

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

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

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

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

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

Date:	Aug 05, 2019
То:	"Shravya Govindappagari"
From:	"The Green Journal" em@greenjournal.org
Subject:	Your Submission ONG-19-1210

RE: Manuscript Number ONG-19-1210

Maternal and neonatal morbidity after four and six hours of protracted active labor in nulliparous term pregnancies

Dear Dr. Govindappagari:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 26, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Govindappagari and colleagues present findings from a retrospective cohort study designed to evaluate whether protracted active phase of labor over 6 hours is associated with an increased incidence of adverse maternal and neonatal outcomes. The authors draw their study cohort from a single institution between August 2016-September 2019. Women were included in the study cohort if they were at least 37 weeks gestation and entered active phase of labor (6 cm or more). Women were excluded if they were completely dilated on admission, had cesarean delivery before 6 cm, cesarean delivery without labor, fetal demise, and fetal anomalies. The cohort was divided into 3 groups related to second stage progression: Group 1 - >=1 cm change within 4 hours; Group 2 - <= 1 cm change over 4-6 hours but not more than 6 hours; and Group 3 - <= 1 cm over 6 hours. The primary study outcome was a composite adverse maternal outcome defined as maternal fever, postpartum hemorrhage, blood transfusion, and post-partum length of stay >=5 days. From their analysis, composite maternal outcome was higher among groups 2 and 3. A point-by-point critique of the paper follows:

1) The Abstract of the paper the authors use Groups 1-3 in the presentation of results and conclusions. While this is reasonable for the results section, it would be more effective to state what the actual groups are in the conclusion statement when making the final summary of the paper.

2) Critically important to any paper evaluating labor progression is a clear definition of how labor was managed. There is no information provided in the paper regarding approach to oxytocin use, definition of labor adequacy (and was it used in determining labor management), approach to labor induction, criteria used for proceeding to cesarean delivery, and consistency of labor management across all women in the cohort. Without these additional details, the data presented provides limited insights. The revised paper should clearly define the labor management, oxytocin protocols used, induction approach, and criteria used for cesarean delivery.

3) Several components of the primary outcome are not defined in the paper. Maternal temperature is not defined. Postpartum hemorrhage is not defined. Both of these components of the primary outcome should be clearly defined in the revised paper. In addition, the authors suggest that maternal temperature may have been defined as chorioamnionitis or endomyometritis (diagnostic criteria used for either is presented in the paper) but this is not clear. The diagnostic criteria for both chorioamnionitis and endomyometritis should be clearly specified in the revised paper. In addition is should be made clear to the reviewer whether only chorioamnionitis or endomyometritis was the criteria for maternal temperature or would isolated maternal temperature have sufficed.

4) How did the authors determine length of stay >= 5 days as part of the primary outcome? Is this primarily a surrogate for cesarean delivery? It would be helpful to include the indication for prolonged length of stay in the revised paper (in either results section text or Table 2).

5) Use of misoprostol has been associated with maternal temperature. No information is provided regarding induction methods in the paper. Given the association between misoprostol use and maternal temperature (one of the components of the primary study outcome), the specific induction approaches should be described and reported in the revised paper.

6) Blood transfusion was included as one of the composite primary outcome components. Was this transfusion post delivery only? What were the indications for blood transfusion?

7) Lines 163-166 of the Methods section of the paper define the 3 study groups. The authors state that Group 2 is comparable to Rouse et al and Groups 3 is comparable to ACOG / SMFM criteria. No references are provided on these lines. In addition, the criteria defined by Rouse et al are similar to the ACOG /SMFM criteria with the exception of the definition of active labor. Are the Rouse et al and ACOG /SMFM criteria for cervical change actually different?

8) In the Results section of the paper (lines 196-239) comparative data is presented. No p values are provided when stating differences between groups. The paper should be revised to provide the p values when statement that a difference exist is presented.

9) Tables 1, 2, 4, 5 - p values are provided but it is not clear what the p value comparison related to. Differences between all groups (and if so the individual post-test p values should be provided for the individual group comparisons) or group 1 vs other? This should be corrected/clarified in the revised manuscript.

10) Table 3 and Supplemental Table - No p value is provided for the last comparison in each row (G3 vs G1) is not provided. This should be corrected in the revised manuscript.

