Date: Sep 25, 2018
To: "Gianna Wilkie" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1479

RE: Manuscript Number ONG-18-1479

Peripartum Bacteremia: Organisms, Resistance Patterns, and Their Association with Neonatal Bacteremia

Dear Dr. Wilkie:

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 Oct 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Abstract:

Line 80-82 Why was E. Coli chosen for comparison to others bacteremia patients? This seems to be a different objective from line 74-75 which was descriptive.

Line 102 The conclusion doesn't fully support the results. Maternal ICU admission rates had aOR 12.2, 95% CI 1.9-77.8.

Introduction:

Line 128 The reference describes fever associated with epidurals. This should be stated somewhere in the introduction including dehydration.

Lines 131 The 3 references for infectious related maternal mortality vary. The most recent study listed which overlaps with the time period for this manuscript would be 12%. This should be changed or corrected to include ranges.

Line 135-138 Traditional management for chorioamnionitis is different than postpartum endometritis. Anaerobic coverage including clindamycin or metronidazole is done either prophylactically with cesarean sections if there is chorio or as first line if new onset postpartum endometritis is diagnosed. This is supported by the newer guidelines from Committee Opinion No. 712.

Line 145. The reported reference includes over 172 confirmed positive cultures from 200-2008 at the same institution. Similar guidelines and protocols were used. The study period from 2008 until 2016 prior to changing diagnostic criteria is similar with fewer patients. The original study was looking at some of the same outcomes in light of changing GBS screening and management. They report a lower E. Coli ampicillin resistant rate of 50%. This seems to be an extension of the other study with little differences other than rates of antibiotic resistance over time.

Materials and methods:

Lines 165 Explain more the protocol for complete blood cultures and urine cultures for an isolated fever. Was this based upon SIRS criteria or just an isolated fever?

Lines 173 How was diagnosis of chorioamnionitis made? ICD 9-10 codes?

Line 184 Elaborate on why E. Coli was the chosen cohort. Although it was the most prevalent positive culture it looks like the remaining positive cultures were lumped into one comparison arm which is not consistent with the main objective of this study. Each should be looked at independently. Gram negative other species, gram positive organisms and anaerobes have different risk for sepsis, DIC and ICU admission. The type of endotoxin or exotoxin differ with each organism.

Results:

Table 1. The demographics could be broken down by clinically relevant organisms instead of dichotomous E. Coli vs. other bacteremia. The pathophysiology and risks as mentioned above are different.

Lines 218-219 Of the 7 admissions to the ICU 4 were from non obstetric indications. This is important to look at separately as the source is more GI or GU than ascending infection associated with the peripartum. This may bias the interpretation and conclusion put forth in the discussion section. The total number is small and large CI noted for both neonatal and ICU outcomes.

Table 4. Are there reported hospital wide ID charts for E. Coli sensitivities over the same time period? E. Coli multidrug resistance can be by plasmid, transpons or mutations which have similar rates across institutions. This would be an important comparison group. The discussion section lists resistance rates of 53% in 2016 which was consistent with prior study.

Discussion:

Line 254-255. The general knowledge of high rates of E. Coli resistance to ampicillin and beta lactams is not new. The low resistance rates to gentamycin are consistent with the literature and don't provide clinically actionable information. Most patients fever and obstetric infection, either intraamniotic infection or endometritis, resolve before the culture results are back. The clinical question of a resolved infection and positive cultures after discharge creates a different clinical conundrum when liberal use of blood culture for fever only are used. Is there any information on resolved fevers and positive cultures that have changed clinical outcomes in your study? The claim of lower mortality rates with liberal blood cultures compared to historic controls from prior study can not be made

Lines 283. Was the maternal infant pair obtained only through the maternal record first? Was there a separate review of all neonatal bacteremia babies over the same time period looking at association of maternal condition ie fever blood cultures.

Line 294-296 When were culture results available in relationship to ICU admission? Did it dictate or change therapy?

Reviewer #2: The authors present the results of a descriptive study on peripartum bacteremia in obstetric patients and their newborn infants. The institutional practice of routinely obtaining blood cultures in febrile pregnant women presenting in labor and post-partum, allowed the estimation of the frequency of bacteremia in mothers, the description of the most common organisms and their susceptibilities, and the relation between maternal and neonatal bacteremia. Data was collected retrospectively for several seasons, and analyses included the evaluation of potential risk factors.

Overall, the results of this study are relevant for both obstetric and neonatal care and suggest an association between maternal bacteremia (which could be missed unless cultures are systematically obtained), and neonatal risk of infection which could guide management practices.

Specific comments below:

Abstract
The conclusion of the abstract should reflect the observation that chorioamnionitis and UTI are commonly associated with E. coli bacteremia.

Methods
Please clarify how patient identification was conducted. The methods describe that subjects were identified through the hospital's microbiology database, to identify febrile patients with positive blood cultures in the peripartum period. How was the fever ascertained? Were patients identified based on blood culture results first, and then charts reviewed to determine if they presented with fever at the time of the blood sampling? Were subjects included if bacteremic but no fever documented concurrent with the sample collection?

How was it determined that the listed bacteria were contaminants vs. pathogens? Among the non-excluded infections is S. hominis - is this a typical pathogen in the peripartum period?

Is the universal screening and treatment policy for OB patients with a fever described at your institution common practice

at most obstetric centers? When was this practice instituted? Are there guidelines on this management and if not, how was this policy developed? How well is it followed?

Please define the following described outcomes: chorioamnionitis, endometritis, neonatal bacteremia (relevant, as opposed to contaminants), and how choriamnionitis and endometritis were ascertained.

Results
Did you look at incidence or prevalence of maternal bacteremia?

Would it be possible for you to show the changes (if any) in the incidence of the various organisms over time ? Was E. coli always the predominant causative agent?

Is it possible for you to calculate the risk of neonatal bacteremia when mother has bacteremia or febrile bacteremia?

Discussion
Much discussion is based on the comparison of the results of this study with a historical cohort - was the same management practice (screening and treatment) in place when the historical cohort was evaluated? If not, when was this practice established? How comparable are these two cohorts?

In page 11, second paragraph, include the the rates of resistance of E. coli to ampicillin in the previous cohort.

