

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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obgyn@greenjournal.org.

Date: Jul 01, 2019
To: "Jessica M Page" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-972

RE: Manuscript Number ONG-19-972

Stillbirth Associated with Infection in a Diverse United States Cohort

Dear Dr. Page:

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 Jul 22, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a secondary analysis of 512 stillbirths enrolled in a large multi-site national population-based study. The authors selected out 66 cases of stillbirth where infection was identified as a probable of possible cause of death to better characterize these cases in regard to pathogenesis and microbiological findings. Of the subset of cases, 36% were categorized as probable and the remainder as possibly the cause of death; the cases were compared to a selected control group. Infection-related stillbirth occurred earlier in gestation than non-infection related stillbirth. Of the cases with positive culture results, the predominant species were *E. Coli*, group B strept, and enterococcus. Placental pathology found inflammation or evidence of infection in nearly all of the selected cases. The authors conclude that of stillbirth cases likely due to infection, that TORCH titers are of little use and that placental pathology with autopsy is more likely to produce clinical relevant findings. Ways in which this manuscript could be improved include:

1. Line 86: I would expand this sentence to describe how you know this (search terms) or give some magnitude of the work that has previously been done.
2. Line 118: Why were all of the tests not obtained? Provider or patient preference?
3. Line 196: I do not think it is needed to state that it is obtained at 36 weeks, a vast majority of readers know this and it is not pertinent to your manuscript.
4. Lines 337-338: I would given some details of this study. What does not clearly linked mean?
5. Lines 339-340: What search terms were exhausted to review the existing literature?
6. Line 336: I would use the would could instead of would, to soften the language.

Reviewer #2: It is a clear and well-written paper on a topic important but with very little published data of quality. Many forces in this study need to be highlighted as the population design and the method used to appraise the case. Assign a cause to a stillbirth is difficult because causes of stillbirth are uncertain and often multiple factors are involved. Thus, the proposed method brings relevant information in view of these difficulties. Even if the results are descriptive and with little direct impact in terms of decision and impact on the prevention of the stillbirth, they bring a better knowledge of the accident.

I have some remarks

1 it seems to me that the results section is too long and that some results may not be reported, both in the text and in tables. For example report on the entire cohort characteristics while it has already been published is not essential. In addition, it seems to me that comparisons with livebirth group and the group "other causes stillbirth" are also cumbersome to read with questionable interest.

2 Indeed, I do not quite understand the purpose of comparing maternal characteristics between livebirths and infections related stillbirth. Indeed, infections related stillbirth is a very heterogeneous group that groups together very different cases and causes; to assume that there are determinants common to this group is debatable.

3 It seems to me that the authors should focus on the description and understanding of infections related stillbirths, and in particular clearly distinguishing within this population the cases without and with predetermined rupture of membranes or preterm labor. Finally, the information concerning cases not related with preterm labor or rupture of membranes has rarely been reported with this design. It is in this subgroup that it is interesting to identify the most useful tests and the predominant microorganisms. In fact the most interesting part of the discussion section concerns this subgroup among the 66 boxes.

4 I do not think 4 digits after the comma for p's are needed

Reviewer #3: In this secondary analysis of 512 stillbirths, the investigators evaluated and characterized stillbirth related to infection using clinical, histologic, and microbiologic data. Not surprisingly, almost 13% of stillbirths had infection as a probable or possible cause of death. Predominant bacterial organisms were E. coli, group B streptococcus, and enterococcus. CMV was the most common non-bacterial organism recovered.

The findings of the study add to our understanding of infection as a cause of stillbirth. Also, the study will provoke more questions and might open the door for more needed research in this area.