Reviewer #2: Thank you for the opportunity to review this important manuscript that expands our understanding of outcomes associated with varying definitions of protracted phase and, perhaps more importantly, notes when varying definitions of protracted phase are not associated with poor outcomes.

This manuscript boasts many strengths. One particular strength is the analytic approach that builds on prior research suggesting maternal fever (and presumably chorioamnionitis) as a potentially important factor related both to longer active labor and worse outcomes. Exploring the possibility that worse maternal/child outcomes may be more importantly linked to infection than to labor duration may open clinically important research directions. It is also a strength that specific neonatal morbidities are shared in Table 5. NICU admission alone is a variable with limited efficacy in marking true neonatal morbidity and composite variables can suggest serious risk when there is only risk for less concerning outcomes-I applaud the authors for providing more detail related to both maternal and neonatal well-being in tables 4 and 5.

Major and minor issues are critiqued separately:

Major:

1) Lines 133-134. A more thoughtful and detailed assessment of prior research regarding the hypothesis that duration of time in labor is associated with maternal/child risk will strengthen the introduction. Perhaps one sentence that lists and cites the maternal morbidity associated with protracted active phase and one sentence with the same for neonatal morbidity?

Further on this point: rather than citing recent commentary and review by Cohen et al. that reifies the hypothesis that labors longer than the 95th% are associated with risk, I recommend examining and then citing the literature that Cohen relies on to make this claim. Specifically, it may benefit the reader to understand that the Friedman publication (Labor: Clinical Evaluation and Management, 1978) that argued for this hypothesis created a composite poor neonatal outcome that included: a) low apgars; b) fetal demise including fetal weight \geq 500 grams; c) neonatal demise (defined in the text); and d) perinatal demise (not defined in the text). This composite raises questions about fetal demise inclusion criteria and, additionally, makes it difficult to develop more refined understanding of factors influencing these poor outcomes and if labor durations >95th% is a meaningful factor or not.

It may be better to indicate that while some research does link longer labor with worse maternal/child outcomes (e.g., fistula in lower-resource nations), other research about the duration of labor and poor outcomes is less conclusive.

2) Lines 196 - 239. The results section will benefit from significant reorganization and the inclusion of headers to guide the reader. I found the tables to be quite straightforward but the text in this section less so. I think that the strategic placement of tables in this section will help quite a bit. But also organizing the text to flow with the tables and then making sure that the text clearly communicates the results will be especially helpful for the clinician audience.

Minor:

1) Verb tense wanders periodically. The manuscript will be stronger if past tense is maintained throughout.

2) Line 155. I did not see where indication for mode of delivery was reported. This should be included or line 155 should be corrected.

3) Lines 241 - 343. Overall, the discussion section is very well written and interesting. The call for maternal-child dyadic data collection and research is welcome. I recommend further discussion of the link between maternal fever and longer protracted active phase labors and comment on this finding. As well, a sentence or two on recommendations for future research related to this association would be valuable.

Reviewer #3: This is an excellent paper. It is well-written and adds significantly to existing literature. Study design is sound. The vaginal delivery rate of 91% is commendable. I do have several comments that I would recommend be addressed to strengthen the paper:

1. In the Abstract and Methods sections, I would elaborate on what are considered to be adverse maternal and neonatal outcomes.

- 2. How often were patients examined in the active phase?
- 3. Was umbilical cord arterial pH assessed? Was GBS status assessed?
- 4. Was information on birth weight obtained?
- 5. How was PPH defined? Was uterotonic use assessed?
- 6. What was the duration from latent to active phase of labor?

STATISTICAL EDITOR COMMENTS:

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

lines 84-85, 93-97: Need to state whether the primary outcome was statistically supported or not, then other comparisons. Also, should state the N for each Group and their rates of composite maternal morbidity. As space permits, could briefly include relevant secondary outcomes.

Table 1: Since the primary outcome was comparison of Group 3 vs the others, should include direct comparisons of Group 3 vs the others, rather than comparisons across all groups, which this stats test does. Need to enumerate all missing data.

Table 2: Same comment re: comparison of Group 3 vs the others, rather than a global stats test. Again, need to enumerate all missing data.