In page 12 - line 307, selection bias is appropriately discussed, consider changing the word "represent" to "select" in the sentence "This may bias our results to select the most clinically significant infections..."

A discussion re. OB vs non-OB sources of infection in the mother would be helpful, as it appears that non-OB sources should be evaluated in cases of maternal fever, as they represented at least 1/3 of the cases.

Conclusions
Make sure to include a statement regarding the most relevant findings in the conclusion, and that the conclusions match those in the abstract. The association with chorioamnionitis and UTI and E. coli, and the association of neonatal bacteremia in bacteremic mothers should be mentioned.

What recommendations do you have on the importance of collecting blood cultures in febrile obstetric patients based on the results of this study.

Tables
Table 1 - please include an asterisk or other form of indicating where the significant (p-value < 0.01) differences are found. It is difficult to follow if the differences observed are based on comparisons between the variables presented in the columns or the rows.

Table 3. For patients 4 and 6, why did these infants return for repeat cultures? where they ill (eg. fever?) or was it because of the maternal blood culture results?

Table 4. Consider adding the threshold MIC that was used to determine resistance.

Reviewer #3: The study examines contemporary microbiology and associated antibiotic resistance patterns among febrile peripartum women. The authors found that E coli is the most commonly isolated organism with high rates of antibiotic resistance. The study supports the use of ampicillin and gentamicin for peripartum bacteremia.

General Comments:
The study addresses an understudied topic and adds valuable information to the current literature. The limitation of the study is that the data is obtained from one institution.

Specific Comments:

1. Abstract: The conclusion (Line 100) is confusing to the readers. It appears that the authors are stating that Ecoli is uncommonly associated with maternal bacteremia. The conclusion written in discussion (Line 313) is much easier for interpretation.

2. Discussion: The authors compare the findings to a different cohort from the same institution. The authors should compare their results with data/findings from other studies performed in other institutions.

3. Table 3: Table 3 may not be necessary. The information mentioned in the manuscript is sufficient.

Reviewer #4:

General: This is a retrospective cohort study of febrile women with blood cultures obtained between 7 days prior to 30 days after delivery. The authors performed chart review to compare characteristics of women with E.coli bacteremia compared with bacteremia from other organisms, and then performed logistic regression to determine strength of association between maternal ICU admission and neonatal bacteremia and E.coli bacteremia. The authors additionally examine resistance patterns for several species of bacteria grown from maternal blood cultures but do not incorporate a variable of antimicrobial resistance into the regression analysis. While the authors' analytic approach focuses on the outcomes of maternal ICU admission and neonatal bacteremia, the conclusions made seem to focus more on antimicrobial resistance and empiric antibiotic regimens used in obstetrics. A clear, concise message that conveys the conclusions made from the statistical analysis is recommended. The data seem to support what is already known about E.coli and maternal and neonatal risk in the era of widespread intrapartum antibiotic prophylaxis, and conclusions about appropriate (versus inappropriate) antibiotics and E.coli resistance patterns seem overreaching.

Abstract: Overall, the abstract is a concise summary of the research. Would consider incorporating a few of the suggestions from the manuscript text in to the abstract.

Page 4, Line 100. The last sentence in the abstract conclusion seems to suggest that the commonly used antibiotics may not be ideal; however, this was not the focus of the analysis. Would suggest rewording to focus more on the selected maternal and neonatal outcomes as analyzed in the results section.

Introduction: The introduction suggests that the focus of the paper will be antibiotic resistance patterns as a primary analysis. This is somewhat different from the focus of the Materials and Methods and the organization of the Tables, which seem to focus instead on maternal ICU admission and neonatal bacteremia as the main outcomes assessed. Would consider the which message is intended, and focus the introduction accordingly.

Materials and Methods: This is an appropriate summary of the approach to data collection.

Page 6, line 165. Is this universal screenin and treatment policy new? If so, it might be helpful to include a statement summarizing this change in policy to understand why the current cohort is chosen. The authors point out in the discussion that the institutional policy for drawing blood cultures changed in 2009 (i.e., from selective to universal blood cultures for peripartum fever), and they draw attention to differences in policy that may contribute to differences in outcomes. It may be helpful to clarify this policy change in the methods.

Page 6, line 172. Did the authors gather data on estimated blood loss at delivery? This would likely be an important variable to consider when the outcome is maternal ICU admission.

Results:
1. Overall, the reviewer recommends reorganization of the structure of this section to better help the reader follow the Tables and Figure. Currently, the reader has to search for the references to tables and figures, which are buried in the text, and then reread the text to find numbers that correlate with data presented in tables, which is confusing. Recommend starting each paragraph with a sentence introducing the corresponding table, etc.

Page 9, line 226. Recommend the numbers in the text exactly match those listed in tables (with same number of decimal places, for example).

Page 9, line 241. There is no reference to a table for this paragraph (see above comment).

Page 9, line 245. Are sensitivities to clindamycin and extended spectrum beta-lactamases tested for enterococcus species at your hospital? The text implies they are, but this is not reflected in Table 4, and seems unusual given the organism's intrinsic resistance profile.

Discussion:
The first paragraph of the discussion focuses on resistance profiles for E.coli, rather than summarizing the results shown in Table 2 (i.e., the main outcome measures from the statistical analysis presented). This is not what the reader expects. If the focus of the paper is antimicrobial resistance profiles, perhaps the investigators should reorganize the presentation and analysis of data. Or, if the authors want to convey a message about maternal and neonatal morbidities associated with E.coli bacteremia as suggested by the statistical analysis, this reviewer suggests reorganizing the discussion to bring the discussion of maternal ICU admission (lines 295-300) to the top of the discussion section.

Tables:
Table 4 appears to be the main focus of the introduction and discussion, although the reader focuses on Table 2 as the main statistical analysis presented. See comments above.

Would also recommend including total "n" under each row in Table 4.

STATISTICAL EDITOR COMMENTS:

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

Table 1: Should cite median (IQR) with upper and lower bounds, not as ± IQR. Need to re-calculate the chi-square p-values, For example for mode of delivery 15 vs 6 compared to 54 vs 45 has p = .16, not < .01. Similarly, for PTB 3 vs 18 compared to 16 vs 83 has p = 0.83, not < .01.