Reviewer's comments:

1. Page 4 (Abstract, Conclusions, lines 79-89): Consider adding CMV infection as the most common non-bacterial cause of infection related stillbirth.
2. Figure 2: The evaluation for stillbirth includes placental membrane culture or nucleic acid testing when there is suspicion of bacterial infection clinically or on pathologic examination. How do the authors propose to culture the placental membrane when, in their study, placental culture results were not useful because of polymicrobial growth and the organisms did not correlate with the clinical scenario (page 10, lines 203-205).
3. Page 10 (Discussion, 2nd paragraph): Parvovirus was addressed in the Discussion; however, CMV infection did not get much attention. First, the test was rarely utilized as part of the evaluation for stillbirth (Table 4). The two positive results were pertinent positive results. In addition, 6 cases were identified by placental pathology or fetal autopsy, although in one case CMV was not considered a probable or possible cause. Please comment about CMV infection and its importance in the evaluation of stillbirths.

STATISTICAL EDITOR'S COMMENTS:

1. lines 63-64: Should report the proportion of stillbirths having probable or possible cause of death as infectious with CIs, ie, 12.9% (95% CI = 10.0%-15.8%).
2. lines 64-78: See later comments re: citing precision to nearest 0.1% when the total N=66 for this subset of stillbirth cases. Also, same issue is noted in Tables and throughout the main text.
3. lines 172-177: The derivation of Nw (the weighted control group of non-stillbirths) should have more detailed explanation (could be as on-line material.)
4. lines 178-179 and Tables 1 and 2: Many of the categorical comparisons involve counts in one or both groups that were < 5, so should have used Fisher's test. The consequence is that many of the p-values are higher than the values cited and some are no longer significant at $p < .05$. e.g., pre-gestational DM for GA > 37 wks: 1:9::15:1258 has p-value = 0.12, not < .0001; pre-eclampsia/gest HTN for GA < 37 weeks 4:47::31:116 has $p = 0.03$, not $p = .0019$. Also, shouldn't one of the GA categories be defined by \leq or \geq ? That is, what happens to GA = 37 wks in this analysis? Many of the sums of subcategories (eg, maternal age) do not equal the Nw given at the column heading. Some are more, some less than the column heading Nw. Is this due to rounding and/or missing data? Need to clarify why these do not sum correctly.
5. Table 1: The "stillbirth, no infection" group had N = 446, so there is no basis for citing %s to nearest 0.01%, should round to nearest 0.1%. For the "infection related stillbirth" group, N = 66, so should cite those %s to nearest integer %, not to nearest 0.01%. Need units for maternal age and for BMI. Need to enumerate all missing data. For medians, should

also include IQR or range

6. Table 2: For the livebirths columns, should round %s to nearest 0.1%, for the infection related stillbirths < 37 wks, (N = 55), need to round to nearest integer %, for the infection related stillbirths > 37 wks, should just round to nearest 10 percent (many of those entries appear to be incorrect).

7. Table 3 and 4: Should round %s to nearest integer %, since the total cohort was N = 66. For Table 3, should indicate the N for each column of GA group.

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.
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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.

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

3. Was this study presented at the SMFM meeting? If so, please disclose the name, dates, and location of the meeting on the title page of your manuscript. .

4. 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.

5. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

6. 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).

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. 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.

11. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG 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 (exceptions could include manuscripts that address items of historical interest). 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 an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

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

"Figure 1: The last exclusion box excludes 2 cases; however, the final total does not reflect these exclusions. Should either of these boxes be updated?"

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.

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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.

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 22, 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

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

Dear Dr. Chescheir:

Thank you for considering our manuscript entitled “Stillbirth Associated with Infection in a Diverse United States Cohort” for publication in Obstetrics and Gynecology. We have addressed each of the reviewers and editors comments in an attempt to improve our paper as follows.

The lead author, Jessica Page, 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.

Thank you again for allowing us to revise this manuscript. Please let us know if we can make additional improvements.

Sincerely,

Jessica Page, MD

A large black rectangular redaction box covering the signature and contact information of the author.