Table 3: Since the primary hypothesis was whether Group 3 differed from the others in the composite maternal morbidity, that should be stated first. From this analysis, that would appear to be negative. Also, the Neonatal composites were therefore secondary outcomes, so should be in a separate Table. Again, NS difference between Group 3 and the others. A separate issue with the Neonatal composite analysis are the counts of adverse outcomes in Groups 2 and 3 vs the number of variables used as adjustors. This is likely an over fitted model.

Table 4: This stats analysis evaluates whether the distribution of proportions among the 3 groups by row variable differed from random, it did not test whether Group 3 specifically differed from the other groups. Also, the counts of adverse outcomes are in some cases low and there is little power to generalize those NS findings.

Table 5: Again, this stats analysis evaluates whether the distribution of proportions among the 3 groups by row variable differed from random, it did not test whether Group 3 specifically differed from the other groups. Also, the counts of adverse outcomes are in some cases low and there is little power to generalize those NS findings.

Suppl Tables: Many of the counts are too few (esp in Group 3 or in CD strata) to allow for multiple adjustment. Insufficient power and over fitting are problems.

EDITOR COMMENTS:

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

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

- We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. For instance, for the objective, just say "To evaluate if....."; We avoid "determine" as you can only study something under the circumstances you are using and "determine" implies finality.

- We prefer to avoid providing p values only unless that is the only appropriate test of significance. Where possible in the abstract AND the text, please provide an effect size (such as an OR or RR) and 95% CI's as well as the absolute numbers.

- include the name of the IRB here.

- Please note the Statistical Editor's comments: As you have stated the primary outcome here, its unclear if this a descriptive study of the outcomes in each group or a comparison study of Group 3 versus the other 2 groups. Please be completely clear about that and then organize your paper appropriately. Your primary outcome should be reported first, followed by secondary outcomes and then secondary analyses. Your results and discussion should both be organized in this manner.

- define PPH, chorioamnionitis, endometritis and the pediatric diagnoses that aren't absolutes (like 5 min Apgar < 3). By the way, Apgar is a woman's name, not an acronym, so should not be in all caps).

- Not sure what this means. Are private and self pay the same (thus the virgule between them?)

- 91%

- either "contrary to other studies" or "In contrast to other studies".

- We do no allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout.

- please comment on the association of chorioamnionitis with fetal brain injury. Am J Reprod Immunol. 2018 May;79(5):e12803. doi: 10.1111/aji.12803. Epub 2017 Dec 22. Chorioamnionitis, IL-17A, and fetal origins of neurologic disease.

- Thoughout your tables, please include definition of G1, G2, G3 in your footnotes. When I first looked at this I thought you were comparing outcomes by gravidity. I may be the only one who would "go there" but I suspect not.

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

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

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

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research,

and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission.

Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com.

In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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 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.

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 print appendixes) but exclude references.

7. 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).

8. 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.

9. 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.

10. 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.

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

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

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

12. 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.

13. 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.

14. Figure 1 should be uploaded as a figure file in Editorial Manager.

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

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

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

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and

* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 26, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD Editor-in-Chief

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.

August 26, 2019

Re: ONG-19-1210 - Manuscript Revision- "Maternal and neonatal morbidity after four and six hours of protracted active labor in nulliparous term pregnancies"

Attn: Dr. Nancy Chescheir, Editor, Obstetrics & Gynecology

Dear Dr. Chescheir,

Thank you for the opportunity to revise our manuscript ONG 19-1210, "Maternal and neonatal morbidity after four and six hours of protracted active labor in nulliparous term pregnancies".

We have carefully reviewed your email dated August 5th, 2019, and we enclosing our responses to your comments and the reviewers' comments of our manuscript. We have revised the manuscript according to these comments and we have provided our responses in a point-by-point manner. Revisions in the manuscript are updated using Track Changes feature in Microsoft Word. This revision als been approved by all the authors. We hope the revised version is now suitable for publication in Obstetrics & Gynecology and we look forward to sharing this work with your readers.

Finally, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained."