Table 2: The counts of adverse events is small, hence the CIs for aORs are wide. There is no justification for use of adjustment model using 4 covariates as adjustors. Should instead use Fisher's test and then cite as limitations that one cannot based on these samples, adjust for all the baseline differences. Should include the p-value for neonatal death comparison, although it will be NS and there is little power to generalize based on so few cases.

lines 208-214: This is a misapplication of the meaning of chi-square methods. The chi-square tests the overall allocation of proportions or counts, not specific row entries (in the case of race/ethnicity). The comparison of % Hispanic is NS, the comparison of % black is significant, but the result is by pairwise testing, not the overall chi-square. The % vaginal delivery is NS different, not p < .01. Similarly, the comparison of % with antepartum blood cultures needs a pairwise test, not the overall chi-square result. There is no statistical difference between 66.7% vs 57.1% nor 2% vs 0% for the sample sizes here. Individual pairwise testing should be done, not extrapolating the overall chi-square test result.

lines 230-231: Did all neonates whose mothers had bacteremia also have blood cultures, or are the 8 (+) the numerator of a smaller subset of those tested? If not all neonates of mothers with bacteremia were tested, then the estimates of Table 2 re: neonatal bacteremia for E. Coli vs other is biased and should be cited as severe limitation.

After altering Table 2, should re-do results and discussion without multivariable analysis.

EDITOR COMMENTS:

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

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

- The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read.

- Could you provide the N for number of women delivered in this time period, the n for # of women who got blood cultures? Also, when you say "3,797 blood cultures" does that mean separate cultures or women? At my hospital, when someone has blood cultures ordered they typically get 2 samples from different sites. If that is similar at your hospital, are those counted separately?

- please provide the n's here. You had 21 E.Coli positive cultures. Of these, how many were antenatal? (for eg, x/21) and the percentage. The percentages here for each bacterium should add up to 100 if you trying to make the comparison of timing by different bug.

- not sure what you mean by "are emerging"

- please more clearly state your primary and secondary outcomes

- please name the academic center and the IRB

- why was it exempt?

- For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

- Give same data here I requested above for the abstract.

- Does your lab look for Ureaplasma?

- any endometritis?

- please edit: this sentence is unclear regarding who has the bacteremia. I assume its 6.5% of the neonates but it could be interpreted to be the mothers.

- provide numerators and denominators

2. The Statistical Editor's comments are quite important and need to be addressed. I agree with his recommendation to report this as a descriptive study rather than any comparisons between bacteria. Your numbers are just too small for comparisons. Can you also comment on whether your laboratory assesses for ureaplasmas? Likewise, your universal policy of work up for fevers does not seem to be universal--can you comment further?

3. 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.

4. Author Agreement Forms: Please note the following issues with your forms. Updated or corrected forms should be submitted with the revision.

Malavika Prabhu, MD - Please provide an ink signature on the third page of the Author Agreement Form.

5. 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.

6. 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.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

8. 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).

9. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25

words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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. Figure 1 may be resubmitted as-is.

15. 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 Oct 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

Dear Editors,

Thank you for the opportunity to revise our manuscript (ONG-18-1479) submission and resubmit. We have reviewed the entirety of the comments provided by all reviewers and editors, and have strived to address all of their concerns. We are happy to work on it further should you desire further revision after review of this updated manuscript. Please see our detailed responses to all comments below.

Sincerely,

Gianna Wilkie MD, Malavika Prabhu MD, Sarah Rae Easter MD, Samsiya Ona MD, Ruth Tuomala MD, Laura Riley MD, Khady Diouf MD

Reviewer #1 Comments

Line 80-82 Why was E. Coli chosen for comparison to others bacteremia patients? This seems to be a different objective from line 74-75 which was descriptive.

After review of all edits and revisions suggested by the reviewers, the comparison groups were changed to be more in line with bacterial type grouping (gram positive, gram negative, and anaerobic). *E. coli* is no longer chosen for comparison after editing of this manuscript.

Line 102 The conclusion doesn't fully support the results. Maternal ICU admission rates had aOR 12.2, 95% CI 1.9-77.8.

This was deleted as the multivariable analysis was removed, based on the comments from the reviewers and editors. A univariate analysis was completed, which showed no difference in maternal ICU admission between groups.

Introduction:

Line 128 The reference describes fever associated with epidurals. This should be stated somewhere in the introduction including dehydration.

In the introduction section, lines 138 through 139 were amended to include "and may be attributed to dehydration, neuraxial analgesia or prostaglandins."

Lines 131 The 3 references for infectious related maternal mortality vary. The most recent study listed which overlaps with the time period for this manuscript would be 12%. This should be changed or corrected to include ranges.

Lines 141 through 142 were amended to include a range of 10 to 12% as the references included a range of maternal mortality from 10 to 12%.

Line 135-138 Traditional management for chorioamnionitis is different than postpartum endometritis. Anaerobic coverage including clindamycin or metronidazole is done either prophylactically with cesarean sections if there is chorio or as first line if new onset postpartum endometritis is diagnosed. This is supported by the newer guidelines from Committee Opinion No. 712.

This sentence regarding the standard of care for empiric antibiotic selection of chorioamnionitis and endometritis was deleted in order to meet word limits. It was assumed that most readers would be familiar with routine treatment of chorioamnionitis and endometritis per ACOG recommendations.

Line 145. The reported reference includes over 172 confirmed positive cultures from 200-2008 at the same institution. Similar guidelines and protocols were used. The study period from 2008 until 2016 prior to changing diagnostic criteria is similar with fewer patients. The original study was looking at some of the same outcomes in light of changing GBS screening and management. They report a lower E. Coli ampicillin resistant rate of 50%. This seems to be an extension of the other study with little differences other than rates of antibiotic resistance over time.

The cited study, *Cape et al.* (2008), is from the same institution, however the patient populations were not the same. In *Cape et al.* (2008), patients did not have universal blood cultures collected, but rather selective selection of patients that appeared ill. The protocols were therefore not the same and the main outcome of the study was to examine bacteremia as a surrogate for genital track flora of obstetric infections surrounding the universal GBS protocol. Therefore, our populations are not the same and the results of the previous studies are limited by the variations in practice surrounding intrapartum fever.

