Date: Aug 02, 2018
To: "Samsiya Ona" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1290

RE: Manuscript Number ONG-18-1290

Diagnostic validity of the proposed NICHD criteria for intrauterine inflammation or infection.

Dear Dr. Ona:

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 23, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This was a retrospective cohort study which was investigating the validity of the NICHD diagnostic criteria for intrauterine inflammation or infection (Triple I). The aim was to assess whether outcomes are similar for those patients who are febrile but don't meet the strict NICHD criteria for triple I.

- I was confused regarding the distinction between isolated maternal fever and unspecified fever. I fully understand that isolated maternal fever is for those women who have a documented fever (>102.2 or >100.4 over 2 measurements 45 minutes apart). However, what exactly is unspecified fever? The paper states that it is defined as febrile women not meeting the documented fever criteria. However, if it doesn't meet the documented fever criteria, then how is it a fever? Some clarity regarding this definition would be extremely helpful.

- Box 1 is excellent and compares the definition of triple I by NICHD definition and the characteristics of your study group. It made it clear to see your thinking in how you organized this study. However, I still was lost trying to find the unspecified fever group. Was this the same as "Documented fever" column?

- Unclear of inclusion criteria. Was it those who had a fever of >100.4 over 2 separate measurements, 45 minutes apart as well as those with initial temperature >102.2? Or was it only those with fever and (+) blood cultures (you commented on 80% of febrile intrapartum women). Figure 1 seems to clarify this, as it shows that included women were those who were febrile with blood cultures sent. Recommendation would be to clarify this in the text of the paper.

- I appreciated your examination of the NICHD diagnostic criteria, as your paper proves that we may be undertreating patients if we follow the strict definition per NICHD. It is important to note that "low risk" febrile women may still have the same (or worse) adverse outcome when compared to those patients who meet the strict criteria for triple I. This was well explained by you.

- Excellent comments regarding ACOG's recommendation and how early treatment of these women likely would benefit these patients, and waiting until they meet criteria for triple I per NICHD may not be in the best interest of the patient. Your review of the data supports this.

- Your paper was important in that it challenged the current NICHD definition for triple I and questioned whether not treating febrile women who don't meet the criteria for triple I may not be the best course of treatment.

Reviewer #2:

Single center retrospective study of adverse outcomes in pregnant women >24 weeks 6/2015-9/2017 who met the Triple I criteria vs those who were febrile and did not meet criteria

Institutional protocol in place since 2009 that all women with intrapartum fever received blood cultures, CBC, urine culture with standardized antibiotics and placenta is sent to Pathology. Does not mandate a repeat temperature at 30 minutes like NICHD. All women with a fever to 100.4 during labor or within 1 hour of delivery were included

good exclusion criteria

Confirmed Triple I was defined as suspicious Triple I with placental pathology confirmed infection
Defined a composite adverse outcomes: makes sense
Placental Pathology 87%

Methods
I still don't really understand the clinical difference between isolated and unspecified, Can you describe in more detail. You might consider merging the two groups so that you have Triple I and Non triple I intra partum fever. Line 161-162 states that women with a fever to 100.4 but less than 102.2 without a repeat temperature were excluded from the analysis

Discussion
I think a discussion on correlation of placenta chorioamnionitis and clinical outcomes is warranted? Example Some baseline characteristics of placenta histology percentages in normal pregnancies

Reviewer #3:

This retrospective cohort study evaluates the NICHD diagnostic criteria for triple I, comparing to modified criteria in the context of a specific institutional protocol for management of intrapartum fever.

1. Primary and secondary outcomes are well-defined in the Materials and Methods section.

2. The rationale for combining primary outcome with the (already) composite secondary outcomes is unclear, and is not stated as a pre-defined analytic outcome (lines 181-198).

3. Using obstetric hemorrhage, maternal readmission, and maternal additional procedures as infectious outcomes seems a stretch, and this should be explained or validated in the manuscript.

4. The number of patients remaining after application of exclusion criteria is quite small, with most being excluded due to absence of a second temperature measurement within 45 minutes.

5. It is unclear why the second temperature measurement used in the study is at the 45 minutes time point rather than the 30 minutes designated in the NICHD criteria. These are not directly comparable approaches to diagnosis.

6. Box 1: Suggest adding "unspecified fever" category and criteria to this box, as this is the third group analyzed and a very careful reading of manuscript is needed to identify criteria for this diagnosis. It is also unclear whether the occurrence of an adverse clinical outcome is itself enough for diagnosing a Confirmed Infectious Outcome? This has serious implications for the test validity calculations.

7. Table 2, lines 1-6: Assuming that "positive placental pathology" represents the presence of any of the below pathologic findings, these case numbers do not add up to the total top line. If "positive pathology" has another meaning, it should be made explicit.

8. Line 229: clarify the comparison group for the "more likely" statement

9. Lines 233-235 clarify which criteria are used as "clinical signs of intrauterine infection" for defining Suspected Triple I.