Sincerely,

Shravya Govindappagari



Authors' response to reviewers' comments

Reviewer #1: Govindappagari and colleagues present findings from a retrospective cohort study designed to evaluate whether protracted active phase of labor over 6 hours is associated with an increased incidence of adverse maternal and neonatal outcomes. The authors draw their study cohort from a single institution between August 2016-September 2019. Women were included in the study cohort if they were at least 37 weeks gestation and entered active phase of labor (6 cm or more). Women were excluded if they were completely dilated on admission, had cesarean delivery before 6 cm, cesarean delivery without labor, fetal demise, and fetal anomalies. The cohort was divided into 3 groups related to second stage progression: Group 1 - >=1 cm change within 4 hours; Group 2 - <= 1 cm change over 4-6 hours but not more than 6 hours; and Group 3 - <= 1 cm over 6 hours. The primary study outcome was a composite adverse maternal outcome defined as maternal fever, postpartum hemorrhage, blood transfusion, and post-partum length of stay >=5 days. From their analysis, composite maternal outcome was higher among groups 2 and 3. A point-bypoint critique of the paper follows:

Comment #1 The Abstract of the paper the authors use Groups 1-3 in the presentation of results and conclusions. While this is reasonable for the results section, it would be more effective to state what the actual groups are in the conclusion statement when making the final summary of the paper.

Response: We have made this change in the revised manuscript line 107-110. We described the actual groups in the conclusion of the abstract.

Comment #2 Critically important to any paper evaluating labor progression is a clear definition of how labor was managed. There is no information provided in the paper regarding approach to oxytocin use, definition of labor adequacy (and was it used in determining labor management), approach to labor induction, criteria used for proceeding to cesarean delivery, and consistency of labor management across all women in the cohort. Without these additional details, the data presented provides limited insights. The revised paper should clearly define the labor management, oxytocin protocols used, induction approach, and criteria used for cesarean delivery.

Response: Labor was induced and managed at the discretion of the provider. Low dose oxytocin protocol was used in our hospital. We use a standardized form to document that SMFM/ACOG criteria for cesarean delivery had been met, or the physician is required to write an explanation about why a cesarean delivery was performed (e.g. concerns about fetal heart rate tracing, or maternal request). This has been explained in the revised manuscript. Line 181-185.

Comment #3 Several components of the primary outcome are not defined in the paper. Maternal temperature is not defined. Postpartum hemorrhage is not defined. Both of these components of the primary outcome should be clearly defined in

the revised paper. In addition, the authors suggest that maternal temperature may have been defined as chorioamnionitis or endomyometritis (diagnostic criteria used for either is presented in the paper) but this is not clear. The diagnostic criteria for both chorioamnionitis and endomyometritis should be clearly specified in the revised paper. In addition is should be made clear to the reviewer whether only chorioamnionitis or endomyometritis was the criteria for maternal temperature or would isolated maternal temperature have sufficed.

Response: The definition of the each component of the primary outcome is explained in the revised manuscript. Postpartum hemorrhage was determined by ICD-10 codes with validation by use of uterotonic agents in addition to oxytocin. Similarly maternal fever was determined by ICD10 code and validated by maternal temperature \geq 100.4 with administration of antibiotics. Other diagnoses including neonatal diagnoses were abstracted from ICD 10 codes. Lines 216-225.

Comment #4 How did the authors determine length of stay ≥ 5 days as part of the primary outcome? Is this primarily a surrogate for cesarean delivery? It would be helpful to include the indication for prolonged length of stay in the revised paper (in either results section text or Table 2).

Response: Postpartum length of stay >=5 days is determined as a component of primary outcome. This is derived from the prior composite defined by NICHD paper "Timing of Elective Repeat Cesarean Delivery at Term and Maternal Perioperative Outcomes" byTita et al (Obstet Gynecol 2011) In our hospital patients are discharged home on POD#3 or 4 after cesarean delivery. Consistent with Tita et al, postpartum length of stay >=5 days is defined as extended stay. We agree indications for prolonged length of stay would have provided additional insight. Unfortunately, we don`t have the information for the indication of prolonged length of stay in our dataset.

Comment #5 Use of misoprostol has been associated with maternal temperature. No information is provided regarding induction methods in the paper. Given the association between misoprostol use and maternal temperature (one of the components of the primary study outcome), the specific induction approaches should be described and reported in the revised paper.

