OBSTETRICS & GYNECOLOGY

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: Jan 31, 2020
To: "Ashish Premkumar" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-43

RE: Manuscript Number ONG-20-43

Does perioperative use of cefazolin and indomethacin for physical examination-indicated cerclages improve gestational latency?

Dear Dr. Premkumar:

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 14 days from the date of this letter. If we have not heard from you by Feb 14, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Precis - perioperative Ancef/indomethacin during cerclage is associated with prolonged gestational latency

Abstract
Objective: To evaluate gestational latency - perioperative Ancef/indomethacin during physical exam indicated cerclage (PEIC)
Design: retrospective cohort of PEIC between 2009-2018, after 2014 the protocol was changed to include perioperative ancef and indomethacin
primary outcome: pregnancy latency - >/= 28 days after cerclage
secondary outcomes - median latency, gestational age, preterm birth, PPROM, chorio
Results - 142 PEIC, 69 (48.6%) with prophylaxis - baseline demographics are not different
perioperative prophylaxis - higher incidence pregnancy latency >/=28d, improved gestational latency, GA at delivery and decreased incidence of preterm birth <28wk, no difference in PPROM or chorio rates
Conclusion - perioperative Ancef/indomethacin - lead to prolongation of gestational latency without an increased risk of chorio

Intro - cervical dilation in the 2nd trimester was evaluated - limited analysis of perioperative management of PEIC
2014 - perioperative ancef/indomethacin were shown to increase latency beyond 28d but ACOG has not changed guidance
retrospective cohort done to compare outcomes

Methods - retrospective cohort - PEIC 2009-2018, starting in 2014 protocol changed to include ancef/indomethacin and cerclage procedure is standard
primary outcome - gestational latency > 28 d
secondary outcome - median latency, GA at delivery, PTB <28 wk, PPROM, chorio, birthweight, p value 0.05 considered significant

Results - 142 cerclage - 69 (48.6%) perioperative ancef/ indomethacin
this treatment increased latench >28 d from 76.7% to 94.2%
longer latency - 112 vs 91 d, higher median GA, 37 wk 32 wk, and decrease PTB 15.9% vs 41.1
there was no difference in chorio or PPROM

Discussion - retrospective cohort study of perioperative treatment - increased gestational latency >28 days, decreased

PTB, increased gestational latency
strengths - large sample size, homogeneous practice
weakness - not standardized until 2014
study supports clinical utility of treatment

Comments -
1. It is not entirely clear to me that there is new data presented, but this study does show convincingly that the change in practice to include perioperative antibiotics and indomethacin has convincing benefits by increasing latency and as a result, decreasing preterm birth, increasing gestation age and birthweight. These findings are presented as distinct which they are not as they are all direct consequences of each other regardless, it is well written with evidence of convincing clinical benefit with no harm.

Reviewer #2: This is a carefully done well-written retrospective cohort study supporting findings of a 2014 RCT. It is important since, as the article notes, the RCT did not change ACOG guidelines to recommend the use of antibiotics and indocin during PEIC placement. Thus, further data on this topic is of particular importance. The significant beneficial patient outcomes with this intervention were compelling. I find the document particularly well-written. The manuscript is precise in enumerating the limitations of the study's retrospective cohort design and the limitations particular to this study population. This includes noting a potential bias because a higher frequency of patients that received the study intervention after 2014 compared with the earlier years of the study. In my opinion, this results in an important manuscript that appropriately describes how it fits into the available data on the topic.

Reviewer #3: Well written manuscript. Adds to the literature and important for counseling patients.

- For your inclusion criteria, you have delivery or termination of pregnancy. In your Tables, you don't mention how many had terminations and indication of the termination. Were most of them secondary to chorioamnionitis or another reason.

- Also how long do you observe them preoperatively for contractions on tocometry.

- Table 1. demographics mention cervical dilation >2cm prior to cerclage placement but in the manuscript it describes greater than 1cm prior to placement.