Materials and methods:

Lines 165 Explain more the protocol for complete blood cultures and urine cultures for an isolated fever. Was this based upon SIRS criteria or just an isolated fever?

Line 268 was amended to include isolated fever for further clarification, and lines 268-270 detail the evaluation included what evaluation is required.

Lines 173 How was diagnosis of chorioamnionitis made? ICD 9-10 codes?

The diagnosis of chorioamnionitis was made from the medical record notes documenting chorioamnionitis or other assigned diagnoses. Lines 241 through 265 was added for clarification.

Line 184 Elaborate on why E. Coli was the chosen cohort. Although it was the most prevalent positive culture it looks like the remaining positive cultures were lumped into one comparison arm which is not consistent with the main objective of this study. Each should be looked at independently. Gram negative other species, gram positive organisms and anaerobes have different risk for sepsis, DIC and ICU admission. The type of endotoxin or exotoxin differ with each organism.

After review of the comments from all editors, the comparison groups were changed to highlight the focus on bacterial organisms and resistance and further subdivide the organisms. Therefore, the comparison groups were changed to gram positive vs. gram negative vs. anaerobic organisms. *E. coli* is no longer chosen as a cohort.

Results:

Table 1. The demographics could be broken down by clinically relevant organisms

instead of dichotomous E. Coli vs. other bacteremia. The pathophysiology and risks as mentioned above are different.

The demographics table was amended to include a comparison of clinically relevant gram positive vs. gram negative vs. anaerobic organisms.

Lines 218-219 Of the 7 admissions to the ICU 4 were from non obstetric indications. This is important to look at separately as the source is more GI or GU than ascending infection associated with the peripartum. This may bias the interpretation and conclusion put forth in the discussion section. The total number is small and large CI noted for both neonatal and ICU outcomes.

The multivariate analysis was no longer included in the study per the editor's comments and the focus was changed to be more descriptive. Due to the small numbers of observed outcomes with ICU admission, it is not possible to draw meaningful conclusions regarding the clinical or bacteriologic etiology of ICU admission. This is now stated as a limitation in the paper in lines 747-748.

Table 4. Are there reported hospital wide ID charts for E. Coli sensitivities over the same time period? E. Coli multidrug resistance can be by plasmid, transpons or mutations which have similar rates across institutions. This would be an important comparison group. The discussion section lists resistance rates of 53% in 2016 which was consistent with prior study.

The authors were unable to find hospital wide E. coli sensitivities for the exact study period. The only data available regarding previous years comes from the prior study done at the same study institution and from the antibiogram data in 2016.

Discussion:

Line 254-255. The general knowledge of high rates of E. Coli resistance to ampicillin and beta lactams is not new. The low resistance rates to gentamycin are consistent with the literature and don't provide clinically actionable information. Most patients fever and obstetric infection, either intraamniotic infection or endometritis, resolve before the culture results are back. The clinical question of a resolved infection and positive cultures after discharge creates a different clinical conundrum when liberal use of blood culture for fever only are used. Is there any information on resolved fevers and positive cultures that have changed clinical outcomes in your study? The claim of lower mortality rates with liberal blood cultures compared to historic controls from prior study can not be made

Thank you for this comment. We agree that the antibiotic resistance patterns are consistent with the prior literature. We also agree that most patients with a diagnosis of chorioamnionitis/endometritis have clinical improvement with time and antibiotic administration, without culture data to guide antibiotic therapy. However, a subset of patients have worsening clinical status and adverse outcomes, often without clear risk factors. Our goal with this study was to document contemporary resistance patterns in a population of intrapartum women to help guide the care and empiric antibiotic regimens at institutions in which cultures are not the routine.

We did not specifically investigate the impact of positive blood cultures among women with clinical improvement prior to culture data being available, and cannot comment on how this influenced the clinical outcome. This is an interesting clinical question for future investigation.

Lines 673 through 675 were changed to draw attention that we are not able to comment on the difference in mortality, however we do want to continue to draw attention to the difference in mortality between the previous cohort and our study cohort.

Lines 283. Was the maternal infant pair obtained only through the maternal record first? Was there a separate review of all neonatal bacteremia babies over the same time period looking at association of maternal condition ie fever blood cultures.

The infant data was obtained through maternal record review first. There was not a separate review of all neonates with bacteremia over the same time period.

Line 294-296 When were culture results available in relationship to ICU admission? Did it dictate or change therapy?

For all 7 women, ICU admission occurred prior to the results of the blood cultures being known, as noted in line 519-520. Blood cultures were used to dictate subsequent antibiotic treatment choice in the ICU.

Reviewer #2 Comments

Abstract

The conclusion of the abstract should reflect the observation that chorioamnionitis and UTI are commonly associated with E. coli bacteremia.

As we have altered the focus of the paper based on the suggestions of the editor, we no longer focus on E. coli bacteremia specifically and therefore cannot address this comment.

Methods

Please clarify how patient identification was conducted. The methods describe that subjects were identified through the hospital's microbiology database, to identify febrile patients with positive blood cultures in the peripartum period. How was the fever ascertained? Were patients identified based on blood culture results first, and then charts reviewed to determine if they presented with fever at the time of the blood sampling? Were subjects included if bacteremic but no fever documented concurrent with the sample collection?

We have clarified our identification of patients in lines 228-230. Briefly, the microbiology department provided a list of obstetric patients (identified due to the geographical provenance of the blood culture) with positive blood cultures during the time frame of interest. Each chart was reviewed to confirm the presence of a fever, as well as other inclusion criteria. There were no subjects with bacteremia and no fever.

How was it determined that the listed bacteria were contaminants vs. pathogens?

Among the non-excluded infections is S. hominis - is this a typical pathogen in the peripartum period?

S. hominis was excluded as a contaminant and incorrectly included in the figure text; we have since removed this from the figure. We determined the list of contaminants based on discussion with the hospital microbiology lab and have included this information in lines 233-235.

Is the universal screening and treatment policy for OB patients with a fever described at your institution common practice at most obstetric centers? When was this practice instituted? Are there guidelines on this management and if not, how was this policy developed? How well is it followed?