Response: We agree with the reviewers that misoprostol is associated with maternal fever. Unfortunately we do not have the data regarding all the induction methods used at the patient level. However we validated ICD10 codes for chorioamnionitis and endometritis by maternal temperature $\geq 100.4^{\circ}$ F and treatment with appropriate antibiotics. Line 218-225.

Comment #6 Blood transfusion was included as one of the composite primary outcome components. Was this transfusion post delivery only? What were the indications for blood transfusion?

Response: Yes transfusion was post delivery only. Hemorrhage was the indication for blood transfusion.

Comment#7 Lines 163-166 of the Methods section of the paper define the 3 study groups. The authors state that Group 2 is comparable to Rouse et al and Groups 3 is comparable to ACOG / SMFM criteria. No references are provided on these lines. In addition, the criteria defined by Rouse et al are similar to the ACOG /SMFM criteria with the exception of the definition of active labor. Are the Rouse et al and ACOG /SMFM criteria for cervical change actually different?

Response: We agree with the authors. To avoid confusion to the audience we deleted the specific references to Friedman and Rouse names and defined the groups by the time required for cervical change. Line 199-201.

Comment #8 In the Results section of the paper (lines 196-239) comparative data is presented. No p values are provided when stating differences between groups. The paper should be revised to provide the p values when statement that a difference exist is presented.

Response: Thanks for the suggestion. We agree with the reviewers and incorporated the percent values, Odds ratios with confidence intervals and/or p values in the results section of the revised manuscript. Line 254- 299.

Comment #9 Tables 1, 2, 4, 5 - p values are provided but it is not clear what the p value comparison related to. Differences between all groups (and if so the individual post-test p values should be provided for the individual group comparisons) or group 1 vs other? This should be corrected/clarified in the revised manuscript.

Response: Tables 1,2,4, and 5 present univariate analyses to look for overall differences in the distribution of patient and delivery characteristics by labor group (i.e. does race/ethnicity differ by length of time to make change in labor?). However as per the reviewer's suggestion p values are presented comparing Group 3 vs Group1 and Group 3 vs Group 2 in the revised manuscript

Comment #10 Table 3 and Supplemental Table - No p value is provided for the last comparison in each row (G3 vs G1) is not provided. This should be corrected in the revised manuscript.

Response: We presented global p-values to demonstrate the overall importance of increasing time to make change. We also provided 95% confidence limits which would show statistical significance at alpha = 0.05. However, we respect your suggestion that the individual inter-group p-values would be more important and have thus substituted the individual p-values for the global-p-values.

Reviewer #2: Thank you for the opportunity to review this important manuscript that expands our understanding of outcomes associated with varying definitions of protracted phase and, perhaps more importantly, notes when varying definitions of protracted phase are not associated with poor outcomes.

This manuscript boasts many strengths. One particular strength is the analytic approach that builds on prior research suggesting maternal fever (and presumably chorioamnionitis) as a potentially important factor related both to longer active labor and worse outcomes. Exploring the possibility that worse maternal/child outcomes may be more importantly linked to infection than to labor duration may open clinically important research directions. It is also a strength that specific neonatal morbidities are shared in Table 5. NICU admission alone is a variable with limited efficacy in marking true neonatal morbidity and composite variables can suggest serious risk when there is only risk for less concerning outcomes- I applaud the authors for providing more detail related to both maternal and neonatal well-being in tables 4 and 5.

Major and minor issues are critiqued separately:

Major:

Comment #1 Lines 133-134. A more thoughtful and detailed assessment of prior research regarding the hypothesis that duration of time in labor is associated with maternal/child risk will strengthen the introduction. Perhaps one sentence that lists and cites the maternal morbidity associated with protracted active phase and one sentence with the same for neonatal morbidity?

Further on this point: rather than citing recent commentary and review by Cohen et al. that reifies the hypothesis that labors longer than the 95th% are associated with risk, I recommend examining and then citing the literature that Cohen relies on to make this claim. Specifically, it may benefit the reader to understand that the Friedman publication (Labor: Clinical Evaluation and Management, 1978) that argued for this hypothesis created a composite poor neonatal outcome that included: a) low apgars; b) fetal demise including fetal weight \geq 500 grams; c) neonatal demise (defined in the text); and d) perinatal demise (not defined in the text). This composite raises questions about fetal demise inclusion criteria and, additionally, makes it difficult to develop more refined understanding of factors influencing these poor outcomes and if labor durations >95th% is a meaningful factor or not.

