification likely would be to contribute to residual confounding. [do you want to state here what you included in the text re: timing of the self-reported information] We have included this possibility in the discussion as follows:

> Information about maternal characteristics and medical conditions obtained from birth certificates may be inaccurate, therefore models adjusting for these variables may not fully remove confounding. Of note, as the self-reported variables used for the birth certificate are usually documented at the first obstetric visit, most women would have provided these data prior to receiving information on their ZIKV infection status, thereby diminishing potential recall bias related to ZIKV infection status.

1. Dietz P, Bombard J, Mulready-Ward C, et al. Validation of selected items on the 2003 U.S. standard certificate of live birth: New York City and Vermont [published correction appears in Public Health Rep. 2015 May-Jun;130(3):192]. *Public Health Rep*. 2015;130(1):60–70. doi:10.1177/003335491513000108

Abstract:

1. Page 5, line 56: Why did the authors prefer to use Poisson regression with a robust error variance (modified Poisson regression) instead of a negative binomial regression for analysis?

We chose to use the Poisson with robust variance model because this model is more robust to biased estimates than negative binomial regression if there is misspecification of the model.
See Chen *et al*., Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. BMC Medical Research Methodology. 2018; 18:63. (https://doi.org/10.1186/s12874-018-0519-5)

2. Page 5, lines 60-62: Was the difference in birth weight between Zika exposed and non-exposed infants of 64 grams statistically significant?

We have revised our birth weight analyses to include adjustment for completed weeks of gestation among term births in response to a reviewer's comment that the original finding we reported was small in comparison to weekly weight gain in the latter weeks of pregnancy. With this adjustment, the difference in birth weight in the primary analysis is no longer statistically significant. The manuscript has been updated to reflect this finding.

3. Page 5, line 69:….."This supports a putative association between ZIKV infection during pregnancy and fetal growth restriction"...If the authors studied the association between Zika virus infection and SGA/preterm birth, why would they make a conclusion, extrapolating the association between Zika virus infection to fetal growth restriction? In other words, the fact that these fetuses were SGA doesn't necessarily mean there was fetal growth restriction during pregnancy. To buttress my point, if these babies exposed to Zika virus develop microcephalic heads (one of the known complications of Zika virus infection), two components of growth ultrasounds will be abnormal (head circumference and biparietal diameter). Hence, it would be difficult to determine accurate growth evaluations on these babies. The authors should reword this sentence to reflect the conclusions from their study.

We agree with the reviewer and have removed this wording from the conclusion. We now state that we found maternal ZIKV infection was associated with an increased risk of having a small-for-gestational age infant, and do not mention growth restriction.

Introduction:
The introductory section of this paper was well written and of appropriate length.

Materials and methods:

1. Page 8, Line 126: "…Infants with birthweight <400 or >6000 grams or gestational age <24 or >42 completed weeks were excluded"… How did the authors decide to use 400 grams and 6000 grams? The standard definitions for extremely low birth weight and large for gestational age are 1000 grams and 5000 grams respectively.

These exclusions (<400 and >6000 grams) serve to remove likely implausible values for birthweight from the birth record dataset; these criteria have been employed by other authors using NYC birth records (e.g., Stein CR, Savitz DA, Janevic T, et al. Maternal ethnic ancestry and adverse perinatal outcomes in New York City. Am J Obstet Gynecol 2009;201:584 e1-9).

The number of extreme values is reported in Figure 1 (181 infants were excluded because of extreme birthweight or gestational age).

2. Page 8, lines 144-145: "…maternal age, parity, race/ethnicity, education, neighborhood poverty, pre-pregnancy BMI, and infant sex"… How did the authors select these potential predictors/confounders to include in their Poisson model?

Potential predictors were selected based on review of literature on birthweight, SGA and preterm birth and an evaluation of the distribution of each predictor by level of our primary exposure, ZIKV infection status. In response to other reviewers' comments, we have reduced the number of covariates in our models for SGA and preterm birth, given the limited number of these events in our exposed group. We have revised our explanation of the included predictors in the Methods section, see lines 165-185.