This universal screening and treatment policy for obstetric patients with a fever is not the common practice at most obstetrics centers. Our universal policy was instituted in 2009 and it was developed by an expert group of Maternal Fetal Medicine Physicians at the hospital with an interest in infectious disease in pregnancy, after a few adverse maternal outcomes. The guidelines are formally published as management recommendations at the institution and are periodically reviewed and reaffirmed.

In the current study, we cannot ascertain what fraction of febrile women had cultures drawn, as the manner of identifying patients was via culture data. In review of our data between for another project, we have noted that the clinical care of women with a fever follows the protocol among 88.5% of women between 2015 and 2017.

Please define the following described outcomes: chorioamnionitis, endometritis, neonatal bacteremia (relevant, as opposed to contaminants), and how choriamnionitis and endometritis were ascertained.

We have included definitions for chorioamnionitis, endometritis, and neonatal bacteremia, as well as how these diagnoses were ascertained in lines 241-244 and lines 279-282.

Results

Did you look at incidence or prevalence of maternal bacteremia?

We describe the prevalence of maternal bacteremia in lines 307-308.

Would it be possible for you to show the changes (if any) in the incidence of the various organisms over time ? Was E. coli always the predominant causative agent?

The incidence of organisms over time was examined in the preliminary analysis for this paper, however the individual numbers of organisms per year of the study were overall quite small (<5 per year). It was therefore difficult to draw any meaningful conclusions regarding incidence rates over time.

Is it possible for you to calculate the risk of neonatal bacteremia when mother has bacteremia or febrile bacteremia?

All mothers in this cohort had febrile bacteremia, therefore it is not possible calculate the risk ratio of neonatal bacteremia by maternal bacteremia versus febrile bacteremia.

Discussion

Much discussion is based on the comparison of the results of this study with a historical cohort - was the same management practice (screening and treatment) in place when the historical cohort was evaluated? If not, when was this practice established? How comparable are these two cohorts?

We have added clarification regarding the implementation of the universal screening and treatment policy regarding intrapartum fever in lines 536, 598-600 as well as hypotheses for differences in these populations. The policy was implemented in 2009.

In page 11, second paragraph, include the rates of resistance of E. coli to ampicillin in the previous cohort.

Lines 608-609 were edited to include the resistance rates of *E. coli* to ampicillin in the historical cohort, which was 50%.

In page 12 - line 307, selection bias is appropriately discussed, consider changing the word "represent" to "select" in the sentence "This may bias our results to select the most clinically significant infections..."

Lines 682-684 were edited to rephrase the entire sentence. It now reads, “Women who appear to be clinically ill may be more likely to be cultured, possibly over representing more virulent organisms and biasing our results towards a greater incidence of morbidity.”

A discussion re. OB vs non-OB sources of infection in the mother would be helpful, as it appears that non-OB sources should be evaluated in cases of maternal fever, as they represented at least 1/3 of the cases.

Non-obstetric causes of bacteremia account for 8.4% of all cases; therefore, we do not highlight this finding in our manuscript.

Conclusions

Make sure to include a statement regarding the most relevant findings in the conclusion, and that the conclusions match those in the abstract. The association with chorioamnionitis and UTI and E. coli, and the association of neonatal bacteremia in bacteremic mothers should be mentioned.

Given the overall focus of the manuscript was changed after consideration of the comments from the Editor, the association between chorioamnionitis and UTI and E. coli are no longer focused. *E. coli* was not compared as a separate entity after the analysis was completed, but rather gram negative vs. gram positive vs. anaerobic. The authors therefore cannot address this comment.

What recommendations do you have on the importance of collecting blood cultures in febrile obstetric patients based on the results of this study.

While collecting blood cultures is not routine practice at all institutions, we hope that our study can contribute to the sparse literature that exists regarding peripartum bacteremia. We hope that our information regarding contemporary resistance patterns in a population of intrapartum women can help guide the care and empiric antibiotic regimens at institutions in which cultures are not routine practice, especially in patients with

worsening clinical status and adverse outcomes. While routine blood cultures may not be necessary of all patients with an intrapartum fever, it should be a critical piece of the evaluation process for patients with worsening clinical status. This is highlighted in lines 676-678.

Tables

Table 1 - please include an asterisk or other form of indicating where the significant (p-value < 0.01) differences are found. It is difficult to follow if the differences observed are based on comparisons between the variables presented in the columns or the rows.

Individual pairwise comparisons were not done as the editors made comments requesting the focus of the paper as more descriptive. The authors are happy to do further pairwise comparisons if the editors so desire this. The differences in clinical source of bacteremia and timing of blood culture collection were not emphasized as the overall focus of the paper was on bacterial isolates in peripartum bacteremia and resistance patterns.

Table 3. For patients 4 and 6, why did these infants return for repeat cultures? where they ill (eg. fever?) or was it because of the maternal blood culture results?

The infants returned to the hospital because they were discharged prior to maternal blood culture results being available. Once maternal cultures were positive, the parents were requested to represent with the infant for additional evaluation of the infant, including blood cultures.

Reviewer #3 Comments

1. Abstract: The conclusion (Line 100) is confusing to the readers. It appears that the authors are stating that Ecoli is uncommonly associated with maternal bacteremia. The conclusion written in discussion (Line 313) is much easier for interpretation.

The abstract conclusion was reworded to match the discussion of the manuscript text conclusion as seen in lines 76-77.

2. Discussion: The authors compare the findings to a different cohort from the same institution. The authors should compare their results with data/findings from other studies performed in other institutions.

There is limited data available regarding peripartum bacteremia from other institutions. The largest available dataset for peripartum bacteremia is from the same study institution. Additional resources (10-14) were included for comparison and discussion of the literature. Citation 10 (Blanco et al.) noted a rate of bacteremia of 0.9% of patients sampled with *E. coli* and *Group B Streptococcus* as the most frequently isolated organisms in 1975-1979. Citation 11 (Ledger et al.) comments on bacteremia in both obstetric and gynecologic patients in 1975 in California with a incidence rate of 7/1000 admissions with E. coli, Enterococci, and Group B streptococcus as the most frequently identified isolates. Citation 12 (O'Higgins et al.) comments on a 4 year review of cases of bacteremia among obstetric patients where *E. coli* was the found to be most frequently isolated cause of antepartum and postpartum bacteremia while Group B

streptococcus was the most common of intrapartum bacteremia. Citation 13 (Kankuri et al.) describes maternal sepsis in the peripartum period with a bacteremia rate of 5.1%. The most common bacterial isolates in the study were *Group B streptococcus, E. coli*, and *Staphylococcus aureus*.