It may be better to indicate that while some research does link longer labor with worse maternal/child outcomes (e.g., fistula in lower-resource nations), other research about the duration of labor and poor outcomes is less conclusive.

Response: Thank you, per your suggestion, we added a few more references that have demonstrated adverse maternal and neonatal outcomes with prolonged labor. Line 147-148 and references 6-10.

Comment #2 Lines 196 - 239. The results section will benefit from significant reorganization and the inclusion of headers to guide the reader. I found the tables to be

quite straightforward but the text in this section less so. I think that the strategic placement of tables in this section will help quite a bit. But also organizing the text to flow with the tables and then making sure that the text clearly communicates the results will be especially helpful for the clinician audience.

Response: Per your suggestion, we reorganized the results and included headers to guide the reader. Lines 253-323.

Minor:

Comment#1 Verb tense wanders periodically. The manuscript will be stronger if past tense is maintained throughout.

Response: This has been addressed in the revised manuscript

Comment# 2 *Line* 155. *I did not see where indication for mode of delivery was reported. This should be included or line* 155 *should be corrected.*

Response: The indication for why a cesarean delivery was performed was abstracted, however not analyzed as a covariate in the data analysis. To avoid confusion for the audience the indication was deleted in the revised manuscript.

Comment#3 Lines 241 - 343. Overall, the discussion section is very well written and interesting. The call for maternal-child dyadic data collection and research is welcome. I recommend further discussion of the link between maternal fever and longer protracted active phase labors and comment on this finding. As well, a sentence or two on recommendations for future research related to this association would be valuable.

Response: Association between long labor and chorioamnionitis from prior studies is cited between lines 386-391. Also necessity for future studies looking at the effects of chorioamnionitis on neonates and long-term follow up is addressed.

Reviewer #3: This is an excellent paper. It is well-written and adds significantly to existing literature. Study design is sound. The vaginal delivery rate of 91% is commendable. I do have several comments that I would recommend be addressed to strengthen the paper:

Comment #1. In the Abstract and Methods sections, I would elaborate on what are considered to be adverse maternal and neonatal outcomes.

Response: Unfortunately given the space constraints, we were not able to list the individual components of the composite outcomes in the abstract. However we described all the components of the composite in the methods section of the manuscript.

Comment # 2. How often were patients examined in the active phase? Response: We do not have this data available. Labor was managed at the discretion of the provider and cervical exams were performed as clinically indicated by residents, midwives or attending physicians.

Comment # 3. Was umbilical cord arterial pH assessed? Was GBS status assessed?

Response: We do not have the data available for umbilical cord arterial pH. GBS status was not assessed.

Comment # 4. Was information on birth weight obtained?

Response: We have the data available for birth weight but not estimated fetal weight (EFW). However since our primary exposure was length of labor, EFW would be optimal. ACOG-SMFM labor management guidelines did not include birth weight in their algorithm. Patient's undergoing cesarean delivery for suspected macrosomia without undergoing labor were not included in the analysis

Comment # 5. How was PPH defined? Was uterotonic use assessed?

Response: Postpartum hemorrhage was determined by ICD-10 codes with validation by use of uterotonic agents other than oxytocin. Line 216-218

Comment # 6. What was the duration from latent to active phase of labor?

Response: Unfortunately, we do not have the data for the length of latent phase. To be included in our study, patients had to be in active phase defined as at least 6 cm dilation. Total length of labor, defined as duration between admission time and delivery time is described in the manuscript. Also duration of second stage of labor is incorporated in the analyses.

STATISTICAL EDITOR COMMENTS:

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

Comment #1 lines 84-85, 93-97: Need to state whether the primary outcome was statistically supported or not, then other comparisons. Also, should state the N for each Group and their rates of composite maternal morbidity. As space permits, could briefly include relevant secondary outcomes.