In the adjusted Poisson model(s), did the authors include all potential predictors/confounders, or did they eliminate predictive factors that were not statistically significant? If yes, which factors were eliminated?

Our models for analysis have changed based on reviewers' comments. Please see above explanation regarding how predictors were selected. We did not eliminate predictive factors.

3. Page 9, line 151: Please change "restricting" to 'restricted'. Done

4. Page 9, line 152: Please change "comparing" to 'compared'. Done

5. Please show a power analysis so that reviewers and authors will know if the authors were adequately powered to show statistically significant findings.

Although we understand the reviewer's concerns about the power of our analyses, we believe that power calculations are unnecessary as the confidence intervals and p-values are the best reflection of a study's power after it has been conducted.[1] We have found support for our approach in the statistical literature, as in the Hoenig and Heisey publication cited here.[1] Additionally, we would like to note that a power calculation can provide information on a statistically significant difference but not a clinically significant difference.[2] Therefore, we respectfully decline the reviewer's suggestion to provide power calculations.

However, we have reconsidered whether our results are adequately powered in light of reviewers' comments, and we agree that our analysis of preterm birth is underpowered, and several sub-analyses do not have sufficient power.

We have changed our analyses as follows:

- Removed the analysis by trimester of exposure due to concerns about low power and the imprecision of these data as a proxy for timing of ZIKV infection
- Removed statistical testing from the subgroup analysis of infants born to women with ZIKV infection during pregnancy in recognition of the low power these tests had to detect a statistically significant difference

We have commented on the wide confidence intervals around the estimates for preterm birth risk, highlighting the lower power in this analysis:

> For women with and without ZIKV infection during pregnancy, prevalence of preterm birth was 8.8% and 7.8%, respectively; there was no association between ZIKV infection during pregnancy and preterm birth in the adjusted model, however, confidence intervals were wide (RR, 1.0; 95% CI, 0.69 to 1.5).

1. Hoenig JM, Heisey DM. The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis. The American Statistician 2001; 55 (https://www.vims.edu/people/hoenig_jm/pubs/hoenig2.pdf)
2. Wasserstein RL, Lazar NA. The ASA's statement on p-values: context, process, and purpose. The American Statistician. 2016;70(2), 129-133.

Results:

1. Page 10, lines 178-180: Why do you think that women with and without ZIKV infection during

pregnancy differed with respect to self-reported age, race/ethnicity, geographic area of birth, education, neighborhood poverty, and pre-pregnancy BMI (Table 1)? What effect would this difference have on your results?

Almost 90% of NYC women with ZIKV infection were born outside of the US, mostly in countries affected by the ZIKV outbreak. This is consistent with the demographics of the wider cohort of NYC residents who were diagnosed with ZIKV during 2016, and likely indicates these populations had greater exposure to ZIKV through travel to countries with mosquito-borne ZIKV transmission. Geographic area of birth is correlated with many of the other covariates we measured, including race/ethnicity, education and neighborhood poverty. These demographic differences may confound any associations we find between ZIKV infection and birth outcomes; as a result, we have addressed potential confounding in our study design and analyses.

First, in response to this and other reviewer comments, we have restricted the study to non-White women as no women with ZIKV infection in NYC identified as non-Hispanic White. This has made the two groups (i.e, exposed and not exposed) more comparable, as reflected in the updated Table 1. In addition, we control for all measured demographic and clinical variables that we identified as potential confounders in our analysis of birth weight. We are limited in the number of confounding variables we can meaningfully include in our SGA and preterm analyses because of the small number of outcome events in exposed women.

There may be unmeasured residual confounding that has affected our results, which we acknowledge in our discussion as follows:

> Although we were able to control for some important predictors of birthweight, residual confounding might have influenced our findings.

2. Page 10, lines 196-197: "……For 28 (11.4%) of these women, exposure occurred in the first trimester only, while the remaining 217 women had exposure during the second and/or third trimester….." This suggests that more fetuses were exposed to Zika virus infection during the 2nd and 3rd trimesters, when fetal organ development is near complete. It this pattern typical of Zika virus exposure? How might more exposure in the 2nd/3rd trimester compared to 1st trimester affect your results?