3. Table 3: Table 3 may not be necessary. The information mentioned in the manuscript is sufficient.

We chose to keep Table 3 in the manuscript in order to provide ample description regarding the neonates with bacteremia. We would be happy to remove if the Editors would like for us to remove this table, and focus the information in the manuscript.

Reviewer #4 Comments

Abstract: Overall, the abstract is a concise summary of the research. Would consider incorporating a few of the suggestions from the manuscript text in to the abstract.

The abstract has been edited to reflect the changes within the manuscript as the overall focus of the paper was changed to focus on a more descriptive aim.

Page 4, Line 100. The last sentence in the abstract conclusion seems to suggest that the commonly used antibiotics may not be ideal; however, this was not the focus of the analysis. Would suggest rewording to focus more on the selected maternal and neonatal outcomes as analyzed in the results section.

The abstract was modified after restructuring of the results and discussion with greater focus on antibiotic resistance rather than neonatal and maternal outcomes after review of the comments and suggestions from the editors.

Introduction: The introduction suggests that the focus of the paper will be antibiotic resistance patterns as a primary analysis. This is somewhat different from the focus of the Materials and Methods and the organization of the Tables, which seem to focus instead on maternal ICU admission and neonatal bacteremia as the main outcomes assessed. Would consider the which message is intended, and focus the introduction accordingly.

The results and discussion were reorganized to highlight the focus on antibiotic resistance patterns and isolated organisms rather than maternal ICU admission. Line 157-159 highlights the objective of the study with a focus on descriptive analysis of isolated organisms and antibiotic resistance.

Materials and Methods: This is an appropriate summary of the approach to data collection.

Page 6, line 165. Is this universal screening and treatment policy new? If so, it might be helpful to include a statement summarizing this change in policy to understand why the current cohort is chosen. The authors point out in the discussion that the institutional policy for drawing blood cultures changed in 2009 (i.e., from selective to universal blood cultures for peripartum fever), and they draw attention to differences in policy that may contribute to differences in outcomes. It may be helpful to clarify this policy change in the methods.

The text was amended to include that the universal screening policy was developed in 2009 in the methods section in line 268.

Page 6, line 172. Did the authors gather data on estimated blood loss at delivery? This would likely be an important variable to consider when the outcome is maternal ICU admission.

We did not collect estimated blood loss at delivery as part of this study.

Results:

1. Overall, the reviewer recommends reorganization of the structure of this section to better help the reader follow the Tables and Figure. Currently, the reader has to search for the references to tables and figures, which are buried in the text, and then reread the text to find numbers that correlate with data presented in tables, which is confusing. Recommend starting each paragraph with a sentence introducing the corresponding table, etc.

The results section has been restructured to emphasize the focus on descriptive analysis of isolated organisms and antibiotic resistance. Therefore the tables and figures were restructured and are organized as such in the results section.

Page 9, line 226. Recommend the numbers in the text exactly match those listed in tables (with same number of decimal places, for example).

Thank you for this comment. We have reviewed all manuscript text to ensure the numbers in the text match those listed in the tables exactly.

Page 9, line 241. There is no reference to a table for this paragraph (see above comment).

We have edited the results to ensure that each paragraph appropriately refers to the relevant results table.

Page 9, line 245. Are sensitivities to clindamycin and extended spectrum beta-lactamases tested for enterococcus species at your hospital? The text implies they are, but this is not reflected in Table 4, and seems unusual given the organism's intrinsic resistance profile.

Enterococcus is not tested for sensitivity to clindamycin and extended spectrum beta-lactamases as shown in table 4. The text in lines 611-613 was amended to say, "We did not identify any cases of ampicillin resistant *Enterococci*; *Bacteroides* was pansensitive; and, as expected, Group A and Group B *Streptococci* were ampicillin sensitive."

Discussion:

The first paragraph of the discussion focuses on resistance profiles for E.coli, rather than summarizing the results shown in Table 2 (i.e., the main outcome measures from the statistical analysis presented). This is not what the reader expects. If the focus of the paper is antimicrobial resistance profiles, perhaps the investigators should reorganize the presentation and analysis of data. Or, if the authors want to convey a message about maternal and neonatal morbidities associated with E.coli

bacteremia as suggested by the statistical analysis, this reviewer suggests reorganizing the discussion to bring the discussion of maternal ICU admission (lines 295-300) to the top of the discussion section.

The results and discussion sections have been reorganized to focus on isolated organisms and resistance profiles.

Tables:

Table 4 appears to be the main focus of the introduction and discussion, although the reader focuses on Table 2 as the main statistical analysis presented. See comments above.

Table 4 and Table 2 have been changed to emphasize the focus on resistance patterns rather than maternal or neonatal outcome.

Would also recommend including total "n" under each row in Table 4.

We have added the denominator for each bacterium in Table 2. Table 4 was switched to the table 2 position.

Statistical Editor Comments:

Table 1: Should cite median (IQR) with upper and lower bounds, not as ± IQR. Need to re-calculate the chi-square p-values, For example for mode of delivery 15 vs 6 compared to 54 vs 45 has p = .16, not < .01. Similarly, for PTB 3 vs 18 compared to 16 vs 83 has p = 0.83, not < .01.

The median and IQR was edited to remove the plus or minus and rather put the IQR in parenthesis. The Chi-square p values were all recalculated as the comparison groups were changed.

Table 2: The counts of adverse events is small, hence the CIs for aORs are wide. There is no justification for use of adjustment model using 4 covariates as adjustors. Should instead use Fisher's test and then cite as limitations that one cannot based on these samples, adjust for all the baseline differences. Should include the p-value for neonatal death comparison, although it will be NS and there is little power to generalize based on so few cases.