Response: The primary outcome is described in the revised manuscript in abstract section; lines 91-104. Also individual group percent values are also included. Because of the space constraints we were not able to describe secondary outcomes.

Comment #2 Table 1: Since the primary outcome was comparison of Group 3 vs the others, should include direct comparisons of Group 3 vs the others, rather than

comparisons across all groups, which this stats test does. Need to enumerate all missing data.

Response: Table 1 is modified as per the suggestion. p-values comparing Group 3 to Group 1 and Group 3 to Group 2 are provided in the revised manuscript. Missing data has been provided in the footnote.

Comment #2 Table 2: Same comment re: comparison of Group 3 vs the others, rather than a global stats test. Again, need to enumerate all missing data.

Table 2 is modified as per the reviewers suggestion. p-values comparing Group 3 to Group 1 and Group 3 to Group 2 are provided in the revised manuscript. No missing data.

Comment #3 Table 3: Since the primary hypothesis was whether Group 3 differed from the others in the composite maternal morbidity, that should be stated first. From this analysis, that would appear to be negative. Also, the Neonatal composites were therefore secondary outcomes, so should be in a separate Table. Again, NS difference between Group 3 and the others. A separate issue with the Neonatal composite analysis are the counts of adverse outcomes in Groups 2 and 3 vs the number of variables used as adjustors. This is likely an over fitted model.

Response: p-values comparing Group 3 vs Group 1 and Group 3 vs Group 2 are stated first. Neonatal composite is secondary outcome, however it is presented in the same table given the space constraints. We have 5 tables in the manuscript with 2 supplemental tables and splitting maternal and neonatal composite outcomes will add one more table, so we did not revise this table, but willing to do so at the editor's discretion.

We agree the counts in some cells are quite small thus we provided both the unadjusted and adjusted results and used exact logistic regression to at least partially address data sparsity. The unadjusted and adjusted point estimates did not differ by more than 0.1.

Comment #4 Table 4: This stats analysis evaluates whether the distribution of proportions among the 3 groups by row variable differed from random, it did not test whether Group 3 specifically differed from the other groups. Also, the counts of adverse outcomes are in some cases low and there is little power to generalize those NS findings.

Response: Table 4 is modified as per the suggestion. p-values comparing Group 3 to Group 1 and Group 3 to Group 2 are provided in the revised manuscript. We agree data are sparse in some cells but we wanted to at least describe, to the extent possible, whether the drivers of maternal composite morbidity differed by delivery route.

Comment #5 Table 5: Again, this stats analysis evaluates whether the distribution of proportions among the 3 groups by row variable differed from random, it did not test

whether Group 3 specifically differed from the other groups. Also, the counts of adverse outcomes are in some cases low and there is little power to generalize those NS findings.

Response: Table 5 is modified as per the suggestion. p-values comparing Group 3 to Group 1 and Group 3 to Group 2 are provided in the revised manuscript. We agree data are sparse in some cells but we wanted to at least describe individual neonatal outcomes to the extent possible.

Comment #6 Suppl Tables: Many of the counts are too few (esp in Group 3 or in CD strata) to allow for multiple adjustment. Insufficient power and over fitting are problems.

Response: We agree the data are sparse, particularly in Group 3 and in the cesarean stratum. Rather than focusing on the p-values, we hope that readers will get a sense of the direction and magnitude of the associations and will note that the point estimates and confidence intervals do not differ greatly between the unadjusted and adjusted analyses.

EDITOR COMMENTS:

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

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

- We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as

well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. For instance, for the objective, just say "To evaluate if....."; We avoid "determine" as you can only study something under the circumstances you are using and "determine" implies finality.

Response: This change has been made in the revised manuscript. Abstract section line 75 and introduction portion of the manuscript line 152

- We prefer to avoid providing p values only unless that is the only appropriate test of

significance. Where possible in the abstract AND the text, please provide an effect size (such as an OR or RR) and 95% CI's as well as the absolute numbers.

Response: We described effect size, OR and 95% CI as appropriate in the revised manuscript.

- include the name of the IRB here.

Response: Cedars-Sinai IRB is mentioned in the methods section of the manuscript. Line 171.