RE: Manuscript Number ONG-19-972
Stillbirth Associated with Infection in a Diverse United States Cohort
REVIEWER COMMENTS:

Reviewer #1: This is a secondary analysis of 512 stillbirths enrolled in a large multi-site national population-based study. The authors selected out 66 cases of stillbirth where infection was identified as a probable or possible cause of death to better characterize these cases in regard to pathogenesis and microbiological findings. Of the subset of cases, 36% were categorized as probable and the remainder as possibly the cause of death; the cases were compared to a selected control group. Infection-related stillbirth occurred earlier in gestation than non-infection related stillbirth. Of the cases with positive culture results, the predominant species were E. Coli, group B strept, and enterococcus. Placental pathology found inflammation or evidence of infection in nearly all of the selected cases. The authors conclude that of stillbirth cases likely due to infection, that TORCH titers are of little use and that placental pathology with autopsy is more likely to produce clinically relevant findings. Ways in which this manuscript could be improved include:

1. Line 86: I would expand this sentence to describe how you know this (search terms) or give some magnitude of the work that has previously been done.

Thank you for this comment. Our intention was to highlight the lack of prospective, well-characterized studies of infection stillbirth and we have edited the text. Indeed, there are numerous retrospective and heterogeneous studies of stillbirth due to infection, many of which focus on specific pathogens. This was assessed with a PubMed search utilizing the search terms stillbirth and infection. We hope that this study will provide information regarding infectious stillbirth in a prospective, well-characterized high-income setting.

Line 113: Maternal and/or fetal infection is an important cause of fetal death for which prospective, well-characterized studies are lacking.

2. Line 118: Why were all of the tests not obtained? Provider or patient preference?

A standard set of laboratory tests were recommended to enrolled participants but in some cases the providers did not have them performed. As part of the study protocol, testing for syphilis and parvovirus was performed utilizing stored maternal serum. Samples that did not undergo testing on stored specimens was due to either patient request or lack of sample. The remaining tests were ordered at the discretion of the provider. We have edited the text to better reflect this.

Line 147: However, all of these tests were not obtained in every case of stillbirth, either due to patient or provider preference or due to lack of stored serum sample.

3. Line 196: I do not think it is needed to state that it is obtained at 36 weeks, a vast majority of readers know this and it is not pertinent to your manuscript.

Thank you for this comment, we have edited the text as below.

Line 224: Results of vaginal culture for group B streptococcus (GBS) were available for 105 (20.5%).

4. Lines 337-338: I would given some details of this study. What does not clearly linked mean?

Thank you for this clarification. This statement is referencing a prior SCRN study which examined pre-pregnancy risk factors for stillbirth. In our updated analysis, which used a Fisher's Exact test for this comparison, diabetes no longer had a significant association with infection stillbirth. Given this, we have removed this section from the discussion and results sections.

5. Lines 339-340: What search terms were exhausted to review the existing literature?

Thank you for this comment, we agree that transparency regarding the assessment of the prior data is important. In our assessment of prior data, we used the search terms stillbirth and infection as well as a more focused search of stillbirth and infection and prospective in a pubmed search. The majority of literature regarding infection stillbirth is comprised of studies focused on specific pathogens in a variety of settings. There are very few studies which evaluate infection stillbirth and characterize it more globally. We have updated our text as follows to better reflect the existing data.

Line 479: A literature search was performed utilizing the search terms "stillbirth" and "infection". Existing data on infection stillbirth are comprised primarily of case series examining specific bacterial or viral pathogens with only a small number evaluating infection stillbirth in a prospective, comprehensive fashion.

6. Line 336: I would use the would could instead of would, to soften the language.

Thank you for this revision, we have updated the text to reflect this.

Line 520: It is possible that a more comprehensive approach could identify additional infectious causes of stillbirth.

Reviewer #2: It is a clear and well-written paper on a topic important but with very little published data of quality. Many forces in this study need to be highlighted as the population design and the method used to appraise the case. Assign a cause to a stillbirth is difficult because causes of stillbirth are uncertain and often multiple factors are involved. Thus, the proposed method brings relevant information in view of these difficulties. Even if the results are descriptive and with little direct impact in terms of decision and impact on the prevention of the stillbirth, they bring a better knowledge of the accident.

I have some remarks

1 It seems to me that the results section is too long and that some results may not be reported, both in the text and in tables. For example report on the entire cohort characteristics while it has already been published is not essential. In addition, it seems to me that comparisons with livebirth group and the group "other causes stillbirth" are also cumbersome to read with questionable interest.