STATISTICAL EDITOR COMMENTS:

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

Tables 1, 2: Although no stats differences were demonstrated in these baseline characteristics, the groups were not randomized, several characteristics could be important risk factors for PTB (e.g., hx of PTB, antecedent use of progesterone etc). Although the samples are moderately large for each cohort, the n(%)s of the row characteristics limit the power to have discerned differences

The Authors should supplement their aRR analysis with a matching algorithm to corroborate the association of use of cefazolin & indomethacin with longer latency. Also, should expand on hx of PTB to include the number in each cohort with 0, 1, > 1 prior PTBs, rather than as a binary variable of yes vs no.

Fig 1: Need to include the "N" for each cohort at the indicated time points along the x-axis. Either in fig legend or in figure itself, need to indicate the statistical significance of any difference in gestational latency.

EDITOR'S COMMENTS:

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.

Line 68: very picky, I realize, but you say yours is study of all pregnant women….who delivered at a quaternary care center. This was specifically Northwestern. As written, it would be inclusive of those that delivered at Northwestern, UNC, Duke, etc etc….how delivered at a single quaternary care center?

Line 69. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given . same issue on line 70, line 120, line 126

Line 76: THANK YOU for using reVITALize terminology and for using language of association rather than causal language!

Line 79: Please provide some data in the results section of the abstracts. (for instance on line 84, 86, 87)

PRESENTATION OF STATS INFORMATION
P Values vs Effect Size and Confidence Intervals
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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.
This is true for the abstract as well as the manuscript, tables and figures.

Please provide absolute values for variables, in addition to assessment of statistical significance.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.

Line 137: The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.

Line 141: clarity—3 total doses of cefazolin and indomethacin?

Line 154: How many of the characteristics on lines 154-157 were required to make the diagnosis of chorioamnionitis?

Line 179 Do not begin a sentence with a numeral. Either spell out or edit your sentence to avoid the need to start w/ a number.

Line 190: please limit days, weeks to one decimal point. (rather than 19.91 days, etc)

Line 194—not sure I know what you mean that those things were reflective of a higher median birthweight. The median birth weight didn't result in those things. Perhaps starting on line 193 you could say "Consistent with this, the median birthweight of infants born after maternal exposure to perioperative prophylaxis was higher (2930 gram vs 2350 grams ….)

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

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

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the

manuscript's title page.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. It appears that this will be presented at SMFM this year. Please add this meeting presentation to your title page.

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. 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 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).

9. 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.

10. 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.

11. 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.

12. 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%").

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. The American College of Obstetricians and Gynecologists' (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.

15. Figure 1 may be resubmitted with the revised manuscript.

16. 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.

17. 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 14 days from the date of this letter. If we have not heard from you by Feb 14, 2020, 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

_____

[redacted]

Editor
Obstetrics & Gynecolgy

2/12/20

Dear Editor,

Thank you for the opportunity for us to revise our manuscript, entitled "**Does perioperative use of cefazolin and indomethacin for physical examination-indicated cerclages improve gestational latency?**" as Original Research to Obstetrics & Gynecology. Authors include Ashish Premkumar, Nikita Sinha, Emily S. Miller, and Alan M. Peaceman. The authors report no conflict of interest. All authors have approved this version of the manuscript for submission. All authors OPT IN for the publication of our response letter.

Here are our responses to the reviewers and editorial staff. Of note, we have re-validated our cohort and the editorial board will note changes in the sample size of our study in each exposure group (e.g., 72 now exposed to perioperative prophylaxis, instead of 69, and 70 were not exposed to perioperative prophylaxis, instead of 73); the total sample size of the study remains unchanged. Second, in response to Reviewer #3's comments regarding terminations of pregnancy, we have excluded these women from a majority of our secondary outcome analyses. Due to these changes, there are differences in the reported secondary outcomes from what was initially provided in our first manuscript. All point-by-point responses refer to pages and line numbers found in the updated, non-tracked manuscript.