10. A case-control design may be more appropriate to answer the study questions

Reviewer #4:

Please clarify/correct a few items:

Abstract

Line 87-94: Please include °C as well- it increases the value of your article because °C is used in many other international countries.
Line 96: The author mention that their aim was to predict an adverse infectious outcome. In the results no data on this aim is presented. Please adjust your abstract. - Nothing on this aim is written in lines 142-145.
Line 99-100: Please keep the classification in group 1-3 as presented in the method line 90-91.

Material and methods
Line: 147-156: How was the temperature measured? Axillary? Please include further information.
Line 158, 161, 222, 270, 272: Please include °C.
Line 177-178: You describe group 1-3. In Box 1 just group 2 and 3 could be found. Please include group 1 in Box 1 as well. Please clarify the exact difference between group 1 and 2. The unspecified fever group had fever only - and group 2: fever but no clinical signs of intrauterine infections???
Line 193: What was the rationale to include postpartum hemorrhage?
Line 200-203: Did they compare group 2 to 3 as well? Did they check whether there was any differences between the three? Kruskal-Wallis test? Why have they used a Wilcoxon and not a Mann-Whitney test as the groups were independent?
Results:
Line 227-228: Was maternal age and GA not normally distributed? If they were, please present the data as mean +/- SD.

STATISTICAL EDITOR COMMENTS:

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

Table 2: Apart from "positive placental pathology" or the combined "adverse clinical outcomes and/or positive pathology", the counts of adverse outcomes are mostly low single digits. Therefore there is little power to generalize any NS findings. Much larger cohorts would be be needed to discern differences in rare events.

Table 3: PPV and NPV are not useful metrics, since they are dependent on the prevalence of adverse events in this particular cohort. More useful and generalizable metrics would be LR(+), LR(-) or AUC, each with CIs. Should statistically compare the Sens and Spec; they appear to not be statistically discernible. Using the data from Table 2 to corroborate the calculations in Table 3, there appear to be errors in the Positive pathology (confirmed Triple I) vs suspected Triple I section. The Spec = 45.3 (35.0-55.8), but more importantly, the PPV = 75.5 (71.5-79.1) and the NPV = 33.9 (27.9-40.4). The combined outcome group has LR(+) or, LR(-) and AUC that were statistically significant, albeit marginally. For the other test characteristics, only "positive pathology" had marginal AUC with statistical significance, all others were NS.

EDITOR'S NOTE:

Dr. Ona, Thank you for submitting this important work to the Journal. I'm sorry that I did not get to spend more time with you at my home this week but hostessing trumped much in the way of getting to know people. I hope your interviews went well on Monday.

As you will see in my notes on your manuscript, I'm asking you to do 2 major edits to your manuscript which reflect in part the reviewers comments. Also, the statistical editor has made important recommendations.

1. Please consider combining the two febrile groups (undefined and isolated) into one group. Functionally from a clinical perspective they are the same thing--a febrile patient without signs of infection--and the distinction between the two is somewhat unclear.

2. You stated that you have 1 primary outcome--which is placental chorioamnionitis--and one secondary outcome--the composite adverse clinical outcomes. However, you then mostly report a combination of these two. This subverts the idea of a primary and secondary outcome. I would ask you to do one of the following:
A. Keep the primary and secondary outcomes as you have them and don't report a combined outcome at all. Report the data for the primary and secondary outcomes separately. For the clinician, knowing the clinical adverse outcome data is likely more important than knowing the risk of a histologic outcome, so the clinical adverse outcomes needs to be clearly stated.
B. Have the primary outcome as defined, then have 2 secondary outcomes: a) composite clinical adverse outcomes and b) combined primary and secondary outcomes and report the results for both secondary coutcomes.

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 Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

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

3. 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.

4. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

5. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

6. 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

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 appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

9. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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. 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.

11. 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.

12. 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.

13. 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.

14. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

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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, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

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 23, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy Chescheir

Editor in Chief of Obstetrics & Gynecology

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

If you would like your personal information to be removed from the database, please contact the publication office.

BRIGHAM AND WOMEN'S HOSPITAL | HARVARD MEDICAL SCHOOL | MASSACHUSETTS GENERAL HOSPITAL

September 10th, 2018

Dear Editors of Obstetrics and Gynecology,

Thank you so much for the opportunity to revise our paper. It is with great pleasure that we resubmit our manuscript entitled Diagnostic Validity of the Proposed NICHD Criteria for Intrauterine Inflammation or Infection for your continued review. We have addressed the comments from the reviewers below, and also note where in the text we have made the changes using track changes. Given that we have merged the first two initial study groups into one in our revised manuscript, we have presented the clean version for the tables and figure for clarity. We can provide a tracked version if needed. In addition, in order to adequately respond to the comments, we have exceeded the recommended word count; however, we would be happy to work with you to edit the manuscript.

We look forward to your response to our revisions and welcome your ongoing feedback.

The lead author (SO) 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 have been explained.