- Please note the Statistical Editor's comments: As you have stated the primary outcome here, its unclear if this a descriptive study of the outcomes in each group or a comparison study of Group 3 versus the other 2 groups. Please be completely clear about that and then organize your paper appropriately. Your primary outcome should be reported first, followed by secondary outcomes and then secondary analyses. Your results and discussion should both be organized in this manner.

Response: This study is a comparison of Group 3 versus Group 2 and Group 1. This has been made clear in the revised methods portion of the manuscript. Line 205-206. Results section is reorganized as per your recommendation. Primary outcome is described first followed by secondary outcomes and secondary analyses. Lines 253-321.

- define PPH, chorioamnionitis, endometritis and the pediatric diagnoses that aren't absolutes (like 5 min Apgar

< 3). By the way, Apgar is a woman's name, not an acronym, so should not be in all caps).

Response: We defined all the outcomes in the revised manuscript. Neonatal outcomes RDS, TTN, sepsis, HIE are defined by ICD 10 codes. Apgar has been corrected. Lines 212-225.

- Not sure what this means. Are private and self pay the same (thus the virgule between them?)

Response: Private pay and self pay meant to be the same. We deleted self pay and so private pay remains to avoid confusion.

- 91%

- Response: This change has been made. Line 330.

- either "contrary to other studies" or "In contrast to other studies".

- Response: This change has been made

- We do no allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout.

- Response: This has been addressed in the manuscript. Line 357-359.

- please comment on the association of chorioamnionitis with fetal brain injury.

Am J Reprod Immunol. 2018 May;79(5):e12803. doi: 10.1111/aji.12803. Epub 2017 Dec 22. Chorioamnionitis, IL-17A, and fetal origins of neurologic disease.

Response: Thanks for bringing this paper to our attention. Chorioamnionitis triggers fetal/neonatal immune response and release of IL7 which in turn can result in fetal brain injury. This is described in the discussion portion of the manuscript. The study above and few other studies are cited. Incidence of cerebral palsy in full term neonates is extremely low and it is multi-factorial. This has been addressed and and few references are cited. "Long-term neonatal neurological sequelae of chorioamnionitis in term babies remain unclear" line 386-391.

- Thoughout your tables, please include definition of G1, G2, G3 in your footnotes. When I first looked at this I

thought you were comparing outcomes by gravidity. I may be the only one who would "go there" but I

suspect not.

- Response: This change has been made. Groups 1, 2 and 3 are defined in the table headings and footnotes.

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

- Response: A OPT-IN: Yes, please publish my point-by-point response letter.

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

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

Response: confirmed disclosures are accurate as of this time

4. Responsible reporting of research studies, which includes a complete,

transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission.

Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com.

In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

Response: this is a retrospective cohort design, and the STROBE checklist has been provided

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 has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <u>https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize</u>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: we used standard definitions for our primary and secondary outcomes as specified by reVITALize

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 print appendixes) but exclude references.

Response: Abstract and introduction parts of the manuscript were edited to meet the journal requirements for word count and pages

7. Specific rules govern the use of acknowledgments in the journal. Please note

Commented [GKDMM1]: Need to confirm

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).

- Resposne: This has been addressed in the revised manuscript title page.

8. 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.

- Resposnse: Abstract is edited to and is within 300 words currently.

9. 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.

Response: Thank you, the manuscript has been edited to be consistent with these guidelines.

10. 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.

- Response: The virgule symbol(/) has not been used in the revised manuscript

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

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

- Resposne: Results are presented as recommended. Number needed to treat is not applicable for our analyses.

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

- Resposnse: This has been addressed in the manuscript.

12. 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.

- Resposnse: This has been addressed in the manuscript.

13. 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.

Response: We cite the following ACOG/SMFM consensus statement and it is current as of now: American College of O, Gynecologists, Society for Maternal-Fetal M. Obstetric care consensus no. 1: safe prevention of the primary cesarean delivery. Obstet Gynecol. 2014;123(3):693-711.

14. Figure 1 should be uploaded as a figure file in Editorial Manager.

- Resposnse: Figure has been uploaded as a separate file.

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

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

- Response. Thank you

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

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and

* A point-by-point response to each of the received comments in this letter.

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

- Response: Yes revision has been approved by all the co-authors.