For this cohort of NYC women with ZIKV infection, exposure was directly related to time spent in an area with mosquito-borne ZIKV transmission. Therefore, timing of exposure was a reflection of the travel patterns of these women. In addition, we segregated women according to whether exposure to

ZIKV was limited to the first trimester only, or spanned multiple trimesters (including the first). Many women with 2nd and 3rd trimester exposure were also exposed during the 1st trimester, so we cannot infer when potential fetal exposure to maternal ZIKV infection occurred.

As discussed in response to Item 3 (Reviewer 2) above, because the data on trimester of exposure for our cohort are imprecise and serve as a poor proxy for when ZIKV infection occurred, we have elected to remove this analysis from the manuscript.

3. One major concern remains if the authors found any association between Zika virus during pregnancy and SGA. I would think that comparing babies of mothers who tested positive Zika virus infection would be the best way to determine if Zika virus during pregnancy is associated with SGA (i.e infected versus uninfected babies). On Page 10, lines 185-187, The authors state that "…..twenty-eight (11.2%) women with ZIKV infection during pregnancy and 5961 (5.2%) women without ZIKV infection gave birth to an SGA infant; after adjustment, the risk of SGA was 1.8 times higher for women with ZIKV infection during pregnancy (95% CI, 1.3 to 2.6)….." However, on the same page 10, lines 192-195, the authors state that "…..Of the 250 infants born to women with ZIKV infection during pregnancy…..we found no association between congenital ZIKV infection and birthweight, SGA, or preterm birth…" This is very confusing and needs to be clarified - whether there was or wasn't an association
between Zika virus infection and SGA.

We thank the reviewer for pointing out this confusing text. The first statement refers to the overall analysis, which related to maternal ZIKV infection. The second statement refers to the sub-analysis examining only those with evidence of congenital ZIKV infection. Among women with ZIKV infection, only a small proportion of their infants actually had evidence of congenital ZIKV infection.

As other reviewers have highlighted, in the sub-analysis looking only at infants with evidence of ZIKV infection, we did not find a significant association between the outcomes (mean birthweight, SGA, and preterm birth) and congenital ZIKV infection, but our analysis was underpowered. In response to reviewer comments, we have elected to describe the mean birth weight and proportion of SGA and preterm infants for infants with and without positive ZIKV testing after birth, and have removed statistical analysis comparing these groups given the concern about lack of power.

These results are now presented as follows:

> Of the 250 infants born to women with ZIKV infection during pregnancy, 202 (80.8%) had ZIKV testing after birth (Table 3); 20 infants (9.9%) had laboratory evidence of congenital ZIKV infection. The proportion of infants

> born SGA and preterm were similar for infants with positive and negative ZIKV testing, and the difference in mean birth weight was 153 grams, which approximates the average weight gain per week of gestation after 37 weeks for the term infants in our cohort.

Discussion:

4. This raises the same concern I had as stated above. The authors state on Page 11, lines 213-214 that…."women with ZIKV infection during pregnancy gave birth to infants who were more likely to be SGA when born at term compared with women with no ZIKV infection during pregnancy….". However, on Page 12, lines 231-232, the authors again stated that…."we found that among infants born to women with ZIKV infection during pregnancy, the prevalence of SGA was no different among infants with and without laboratory evidence of congenital infection. This needs to be clarified.

As noted in the response to the previous comment, the first statement refers to the overall analysis, which examined the impact of maternal ZIKV infection on the outcomes of interest. The second statement refers to the sub-analysis examining the impact of *congenital* ZIKV infection on the outcomes of interest. We have clarified the wording on this subgroup analysis in the discussion as follows:

> In our cohort, maternal ZIKV infection was associated with a higher risk of SGA, however only two infants of 20 with congenital ZIKV infection were SGA. This raises several possible hypotheses. First, maternal ZIKV infection may be associated with SGA even without congenital ZIKV infection.

Conclusion:

The conclusion is apt, and reflects the hypothesis and findings from the paper.