Sincerely,

Samsiya Ona, MD

RESPONSE TO REVIEWER COMMENTS:

Reviewer #1:

This was a retrospective cohort study, which was investigating the validity of the NICHD diagnostic criteria for intrauterine inflammation or infection (Triple I). The aim was to assess whether outcomes are similar for those patients who are febrile but don't meet the strict NICHD criteria for triple I.

- I was confused regarding the distinction between isolated maternal fever and unspecified fever. I fully understand that isolated maternal fever is for those women who have a documented fever (>102.2 or >100.4 over 2 measurements 45 minutes apart). However, what exactly is unspecified fever? The paper states that it is defined as febrile women not meeting the documented fever criteria. However, if it doesn't meet the documented fever criteria, then how is it a fever? Some clarity regarding this definition would be extremely helpful.

> The NICHD panel standardized the definition of fever, which constitutes "documented fever". Per their definition, "documented fever" is defined as followed: a single temperature $\geq 102.2^{o}F$ ($39^{o}C$), or an initial temperature $\geq 100.4^{o}F$ ($38^{o}C$) but $< 102.2^{o}F$ ($39^{o}F$) that remains $\geq 100.4^{o}F$ ($38^{o}F$) on repeat 30min later. In our analysis, documented fever is as described above by the reviewer. To improve the clarity of our analysis and discussion, and per the Editor's suggestion, we have combined both of these groups of women into a new group, " isolated maternal fever."

- Box 1 is excellent and compares the definition of triple I by NICHD definition and the characteristics of your study group. It made it clear to see your thinking in how you organized this study. However, I still was lost trying to find the unspecified fever group. Was this the same as "Documented fever" column?

> We have addressed this confusion by combining patients into one group "isolated maternal fever" to denote those defined above.

- Unclear of inclusion criteria. Was it those who had a fever of >100.4 over 2 separate measurements, 45 minutes apart as well as those with initial temperature >102.2? Or was it only those with fever and (+) blood cultures (you commented on 80% of febrile intrapartum women). Figure 1 seems to clarify this, as it shows that included women were those who were febrile with blood cultures sent. Recommendation would be to clarify this in the text of the paper.

> All women in the cohort were febrile women who had blood cultures sent at the initial fever. We address this limitation in lines 836-842. All women with initial temperature $>102.2^{o}F$ were included regardless of repeat temperature measurement. All patients who had an initial temperature of $\geq 100.4^{o}F$ but

<102.2°F with an available repeat measurement within 45 minutes were also included in the final analysis. The repeat temperature does not have to be ≥100.4°F. This is to allow appropriate allocation to groups. We have addended the manuscript in lines 226-233 to clarify which patients were included in our analysis.

- I appreciated your examination of the NICHD diagnostic criteria, as your paper proves that we may be undertreating patients if we follow the strict definition per NICHD. It is important to note that "low risk" febrile women may still have the same (or worse) adverse outcome when compared to those patients who meet the strict criteria for triple I. This was well explained by you.

Thank you

- Excellent comments regarding ACOG's recommendation and how early treatment of these women likely would benefit these patients, and waiting until they meet criteria for triple I per NICHD may not be in the best interest of the patient. Your review of the data supports this.

Thank you

- Your paper was important in that it challenged the current NICHD definition for triple I and questioned whether not treating febrile women who don't meet the criteria for triple I may not be the best course of treatment.

Thank you

Reviewer #2:

Single center retrospective study of adverse outcomes in pregnant women >24 weeks 6/2015-9/2017 who met the Triple I criteria vs those who were febrile and did not meet criteria

Institutional protocol in place since 2009 that all women with intrapartum fever received blood cultures, CBC, urine culture with standardized antibiotics and placenta is sent to Pathology. Does not mandate a repeat temperature at 30 minutes like NICHD. All women with a fever to 100.4 during labor or within 1 hour of delivery were included

good exclusion criteria

Confirmed Triple I was defined as suspicious Triple I with placental pathology confirmed infection
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Placental Pathology 87%

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I still don't really understand the clinical difference between isolated and unspecified, Can you describe in more detail. You might consider merging the two groups so that you have Triple I and Non-triple I intra partum fever. Line 161-162 states that women with a fever to 100.4 but less than 102.2 without a repeat temperature were excluded from the analysis

> As suggested, we have combined the unspecified fever and isolated maternal fever groups for clarity.

Discussion
I think a discussion on correlation of placenta chorioamnionitis and clinical outcomes is warranted? Example Some baseline characteristics of placenta histology percentages in normal pregnancies

> Thank you for the comment. We have expanded our literature review in our discussion on this relationship in lines 613-619.

Reviewer #3:

This retrospective cohort study evaluates the NICHD diagnostic criteria for triple I, comparing to modified criteria in the context of a specific institutional protocol for management of intrapartum fever.

1. Primary and secondary outcomes are well-defined in the Materials and Methods section.

2. The rationale for combining primary outcome with the (already) composite secondary outcomes is unclear, and is not stated as a pre-defined analytic outcome (lines 181-198).