Thank you for this suggestion. We agree that it is best to focus on the new data obtained as part of the current study. The additional description of the overall study population has been removed from the text and the first paragraph of the results now reads as below.

Line 220: A total of 663 women with 676 stillbirths were enrolled; of these, 500 women with 512 stillbirths that had complete fetal postmortem examination were included in this analysis (Figure 1). Characteristics of this cohort have previously been described.⁸ Among the 500 women, 495 (99.0%) had serologic testing for syphilis, 451 (90.2%) for parvovirus, 38 (7.6%) for CMV, and 56 (11.2%) for toxoplasmosis. Results of vaginal culture for group B streptococcus (GBS) were available for 105 (20.5%).

2 Indeed, I do not quite understand the purpose of comparing maternal characteristics between livebirths and infections related stillbirth. Indeed, infections related stillbirth is a very heterogeneous group that groups together very different cases and causes; to assume that there are determinants common to this group is debatable.

We respectfully disagree with the reviewer regarding this point. Although infections causing stillbirth are quite heterogeneous, it is possible that certain maternal characteristics are associated with serious infections including those leading to stillbirth. Biologically plausible examples include diabetes, obesity, low socioeconomic status (and surrogates available in this dataset such as education, insurance status, etc.). If certain characteristics are associated with infectious stillbirths, risk stratification might be appropriate. If not, reduction strategies should target the entire population. Although we do not emphasize this part of our analysis, we advocate for keeping it in the paper. Alternatively, we are willing to delete it if the reviewer and / or editors feel strongly about it.

3 It seems to me that the authors should focus on the description and understanding of infections related stillbirths, and in particular clearly distinguishing within this population the cases without and with predetermined rupture of membranes or preterm labor. Finally, the information concerning cases not related with preterm labor or rupture of membranes has rarely been reported with this design. It is in this subgroup that it is interesting to identify the most useful tests and the predominant microorganisms. In fact the most interesting part of the discussion section concerns this subgroup among the 66 boxes.

Thank you for this comment, we agree that the group of cases which do not fall into a preterm labor pathway are of particular interest. To answer the questions above an additional analysis was performed and discussion of the results included in the revised manuscript.

Line 397: Further characterization of the cases which were not due to a preterm labor pathway was performed in order to better understand this cohort of infection-related stillbirths. In this group fetal cultures produced a result less often (20.0% compared to 53.2% in the overall cohort). The pathogens observed most often were E. coli (6; 17.1%), enterococcus (5; 14.3%) and GBS (3; 8.6%). This was similar to the overall cohort with the exception that GBS was less common. Test utility was also similar as placental pathology was useful in 91.4% and fetal autopsy in 51.4%. Maternal parvovirus and syphilis serologies were rarely useful (5.7% and 2.9% respectively). Fetal cultures were less often helpful in identifying a potential cause of death in 20.0% of cases (37.9% in the overall cohort).

Line 459: Given the high percentage of cases of stillbirth associated with infection with similar pathophysiology to preterm labor, we sought to characterize those cases not due preterm labor. This group of cases may require a different strategy for prediction and prevention. Infection stillbirth cases that were not part of the preterm birth pathway had fewer cases involving GBS. Placental pathology and fetal autopsy remained the most useful tests in this subgroup, although fetal cultures had less utility.

4 I do not think 4 digits after the comma for p's are needed

Thank you for pointing this out, we have updated the p-values throughout the text.

Reviewer #3: In this secondary analysis of 512 stillbirths, the investigators evaluated and characterized stillbirth related to infection using clinical, histologic, and microbiologic data. Not surprisingly, almost 13% of stillbirths had infection as a probable or possible cause of death. Predominant bacterial organisms were E. coli, group B streptococcus, and enterococcus. CMV was the most common non-bacterial organism recovered.

The findings of the study add to our understanding of infection as a cause of stillbirth. Also, the study will provoke more questions and might open the door for more needed research in this area.

Reviewer's comments:

1. Page 4 (Abstract, Conclusions, lines 79-89): Consider adding CMV infection as the most common non-bacterial cause of infection related stillbirth.