This comment now applies to table 4, where the data is presented and tested with Fisher’s exact test. The multivariate analysis has been removed and lines 745-748 were included to highlight our small sample size and inability to draw meaningful conclusions about outcome association and bacteremia as a possible limitation of our study.

lines 208-214: This is a misapplication of the meaning of chi-square methods. The chi-square tests the overall allocation of proportions or counts, not specific row entries (in the case of race/ethnicity). The comparison of % Hispanic is NS, the comparison of % black is significant, but the result is by pairwise testing, not the overall chi-square. The % vaginal delivery is NS different, not p < .01. Similarly, the comparison of % with antepartum blood cultures needs a pairwise test, not the overall chi-square result. There is no statistical difference between 66.7% vs 57.1% nor 2% vs 0% for the sample sizes here. Individual pairwise testing should be done, not extrapolating the overall chi-square test result.

Given the focus of the study on a descriptive study, the Chi square calculations were redone. The results text in lines 314 through 318 was reworded to just focus on the overall Chi square result rather than individual comparisons. Therefore, pairwise comparisons were not done as this was no longer a focus of the overall objective of the paper. The authors are happy to complete pairwise comparisons if the editors feel it is necessary for this manuscript.

lines 230-231: Did all neonates whose mothers had bacteremia also have blood cultures, or are the 8 (+) the numerator of a smaller subset of those tested? If not all neonates of mothers with bacteremia were tested, then the estimates of Table 2 re: neonatal bacteremia for E. Coli vs other is biased and should be cited as severe limitation.

At our institution, all neonates of febrile women have blood cultures obtained, thus the sample of neonates with blood cultures drawn is not biased.

After altering Table 2, should re-do results and discussion without multivariable analysis.

The multivariable analysis was removed from the paper.

EDITOR COMMENTS:

The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read.

The précis was edited to 25 words in the present tense and focuses on the objective of the paper.

Could you provide the N for number of women delivered in this time period, the n for # of women who got blood cultures? Also, when you say "3,797 blood cultures" does that mean separate cultures or women? At my hospital, when someone has blood cultures ordered they typically get 2 samples from different sites. If that is similar at your hospital, are those counted separately?

We now cite the total number of women who delivered at the study institution between 2009 and 2016 in line 305 and in the abstract (line 66). The 3,797 women with blood cultures drawn referred to women and not individual cultures, so the language was edited to clarify this.

Please provide the n's here. You had 21 E.Coli positive cultures. Of these, how many were antenatal? (for eg, x/21) and the percentage. The percentages here for each bacterium should add up to 100 if you trying to make the comparison of timing by different bug.

The individual n was included for each data point provided in the results and abstract.

Not sure what you mean by "are emerging" (line 154).

We have reworded our text to be more clear in line 151 with emerging replaced by common for clarity.

Please more clearly state your primary and secondary outcomes

We have edited our primary and secondary outcomes in lines 276-279. Briefly, our primary outcome was the distribution of microbiologic etiologies resulting in peripartum bacteremia, and associated antibiotic resistance patterns among commonly isolated organisms. Our secondary outcomes included maternal intensive care unit (ICU) admission, neonatal bacteremia, and neonatal death.

Please name the academic center and the IRB

The academic center was named the methods section in line 224 and the information regarding the IRB was added in line 225-226.

Why was it exempt? (Referring to IRB approval)

Further detail on why it was exempt from requiring informed consent was added in line 226-227. Briefly, the IRB deemed the study exempt because it was a retrospective chart review that was not a feasible study if informed consent was needed for every patient in the chart review.

For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

The raw sample size or n was included throughout the text for clarification.

Does your lab look for Ureaplasma?

Our lab does not routinely look for ureaplasma. This is commented on in the discussion section in lines 603-605.

Any endometritis? (referring to causes of maternal ICU admission)

There were no cases of endometritis leading to ICU admission. Further details regarding this were not included in the text as this was a secondary outcome and focus was placed on the overall isolated organisms and resistance patterns.

Please edit: this sentence is unclear regarding who has the bacteremia. I assume its 6.5% of the neonates but it could be interpreted to be the mothers.

This sentence was edited to clarify that 6.5% of neonates had bacteremia.

Provide numerators and denominators (within result and abstract text)

We now include numerators and denominators throughout the text for clarification.

2. The Statistical Editor's comments are quite important and need to be addressed. I agree with his recommendation to report this as a descriptive study rather than any comparisons between bacteria. Your numbers are just too small for comparisons. Can you also comment on whether your laboratory assesses for

ureaplasmas? Likewise, your universal policy of work up for fevers does not seem to be universal--can you comment further?

The manuscript was edited to remove all multivariable comparisons and to demonstrate comparisons between gram negative, gram positive, and anaerobic bacteria. Ureaplasma is not assessed in our laboratory.

The universal policy for screening is not necessarily adhered to by every provider at the study institution as there are multiple private practices also providing care through the same maternity center in addition to the academic practice. The overall adherence to the protocol was not assessed in this study as study participants were identified by blood culture results rather than fever alone. From another study at the same institution that is currently in progress assessing bacteremia between 2015 and 2017, the rate of adherence to the blood culture protocol was 88.5%.

3. 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.

We opt in and are happy to have our response letter and subsequent email correspondence published.

4. Author Agreement Forms: Please note the following issues with your forms. Updated or corrected forms should be submitted with the revision. Malavika Prabhu, MD - Please provide an ink signature on the third page of the Author Agreement Form.

A new author agreement for Malavika Prabhu was uploaded.

5. 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.

All definitions were reviewed and chorioamnionitis was defined per the revitalize definitions.

6. 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.

The introduction and discussion were edited to meet the guideline word counts after manuscript revision. The manuscript does not exceed 22 pages.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

The title is 63 characters with spaces and does not include any declarative statements of questions.

8. 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).**

On the title page, there was no financial support, which was written on line 23. A line for no acknowledgements was also added to line 24.

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

The précis was edited to be phrased in 1 sentence in present tense vocabulary.

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.

The abstract was completely edited to reflect the changes of the manuscript and a word count was added at the bottom of the abstract.

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.

All noted abbreviations were amended throughout the abstract and 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.

All of the virgule symbols (/) were removed from the text.

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.

All tables were edited and are in compliance with the Journal’s table checklist.

14. Figure 1 may be resubmitted as-is.

No changes were made to Figure 1.