> We had elected to combine the primary and composite secondary outcomes because not all women had available pathology data, and because we wanted to describe the test characteristics for a combined composite pathologic and clinical outcome. Based on the Editor's suggestions, we kept our primary and secondary outcomes distinct. The definitions of each outcome have not changed.

3. Using obstetric hemorrhage, maternal readmission, and maternal additional procedures as infectious outcomes seems a stretch, and this should be explained or validated in the manuscript.

> Thank you for your comment. We have limited maternal readmission only to those readmitted for presumed obstetric related infectious etiologies. We have

also limited additional procedures to procedures presumed to be related to intraabdominal infection, such as dilation and curettage for source control, intraabdominal drain placement, hysterectomy for intrauterine infection not controlled by drainage or IV antibiotics, all of which are very rare (0.9%) in our cohort. Should the editor desire removal of such outcomes, we can certainly do so.
There is no validated definition of “adverse infectious clinical outcome” that we could find. This was defined based on our clinical experience of adverse event that could be related to infection in the peripartum period.

4. The number of patients remaining after application of exclusion criteria is quite small, with most being excluded due to absence of a second temperature measurement within 45 minutes.

We agree that the exclusion criteria restricted the sample to be approximately 40% of the original cohort of women identified to have an intrapartum or postpartum fever with positive blood cultures. Retaking a temperature measurement is not part of our clinical protocol for the evaluation of a fever. There are multiple potential reasons for repeat measurement not being done. We acknowledge that this creates a selection bias, as requiring a second temperature may have led to selecting a sicker group of women in whom a clinical decision was made to re-evaluate the temperature.

We address this bias in lines 844-852. However, as our goal was to study the Triple I criteria, which requires a repeat temperature as part of its evaluation of a fever, we similarly included such a requirement.

5. It is unclear why the second temperature measurement used in the study is at the 45 minutes time point rather than the 30 minutes designated in the NICHD criteria. These are not directly comparable approaches to diagnosis.

Thank you for this comment. Our approach to the evaluation of an intrapartum fever does not mandate the assessment of a repeat temperature. However, MD and RN providers may check another temperature shortly after the initial fever at their clinical discretion. Given the time it takes to complete the patient evaluation, draw blood cultures, initiate antibiotic treatment, and also manage ongoing labor, if repeat temperatures were checked, they clustered within the 30-45 minutes after the initial fever. Consequently, we felt that a 45 minute cut off for repeat temperature assessment was more realistic in our population than 30 minutes, but similar enough for us to compare our population to the NICHD criteria. We highlight this difference in lines 302-306.

6. Box 1: Suggest adding "unspecified fever" category and criteria to this box, as this is the third group analyzed and a very careful reading of manuscript is needed to identify

criteria for this diagnosis. It is also unclear whether the occurrence of an adverse clinical outcome is itself enough for diagnosing a Confirmed Infectious Outcome? This has serious implications for the test validity calculations.

> As previously discussed, we have combined the unspecified and isolated maternal fever groups, and the definition for the new group is included in Box 1. The occurrence of an adverse infectious clinical outcome was not used to diagnose "confirmed Triple I."

7. Table 2, lines 1-6: Assuming that "positive placental pathology" represents the presence of any of the below pathologic findings, these case numbers do not add up to the total top line. If "positive pathology" has another meaning, it should be made explicit.

> Thank you for this comment. We realized that we inadvertently added other etiologies for abnormal placental pathologic findings that we later on removed as deemed not specific enough for chorioamnionitis per our pathologists. We have updated Table 2 to present the etiologies of abnormal pathologic findings with the guidance of two pathologists (ZOS and DJR), and the case numbers correctly add up to the total.

8. Line 229: clarify the comparison group for the "more likely" statement

> The data presented in lines 519-526 presents the demographic data for the overall cohort, not stratified by whether they met criteria for Triple I or not. We omitted the word more likely, which does suggest a comparative statement that we did not intend.

9. Lines 233-235 clarify which criteria are used as "clinical signs of intrauterine infection" for defining Suspected Triple I.

> Clinical signs of intrauterine infection included any of the following findings: maternal leukocytosis > 15,000 per mm3, fetal tachycardia >160 beats per minute, and purulent amniotic fluid. This is added in lines 315-317 of the method section.

10. A case-control design may be more appropriate to answer the study questions

> Thank you for the suggestion. In a case-control study, we would identify patients based on confirmed Triple I or confirmed infectious outcomes, as defined in the study, and then look back to see what proportion of patients had an intrapartum fever, and other risk factors. This would be a very interesting study design to see if the impacts of intrapartum fever on these outcomes, as presumably some patients without intrapartum fever may also have similar outcomes. However, this design would not answer the prospective question of morbidity among febrile patients meeting vs not meeting suspected Triple I criteria, which was our clinical interest.

Reviewer #4:

Please clarify/correct a few items:

Abstract
Line 87-94: Please include °C as well- it increases the value of your article because °C is used in many other international countries.