Thank you for this comment, we have updated the text as follows:

Line 91: Of stillbirth cases likely due to infection in a large U.S. cohort, E. coli, group B streptococcus and enterococcus were the most common bacterial pathogens and cytomegalovirus the most common viral pathogen.

2. Figure 2: The evaluation for stillbirth includes placental membrane culture or nucleic acid testing when there is suspicion of bacterial infection clinically or on pathologic examination. How do the authors propose to culture the placental membrane when, in their study, placental culture results were not useful because of polymicrobial growth and the organisms did not correlate with the clinical scenario (page 10, lines 203-205).

Thank you for this clarification. In the SCRN study, specialized perinatal pathologists were trained with a standardized placental pathology protocol. This likely represents an ideal situation for obtaining the most accurate and high-yield placental pathologic exam. Given that we did not systematically perform placental cultures nor study this practice specifically, we cannot recommend a particular practice at this time. We have altered the text to reflect this nuance.

Line 233: In this study, placental cultures were not systematically obtained. Accordingly, these findings should be interpreted with caution.

3. Page 10 (Discussion, 2nd paragraph): Parvovirus was addressed in the Discussion; however, CMV infection did not get much attention. First, the test was rarely utilized as part of the evaluation for stillbirth (Table 4). The two positive results were pertinent positive results. In addition, 6 cases were identified by placental pathology or fetal autopsy, although in one case CMV was not considered a probable or possible cause. Please comment about CMV infection and its importance in the evaluation of stillbirths.

Thank you for this comment. We agree that viral pathogens, including CMV, are important contributors to infection-related stillbirth. While we did not systematically test for CMV in this population, we believe our results with regard to CMV are likely accurate given that cases which were identified had overt findings on fetal and placental histopathology. A positive screening test in the absence of additional clinical evidence of CMV infection, either on antenatal ultrasound exam or on postmortem evaluation, is of uncertain, and likely no clinical significance. We have discussed these findings further in the discussion section as recommended.

Line 436: Cases in which CMV was the likely pathologic organism had fetal hydrops, abnormal biometric measurements or CMV on fetal and placental histopathologic examination.

STATISTICAL EDITOR'S COMMENTS:

1. lines 63-64: Should report the proportion of stillbirths having probable or possible cause of death as infectious with CIs, ie, 12.9% (95% CI = 10.0%-15.8%).

Thank you for this correction, the text has been updated with this information.

Line 72: Of these, 36.4% (95% CI 34.9% - 37.8%) were categorized as a probable and 63.6% (95% CI 62.2% - 65.1%) as a possible cause of death.

2. lines 64-78: See later comments re: citing precision to nearest 0.1% when the total N=66 for this subset of stillbirth cases. Also, same issue is noted in Tables and throughout the main text.

Thank you for this comment, and as suggested in the comment below, the main text and tables have been updated to the integer for the infection stillbirth group (N=66) and to the 0.1 for the non-infection stillbirth (N=446) group.

3. lines 172-177: The derivation of Nw (the weighted control group of non-stillbirths) should have more detailed explanation (could be as on-line material.)

Thank you for this clarification. A description of the construction of the data weights is given below and is derived from the original SCRN methods publication. (Parker CB, Hogue CJR, Koch MA, Willinger M, Reddy U, Thorsten VR, et al, for the Stillbirth Collaborative Research Network. Stillbirth Collaborative Research Network: Design, methods and recruitment experience. Paediatric and Perinatal Epidemiology 2011;25:425-35. Appendix 1) We believe this is most suitable either as on-line material or as an appendix, at the discretion of the editors.