From: [redacted]
To: Randi Zung
Subject: Re: Your Revised Manuscript 18-1479R1
Date: Friday, November 2, 2018 12:01:03 AM
Attachments: PeripartumBacteremia_TrackedChanges_FinalRevised.docx
Green Journal - Transparency Declaration.pdf

Dear Editors,

Please find my revised and attached manuscript and declaration form. My comments to each request are outlined below by comment. Please let me know if there is any further revision or information required at this time.

Thank you!
Gianna Wilkie

Requested Edits

1. General (from Dr. Chescheir): I've made edits to the manuscript using track changes. I realize that is asking a lot and I think your paper is much stronger for having done so. The comments I've added below are mostly minor wordsmithing issues related to making stronger, more active statements with parsimonious word choice. Please review them to make sure they are correct.

The authors agree with the wording changes as noted in the text throughout the manuscript. Any changes are noted in the track changes.

2. Please ask the following author to respond the authorship confirmation email we sent. We sent an email from em@greenjournal.org. The message contains a link that needs to be clicked on. We emailed the author at the email addresses listed below– is this the correct addresses?

An alternate email for Dr. Riley is [redacted] We apologize for the inconvenience of resending the authorship confirmation.

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.

A transparency declaration statement was attached to this email and was signed.

4. Precis: Would you consider the alternative below? As you've written it "with high rates of resistance to ampicillin" is a descriptive clause that goes with "bacteremia", not E.Coli if you diagram the sentence (Ms. Goodan, my middle school English teacher would be so proud, even as you are probably groaning).

"Although infrequent, when women with peripartum fever are bacterimic, it is most commonly with Escherichia coli which has a high rate of ampicillin-resistance."

The authors agree that the alternative précis is improved and acceptable.

5. Abstract-Methods: The study type was added to the abstract methods.

The study type was correctly added to the abstract methods.

6. Abstract-Results: In the abstract, please provide absolute numbers as well as whichever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like: "xx (outcome in exposed)/yy (outcome in unexposed) (zz%) (Effect size= ; 95% CI=)." An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

Absolute numbers were added throughout the results section in the abstract and full manuscript. We did not calculate effect size as per our understanding of the recommendations of the statistical editor, the manuscript should have a descriptive focus without a model given our small sample size numbers or limited power. We are unable to present relative effect size as all patients on our cohort are exposed (100% bacteremia). Therefore, the outcome of neonatal bacteremia cannot be calculated in exposed vs. unexposed population. The authors are happy to work with the editors if there is further specific calculation that is desired.

7. Results: For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

The raw numbers (numerators/denominator) were included throughout the results section with percentage calculations. There were no effect sizes or confidence intervals as described in comment 6 above.

8. Line 169: Please don't just say they were different. How were they different?

Lines 190-202 were edited and added to further the details in difference between the groups in a descriptive way. See comments 6 above.

9. Line 190 (and elsewhere): The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances. Should this be "and" or "or"?

The virgule symbol was removed from line 228 and line 282 and edited appropriately.

10. Line 198: Again, please don't just state there was a difference. Describe the difference.

Line 236 was edited to say, "of which 7/8 (87.5%) were attributable to gram negative bacteria and 1/8 (12.5%) were attributable to gram-positive bacteremia (p=0.004)".

11. Line 235: Is this appropriate for presumed chorio but not for postpartum causes of fever, such as endometritis?

Line 278 was edited to state "the treatment of presumed chorioamnionitis and postpartum endometritis" for further clarity.

On Tue, Oct 30, 2018 at 3:48 PM Randi Zung <RZung@greenjournal.org> wrote:

> Dear Dr. Wilkie:
>
> Thank you very much for making the requested changes in your manuscript. 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 (from Dr. Chescheir): I've made edits to the manuscript using track changes. I realize that is asking a lot and I think your paper is much stronger for having done so. The comments I've added below are mostly minor wordsmithing issues related to making stronger, more active statements with parsimonious word choice. Please review them to make sure they are correct.
>
> 2. Please ask the following author to respond the authorship confirmation email we sent. We sent an email from em@greenjournal.org. The message contains a link that needs to be clicked on. We emailed the author at the email addresses listed below– is this the correct addresses?
>
> Laura E. Riley
>
> [redacted]
>
> [redacted]
>
> 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.
>
> Please provide a signed version of this statement.

4. Precis: Would you consider the alternative below? As you've written it "with high rates of resistance to ampicillin" is a descriptive clause that goes with "bacteremia", not E.Coli if you diagram the sentence (Ms. Goodan, my middle school English teacher would be so proud, even as you are probably groaning).

"Although infrequent, when women with peripartum fever are bacterimic, it is most commonly with Escherichia coli which has a high rate of ampicillin-resistance."

5. Abstract-Methods: The study type was added to the abstract methods.

6. Abstract-Results: In the abstract, please provide absolute numbers as well as whichever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like: "xx (outcome in exposed)/yy (outcome in unexposed) (zz%) (Effect size= ; 95% CI=)." An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

7. Results: For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

8. Line 169: Please don't just say they were different. How were they different?

9. Line 190 (and elsewhere): The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances. Should this be "and" or "or"?

10. Line 198: Again, please don't just state there was a difference. Describe the difference.

11. Line 235: Is this appropriate for presumed chorio but not for postpartum causes of fever, such as endometritis?

To facilitate the review process, we would appreciate receiving a response within 48 hours.

Best,

Randi Zung for Nancy C. Chescheir, MD

– –

Randi Zung (Ms.)

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From: [redacted]
To: Stephanie Casway
Subject: Re: O&G Figure Revision: 18-1479
Date: Tuesday, October 30, 2018 4:45:48 PM

Hi Stephanie,

I have reviewed the figure and legend, and it looks good to me!

Thank you!
Gianna Wilkie

On Tue, Oct 30, 2018 at 2:10 PM Stephanie Casway <SCasway@greenjournal.org> wrote:

> Good Afternoon Dr. Wilkie,
>
> Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please review the figure and legend CAREFULLY for any mistakes.
>
> PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article's publication.
>
> To avoid a delay, I would be grateful to receive a reply no later than Thursday, 11/1. Thank you for your help.
>
> Best wishes,
>
> Stephanie Casway, MA
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