> Thank you for the comment. We have edited this in the manuscript

Line 96: The author mention that their aim was to predict an adverse infectious outcome. In the results no data on this aim is presented. Please adjust your abstract. - Nothing on this aim is written in lines 142-145.

> We edited the abstract in lines 97-101 to include the aim to determine test characteristics for patients meeting criteria for suspected Triple I to predict both confirmed Triple I and adverse clinical infectious outcomes and these are presented in the abstract. In the introduction, we have modified lines 200-203 to reflect that our aims included the evaluation aim introduced in the abstract and test characteristics of adverse infectious outcome are presented in the results section in lines 602-604 and 605-606.

Line 99-100: Please keep the classification in group 1-3 as presented in the method line 90-91.

> We have redefined 2 groups for analysis and present results from each group in parallel.

Material and methods
Line: 147-156: How was the temperature measured? Axillary? Please include further information.

> The temperatures are measured orally per the institution RN protocol. In case where the patient had consumed ice or for some other reason RN was unable to obtain temperature orally, an axillary temperature was obtained, which is less common.

Line 158, 161, 222, 270, 272: Please include °C.

> Thank you for the comment. We have edited this throughout the manuscript.

Line 177-178: You describe group 1-3. In Box 1 just group 2 and 3 could be found. Please include group 1 in Box 1 as well. Please clarify the exact difference between

group 1 and 2. The unspecified fever group had fever only - and group 2: fever but no clinical signs of intrauterine infections???

> Groups 1 and 2 have been merged into the “isolated maternal fever” group.

Line 193: What was the rationale to include postpartum hemorrhage?

> We have included postpartum hemorrhage in the setting of presumed intrapartum chorioamnionitis because of the known increased risk of postpartum hemorrhage in the setting of intrauterine infection. We can omit this outcome in our analysis with no significant effect on the analysis if the Editor desires.

Line 200-203: Did they compare group 2 to 3 as well? Did they check whether there was any differences between the three? Kruskal-Wallis test? Why have they used a Wilcoxon and not a Mann-Whitney test as the groups were independent?

> As we are comparing baseline characteristics across two groups, we are using chi-squared tests and Wilcoxon rank sum tests as appropriate in our analyses.

Results:
Line 227-228: Was maternal age and GA not normally distributed? If they were, please present the data as mean +/- SD.

> The maternal age and GA were not normally distributed so we used median and IQR to report these instead.

STATISTICAL EDITOR COMMENTS:

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

Table 2: Apart from "positive placental pathology" or the combined "adverse clinical outcomes and/or positive pathology", the counts of adverse outcomes are mostly low single digits. Therefore there is little power to generalize any NS findings. Much larger cohorts would be needed to discern differences in rare events.

> We agree that the individual counts for components of adverse neonatal and adverse maternal outcomes are low, and it is not possible to interpret any significance in the relative frequencies by group. If you prefer, we can omit these low-frequency outcomes from the table as well as from the composite outcome, or suppress the p-values but present the raw data in the tables.

Table 3: PPV and NPV are not useful metrics, since they are dependent on the prevalence of adverse events in this particular cohort. More useful and generalizable metrics would

be LR(+), LR(-) or AUC, each with CIs. Should statistically compare the Sens and Spec; they appear to not be statistically discernible.

> We have removed the PPV and NPV and added LR (+), LR (-) instead. We now present the sensitivity and specificity of meeting suspected Triple I criteria to predict confirmed Triple I and, separately, to predict adverse clinical infectious outcome. Our results show overlapping confidence intervals for both the sensitivity and specificity, thus we did not pursue statistical testing, as we anticipated lack of statistical difference. We would be happy to pursue statistical testing if you believe this would be beneficial in the interpretation of our findings.

Using the data from Table 2 to corroborate the calculations in Table 3, there appear to be errors in the Positive pathology (confirmed Triple I) vs suspected Triple I section. The Spec = 45.3 (35.0-55.8), but more importantly, the PPV = 75.5 (71.5-79.1) and the NPV = 33.9 (27.9-40.4). The combined outcome group has LR (+) or, LR (-) and AUC that were statistically significant, albeit marginally. For the other test characteristics, only "positive pathology" had marginal AUC with statistical significance, all others were NS.

> Based on editor's recommendation, we only limited our outcomes to the primary and secondary outcomes for the revised document.
> We have also confirmed our calculations for the test characteristics reported in Table 3.

EDITOR'S NOTE:
Dr. Ona, Thank you for submitting this important work to the Journal. I'm sorry that I did not get to spend more time with you at my home this week but hostessing trumped much in the way of getting to know people. I hope your interviews went well on Monday.

As you will see in my notes on your manuscript, I'm asking you to do 2 major edits to your manuscript, which reflect in part the reviewers comments. Also, the statistical editor has made important recommendations.

1. Please consider combining the two febrile groups (undefined and isolated) into one group. Functionally from a clinical perspective they are the same thing--a febrile patient without signs of infection--and the distinction between the two is somewhat unclear.