Reviewer 3

1. For your inclusion criteria, you have delivery or termination of pregnancy. In your Tables, you don't mention how many had terminations and indication of the termination. Were most of them secondary to chorioamnionitis or another reason.
    a. We have added in data on terminations of pregnancy and revised our findings regarding birthweight, gestational age at time of delivery, and preterm birth at less than 28 weeks' gestation (see Tables 2 and 4). We have also included an appendix that includes detailed information about terminations of pregnancy in the cohort. Finally, see pp. 9-10, lines 209-12 regarding statistical evaluation of terminations of pregnancy within the cohort.
2. Also how long do you observe them preoperatively for contractions on tocometry.

    a. Wording has been added to address this issue. See pg 6, line 133
3. Table 1. demographics mention cervical dilation >2cm prior to cerclage placement but in the manuscript it describes greater than 1cm prior to placement.
    a. Our cohort included all cerclages placed at ≥ 1 cm, but we included ≥ 2 cm as a covariate of interest given data suggesting that this population is at higher risk of adverse perinatal outcomes (see Fortner KB, Fitzpatrick CB, Grotegut CA, et al. Cervical dilation as a predictor of pregnancy outcome following emergency cerclage. J Matern Fetal Neonatal Med; 2012;25:1884-8).

Statistical Editor:

1. Tables 1, 2: Although no stats differences were demonstrated in these baseline characteristics, the groups were not randomized, several characteristics could be important risk factors for PTB (e.g., hx of PTB, antecedent use of progesterone etc). Although the samples are moderately large for each cohort, the n(%)s of the row characteristics limit the power to have discerned differences The Authors should supplement their aRR analysis with a matching algorithm to corroborate the association of use of cefazolin & indomethacin with longer latency.
    a. We have included a sensitivity analysis with propensity score matching. See Tables 3-4 for further details
2. Also, should expand on hx of PTB to include the number in each cohort with 0, 1, > 1 prior PTBs, rather than as a binary variable of yes vs no.
    a. We have stratified history of PTB as requested. Please see tables 1 and 3.
3. Fig 1: Need to include the "N" for each cohort at the indicated time points along the x-axis. Either in fig legend or in figure itself, need to indicate the statistical significance of any difference in gestational latency.
    a. We have added these to Figure 1

Editor:

1. Line 68: very picky, I realize, but you say yours is study of all pregnant women….who delivered at a quaternary care center. This was specifically Northwestern. As written, it would be inclusive of those that delivered at Northwestern, UNC, Duke, etc etc….how delivered at a single quaternary care center?
    a. We have added wording to specify location of the study. See pg. 3, lines 70-71
2. Line 69. Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given . same issue on line 70, line 120, line 126
    a. This has been corrected in the manuscript and in the abstract.
3. Line 79: Please provide some data in the results section of the abstracts. (for instance on line 84, 86, 87)
    a. We have added results in this section, though the word count for our abstract is now over 300 words.

4. Line 137: The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.
    a. We have removed all virgules throughout the manuscript
5. Line 141: clarity—3 total doses of cefazolin and indomethacin?
    a. We have clarified that a total of three doses of medication were given over 24 hours. See pg. 7, lines 145-52
6. Line 154: How many of the characteristics on lines 154-157 were required to make the diagnosis of chorioamnionitis?
    a. We have clarified our diagnosis of chorioamnionitis in the dataset. See pg. 7, lines 160-163
7. Line 179 Do not begin a sentence with a numeral. Either spell out or edit your sentence to avoid the need to start w/ a number.
    a. This has been changed.
8. Line 190: please limit days, weeks to one decimal point. (rather than 19.91 days, etc)
    a. We have limited our analysis to include only one decimal point. See Tables 2 and 4.
9. Line 194—not sure I know what you mean that those things were reflective of a higher median birthweight. The median birth weight didn't result in those things. Perhaps starting on line 193 you could say "Consistent with this, the median birthweight of infants born after maternal exposure to perioperative prophylaxis was higher (2930 gram vs 2350 grams ….)
    a. The wording has been changed. See pg. 10, lines 218-20

Thank you for the opportunity to resubmit our manuscript. If there are questions or concerns, do not hesitate to contact me.

Best,

Ashish Premkumar, MD
On behalf of all authors