Analytic weights were created to account for the sampling design and differential participation rates. These weights were created in stepwise fashion. A base weight was designed to account for the staggered start of enrollment at each of the study hospitals. Live births <32 weeks had a selection probability applied to account for lower numbers of women recruited in this subgroup. For live births ≥32 weeks gestation a base weight adjustment was used to account for oversampling of women of African descent. Another base weight adjustment was used to adjust for the sampling strategy for situations in which a live birth ≥32 weeks gestation did not occur within 24 hours of an enrolled stillbirth. A final base weight adjustment was then used to better approximate the number of live births at <32 weeks gestation to the proportion of live births at <32 weeks gestation in the catchment area. A weight was then applied to account for differential participation rates including those who were not approached and those who were approached but did not consent. A final analytic weight was then derived as the product of all the base weighting factors and participation weights. The analytic weight was utilized in the current study. Further details regarding the construction of data weights can be found in the previously published study design paper. (Parker et al. Paediatric and Perinatal Epidemiology 2011;25:425-35. Appendix 1)

4. lines 178-179 and Tables 1 and 2: Many of the categorical comparisons involve counts in one or both groups that were < 5, so should have used Fisher's test. The consequence is that many of the p-values are higher than the values cited and some are no longer significant at $p < .05$. e.g., pre-gestational DM for GA > 37 wks: 1:9::15:1258 has p-value = 0.12, not < .0001; pre-eclampsia/gest HTN for GA < 37 weeks 4:47::31:116 has p = 0.03, not p = .0019. Also, shouldn't one of the GA categories be defined by \leq or \geq ? That is, what happens to GA = 37 wks in this analysis? Many of the sums of subcategories (eg, maternal age) do not equal the Nw given at the column heading. Some are more, some less than the column heading Nw. Is this due to rounding and/or missing data? Need to clarify why these do not sum correctly.

Thank you for this comment. We have updated our analyses with a Fisher's exact test performed for all comparisons in which the expected cell frequency is less than 5. We based our approach to this on the following reference. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5426219/>) The gestational age categories have also been updated; the term category included 37 weeks, and we apologize for this error. The column totals were different due to rounding and missing data. These have been double-checked and revised to ensure they amount to appropriate totals. We are happy to incorporate any additional changes as deemed necessary by the editors.

5. Table 1: The "stillbirth, no infection" group had N = 446, so there is no basis for citing %s to nearest 0.01%, should round to nearest 0.1%. For the "infection related stillbirth" group, N = 66, so should cite those %s to nearest integer %, not to nearest 0.01%. Need units for maternal age and for BMI. Need to enumerate all missing data. For medians, should also include IQR or range

Thank you for this comment. We have updated the rounding as recommended and included labels for BMI and maternal age. We have also enumerated the missing data for both table 1 and table 2. The IQR for gestational age has been included as well.

6. Table 2: For the livebirths columns, should round %s to nearest 0.1%, for the infection related stillbirths < 37 wks, (N = 55), need to round to nearest integer %, for the infection related stillbirths > 37 wks, should just round to nearest 10 percent (many of those entries appear to be incorrect).

We have updated the rounding in table 2 to reflect the above recommendations. Thank you for this revision and we apologize for prior errors.

7. Table 3 and 4: Should round %s to nearest integer %, since the total cohort was N = 66. For Table 3, should indicate the N for each column of GA group.

Thank you for this comment, the tables have been updated as suggested.

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.

We are happy to "opt-in."

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.

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

We have removed the author agreement forms from the submission.

3. Was this study presented at the SMFM meeting? If so, please disclose the name, dates, and location of the meeting on the title page of your manuscript.

We have updated the title page to include this information.

4. 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.

We have reviewed the reVITALize definitions and believe our manuscript is in compliance.

5. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

Our final revision complies with above limitations.

6. 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).

We have reviewed the rules for acknowledgment and our manuscript is in compliance.

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.

The abstract has been carefully reviewed and it corresponds with the results of the paper and meets the word count requirement.

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.

We have reviewed the manuscript and believe it meets this requirement.

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.

This symbol has been removed from the main text of the manuscript.

10. 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.

Our tables have been updated and comply with the table checklist.

11. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you

cite ACOG 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 (exceptions could include manuscripts that address items of historical interest). 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 an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

We have ensured that the ACOG documents that we have cited are the most recent version.

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

"Figure 1: The last exclusion box excludes 2 cases; however, the final total does not reflect these exclusions. Should either of these boxes be updated?"

Thank you for this clarification, the exclusion box included both one excluded case and one included case. This is confusing, and the figure has been updated to make this more clear. It is attached in both pptx and TIFF formats.

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.

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