> Thank you for this comment. We are in agreement and have merged the two additional groups not meeting suspected Triple I criteria into 1 group. We agree this presentation of the data is far clearer.

2. You stated that you have 1 primary outcome--which is placental chorioamnionitis--and one secondary outcome--the composite adverse clinical outcomes. However, you then mostly report a combination of these two. This subverts the idea of a primary and

secondary outcome. I would ask you to do one of the following:

A. Keep the primary and secondary outcomes as you have them and don't report a combined outcome at all. Report the data for the primary and secondary outcomes separately. For the clinician, knowing the clinical adverse outcome data is likely more important than knowing the risk of a histologic outcome, so the clinical adverse outcomes needs to be clearly stated.

B. Have the primary outcome as defined, then have 2 secondary outcomes: a) composite clinical adverse outcomes and b) combined primary and secondary outcomes and report the results for both secondary outcomes.

> Thank you for this comment. We chose to keep the primary and secondary outcomes as you state in option A, and no longer present the combined primary + secondary outcome.

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.

EDITOR'S COMMENTS FROM PDF:

Please spell out all abbreviations on first use.

> Thank you. We have edited this in the text.

Will be interesting to read later why you excluded PROM (Now known as pre-labor rupture of the membranes as ACOG and the Journal have adopted the reVITALize terminology). It would seem that this group is at high risk for Triple I and would have provided a greater n for your outcome. I understand excluding IUFD as their placental pathology can be so mixed and non-ob Infections.

> We have specifically excluded women with preterm prelabor rupture of membrane with no signs of labor on presentation and hence were expectantly managed inpatient because: 1) management is different for this group that receives latency antibiotics, steroids if indicated, which may all affect outcomes including pathology; 2) our main clinical interest was in intrapartum or immediate postpartum fever among women in labor.

As written, the clause "and is clinically diagnosed" refers back to "Maternal intrapartum fever". Would you consider something like "Maternal intrapartum fever is often attributed to chorioamnionitis which is a clinical diagnosis of an infection or

inflammation of.....

> Thank you very much for the suggestion. We have edited the manuscript to reflect this suggestion.

Wouldn't it trigger the same things if the diagnosis is made antepartum?

> Thank you for nothing this. We have removed the term “intrapartum” as chorioamnionitis in the antepartum period would, and should trigger the same management. Lines 189-190.

Journal format does not include subheadings like this. Please exclude here and elsewhere.

> Thank you for the comment. We have excluded similar subheadings throughout the manuscript.

Not sure what this means (line 164-166 in initial submitted manuscript). Is this how you identified your patients (by culture reports)? If so, how do you know you identified about 80% of febrile patients? Does that mean about 20% of the time the protocol is not followed? Why not? Please state more clearly how patients were identified.

> With the implementation of a new electronic medical record system at our institution, we were able to identify all febrile women on Labor and Delivery. We then narrowed this list of patients to those with blood cultures sent as part of the evaluation of fever. We subsequently applied inclusion and exclusion criteria as described in the manuscript. In this method, we noted that 80% of febrile patients had cultures sent, which may introduce a selection bias. Our Labor and Delivery comprises the resident practice, several private practices, and a midwifery service. Although the fever protocol covers all patients on our Labor and Delivery, the implementation is self-enforced, particularly on the private and midwifery services.

Please explain this last exclusion criterium (Editor referring to exclusion of expectantly managed preterm premature rupture of membranes)

> Thank you for the comment. Please see above for response. We have briefly clarified this in our manuscript as well. Lines 236-240

I agree with most of your reviewers who were confused by the distinction between isolated and unspecified fever. Why not combine these 2 groups? At the very least you need to do a better job of describing them and describing why you consider them distinctly different groups.

> We have combined Groups 1 and 2 into a single group named “isolated maternal fever” for clarity, and clarified the defining criteria.

One of your reviewers was concerned about including some of this components of your composite adverse outcomes. I'm fine with what you've included-pph is more common with chorioamnionitis, etc.

> Thank you. We have indeed included postpartum hemorrhage as it is more common with chorioamnionitis. However, excluding this will not significantly affect our analysis if preferred.

The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances.

> Thank you for pointing this out. We have removed throughout the manuscript.

Please see statistical editor's comments re; use of AUC and LR.

> We have removed the PPV and NPV and added LRs.

Then isn't this combined outcome your actual primary outcome? If not, then please present data to address the primary and secondary outcomes. Then if you want to present the combined data (clinical and pathologic outcome) then you need to include that as another secondary outcome.

> We have limited our outcomes analysis to two outcomes: the primary outcome (confirmed Triple I, defined by placenta pathology diagnostic of infection) and secondary outcome (adverse clinical infectious outcome) for clarity as this still conveys the same message.

Wouldn't this be the isolated fever group? (Editor referring to "lack of temperature assessment within 45 minutes for febrile women with initial fever $\geq 100.4^{o}F$ but $<102.2^{o}F$.)

> This group was excluded because following the initial fever that is $\geq 100.4^{o}F$ but $<102.2^{o}F$, there was either no repeat temperature taken for hours or at least beyond 45 min. With a lack of repeat temperature, we could not realistically classify these women in either group as it is unknown whether they would have had a repeat temperature <100.4 or $\geq 100.4^{o}F$, and as this was a requirement of the NICHD criteria.

Its not clear to me hear what your are looking at. On line 240 it looks like that combined primary/secondary outcome but on line 242 it looks like just the clinical adverse outcomes. Again, please present data for the primary and secondary outcomes separately-and make the combined primary/secondary outcomes a 2nd secondary outcome.

> For clarity and clinical relevance, we have presented data for the primary and secondary outcomes separately as suggested.

Haven't you made this comparison on line 242 already? This is your major point of your paper--all groups had a high risk of your composite clinical (primary) outcome. This needs to be stated really clearly.

> Thank you for this comment. We have limited our outcome to the primary outcome and secondary outcome and had edited our statement regarding adverse outcome between the two groups in lines 530-599.

I am unclear about this section. This reads like you are only looking at the Triple I group--not the other 2 groups. Could you present this data for the triple 1 vs the documented vs isolated (or preferably combining the 2 febrile groups) and separate the primary and secondary outcomes.

> Women with isolated maternal fever group comprise our test negative group and those with suspected Triple I our test positive group. We chose to perform our analysis in this way as women with suspected Triple I are presumed more likely to have a true infection and thus are recommended to be treated. We therefore calculate the test characteristics of suspected Triple I to predict (1) Confirmed Triple I and (2) adverse clinical infectious outcomes.

As above--state both separately and then give combined if you want

> Please see responses above. Thank you

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

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:

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

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

3. 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.

We have included this statement in the beginning of our response letter.

4. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

Data on demographic, obstetric and clinical exposures were abstracted from electronic medical records by two obstetricians (S.O., G.W.). Blood culture data were obtained from the microbiology database. Variables were discussed at a general meeting with all authors in case recording of a variable isn’t straightforward. Two pathologists (D.J.R., Z.O.S.) reviewed a randomly generated subset of abstracted data from the pathology records to assess accurate interpretation, and otherwise adjudicated placental pathology reports for correct classification as appropriate.

5. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all

cases, the complete name of the IRB should be provided in the manuscript.

Thank you. We have included this in our manuscript.

6. 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 guidelines, as appropriate.

We have submitted a STROBE checklist.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

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 appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

9. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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. 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.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online athttp://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.

12. 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.

13. 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.

14. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer,

revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications
page at http://www.acog.org/Resources-And-Publications.

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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, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

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 23, 2018, we will assume you wish to withdraw the manuscript from further consideration.

From: [redacted]
To: Randi Zung
Cc: [redacted]
Subject: Re. Your Revised Manuscript 18-1290R1
Date: Tuesday, September 25, 2018 5:24:22 PM
Attachments: 18-1290R1 ms (9-17-18v3)_Edits.docx
Triple I_Suspected Triple I table.pdf
Triple I_Clininal outcomes_table.pdf

Dear Ms. Zung,

Thank you very much for the email. Please see below our responses and attached our edits.

Thank you once more.

Dear Dr. Ona:

The Editors have reviewed your latest version (attached – v3). There are some additional comments from the Statistical Editor at this time. Please edit the version of your manuscript that is attached to this message.

They are as follows:

1. Lines 254-256, 259-260, 263-264, Tables 2 and 3: Placental pathology was available for 86.4% of the overall cohort, yet the counts for positive placental pathology (28 or 22% for maternal fever vs 70 or 33% for suspected Triple I) correspond to denominators of 127 and 212, ie, 100% of the cohort. Need to cite the positive placental pathology using a denominator of only the subset of women who had placental pathology available. Likewise, the LR(+), LR(-), Sens and Spec are all based on the entire groups of n = 127 and 212. So, those calculations are incorrect, and should only be based on the 86.4% (presumably total = 293, not 339).

Thank you for your comments. I sincerely apologize for the error in the denominator for available positive placental pathology. This has been edited in the text and table 2. We recalculated the sensitivity, specificity, LR+ and LR- and these are correctly listed in the results text. Attached is a screen shot of the repeat calculation.

2. I presume the Adverse clinical infectious outcome could be determined for all 339 women, so those proportions, LR(+), LR(-), Sens and Spec are all calculated OK.

Data were available to evaluate the adverse clinical infectious outcomes for all 339 women. We did reconfirm the test characteristics for this as well, and they are included as a screen shot attached.

3. Lines 263-66: The LR(+) and LR(-) comparing suspected Triple I vs confirmed Triple I need to be re-done, but if the numbers and their CI are similar, then as stated, the suspected Triple I criteria do not perform well to identify actual Triple I cases. Similarly, the performance of suspected Triple I to identify adverse clinical infectious outcomes is not very accurate. Both are particularly poor in specificity (large proportion of false positives), but also only moderately good in sensitivity (not insignificant proportion of false negatives), both of which may be equally important to the clinician.

We agree with your interpretation of our data and are happy to clarify this further in the manuscript, if you think that would be helpful.

4. While it is true that fever alone is statistically no worse than fever + clinical evidence of maternal infection, the number of adverse clinical infectious outcomes is relatively small (9.5% vs 11.8%) and there is little statistical power to generalize the NS finding.

Thank you for this comment. We acknowledge such limitation. However, these adverse outcomes are in the setting of our universal fever protocol. We felt this was important as approximately 1 in 10 women has an adverse outcome despite early and aggressive antibiotic treatment. The objective of our paper was to show that use of the Triple I criteria may result in decreased antibiotic treatment of some women, which may be associated with additional adverse clinical outcomes. We are happy to address this further and clarify this in the discussion, if you think that would be helpful.

We look forward to any further comments and thoughts you may have. Thank you once more.

Sincerely,

Samsiya Ona, MD
[redacted]

From: Randi Zung <RZung@greenjournal.org>
Sent: Friday, September 21, 2018 9:12 AM
To: Ona, Samsiya,M.D.

Cc: Diouf, Khady,M.D.
Subject: RE: Your Revised Manuscript 18-1290R1

Dear Dr. Ona:

The Editors have reviewed your latest version (attached – v3). There are some additional comments from the Statistical Editor at this time. Please edit the version of your manuscript that is attached to this message.

They are as follows:

1. Lines 254-256, 259-260, 263-264, Tables 2 and 3: Placental pathology was available for 86.4% of the overall cohort, yet the counts for positive placental pathology (28 or 22% for maternal fever vs 70 or 33% for suspected Triple I) correspond to denominators of 127 and 212, ie, 100% of the cohort. Need to cite the positive placental pathology using a denominator of only the subset of women who had placental pathology available. Likewise, the LR(+), LR(-), Sens and Spec are all based on the entire groups of n = 127 and 212. So, those calculations are incorrect, and should only be based on the 86.4% (presumably total = 293, not 339).

2. I presume the Adverse clinical infectious outcome could be determined for all 339 women, so those proportions, LR(+), LR(-), Sens and Spec are all calculated OK.

3. Lines 263-66: The LR(+) and LR(-) comparing suspected Triple I vs confirmed Triple I need to be re-done, but if the numbers and their CI are similar, then as stated, the suspected Triple I criteria do not perform well to identify actual Triple I cases. Similarly, the performance of suspected Triple I to identify adverse clinical infectious outcomes is not very accurate. Both are particularly poor in specificity (large proportion of false positives), but also only moderately good in sensitivity (not insignificant proportion of false negatives), both of which may be equally important to the clinician.

4. While it is true that fever alone is statistically no worse than fever + clinical evidence of maternal infection, the number of adverse clinical infectious outcomes is relatively small (9.5% vs 11.8%) and there is little statistical power to generalize the NS finding.

Would you please send me your next version when you are finished addressing these comments?

Thank you,
Randi

From: Ona, Samsiya,M.D. [redacted]
Sent: Saturday, September 15, 2018 1:12 PM

To: Randi Zung <RZung@greenjournal.org>
Cc: Obgyn <Obgyn@greenjournal.org>; [redacted]
Subject: Re: Your Revised Manuscript 18-1290R1

Dear Ms. Zung,

Thank you very much for the email. Please see below our responses and attached our edits.

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

We agree with the changes. Thank you

2. Please ask Ruth Ellen Tuomala to respond to her authorship confirmation email. We emailed her at [redacted] The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org.

Dr. Tuomala is aware and will respond. Thank you

3. Precis: All women are at risk for adverse outcomes. I substituted in your abstract-conclusion sentence. Please review.

We reviewed and agree. Thank you

4. Line 96 and Line 136: When you write that a study occurred between date 1 and date 2, it literally excludes those boundary dates. For instance, "This study was performed between Feb 2018 and Jan 2019" would mean it was performed from March 2018 to Dec 2018. Do you instead mean that the study was performed from date 1 to date 2? If so, please edit.

We have edited this in lines 111, 158, 178-187. Thank you

5. Line 258: The information in Table 3 already appears in the text of the manuscript. The Editor has deleted Table 3 because it is redundant.

We agree. Thank you

Sincerely,

Samsiya Ona, MD

[redacted]

From: Randi Zung <RZung@greenjournal.org>
Sent: Thursday, September 13, 2018 11:32 AM
To: Ona, Samsiya,M.D.
Subject: Your Revised Manuscript 18-1290R1

Dear Dr. Ona:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. Please ask Ruth Ellen Tuomala to respond to her authorship confirmation email. We emailed her at [redacted] The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org.

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5. Line 258: The information in Table 3 already appears in the text of the manuscript. The Editor has deleted Table 3 because it is redundant.

To facilitate the review process, we would appreciate receiving a response by September 17.

Best,
Randi Zung

_ _
Randi Zung (Ms.)
Editorial Administrator | *Obstetrics & Gynecology*
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