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: Jun 18, 2020
To: "Emily H Adhikari" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1385

RE: Manuscript Number ONG-20-1385

A cluster randomized trial of the effects of transcervical Foley bulb on a standardized misoprostol induction protocol

Dear Dr. Adhikari:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Jul 18, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overall - this is a huge trial, and while it does not demonstrate superiority of one induction method over another, it gives good data on how inductions can be practiced and the outcomes seen in this particular hospital.

Abstract:

Line 43 - The sample size calculation does not belong in the abstract.
Instead, you could briefly describe your clusters.

Line 49 - would say "vaginal delivery" rather than "primary outcome" so we don't have to go back and remember what it is.

Line 51 - would include the absolute risks of chorio in addition to relative risks.

Line 82 - why do they hypothesize that adding foley would increase vaginal delivery rates? As they say, prior studies on combined and separate cervical ripening regimens support some increased time to delivery with combined methods, but no difference in vaginal delivery rates. In addition, their institution has a low cesarean delivery rate, so hard to understand why adding foley would change this.

Line 86 - This paragraph is confusing, and information about the education and clustering should be put below, when the randomization information is shared. The IRB/CONSORT guidelines can go at the very end of the Methods section.

Line 93 - this is confusing - during the trial, were women informed of both options (miso +/- foley)? Could they decline the proposed method?

Line 123 - This is very interesting. Did they get more cervical ripening after the rest period? I realize that these women were randomized, and thus should be included, but I think their induction is so different, that it is very difficult to include them. Since it was a cluster randomized trial, rather than randomizing individual women, I wonder if they can be excluded.

Line 162 - I still don't understand why a 5% increase in vaginal delivery rate was expected. I guess this doesn't invalidate the results, but it is not surprising to me that there was no difference.

Line 188 - women in spontaneous labor were not "eligible" for the trial.

Line 219 - the text should include the percentages, not the RR.

Line 225 - since time to delivery has been shown to be different with combined methods, and we know nulliparous women have longer inductions (and thus are more likely to benefit from a combined method), time to delivery should be reported separatedly for nulliparous women.

Line 223 - if you are going to talk about chorio, we need to know what the absolute risks are

Line 266 - OK, if this is why you looked at vaginal delivery rates, I'd put this earlier (in the introduction).

Line 252 - I think it is also worth mentioning that your study had a very high rate of vaginal birth, especially compared with the FOR MOMI trial that had a much higher CD rate. RCT data on induction methods and length of labor is very dependent on local practice and we know there is huge variation in CD Rates at different hospitals, which is why studies of induction methods at a single hospital may not truly reflect expected vaginal delivery rates at other hospitals.

In addition, I think rate of vaginal delivery is dependent on overall labor induction management, not just cervical ripening agent.

Line 272 - . I looked at the table for the chorio rates - 18% vs. 14%. Those rates seem high. How do they compare with the literature? Do you think they are generalizable?

Line 278 - I think that you can at least state the reasons you may be overcalling chorio without inadvertently "overstating" it. If you are going to use increased chorio as in important finding that should inform other hospitals' choice of labor induction method, it needs to be clear that these rates are higher than what they may see at their own institutions and thus may not be generalizable.

Line 294 - I understand the desire for standardized labor induction protocols, but here I think you show that it doesn't so much matter which one you choose. If you don't get much benefit with addition of foley, and you can get a high vaginal delivery rate without it, then it makes sense to skip it - I think you can say that.

Reviewer #2: This is a cluster-randomized study of 2227 women, comparing the rate of vaginal delivery among women undergoing labor induction using oral misoprostol and transcervical foley bulb placement and misoprostol alone. The authors found that the rate of vaginal delivery, which was the primary outcome, was similar between the groups and that risk of chorioamnionitis was 30% higher in the misoprostol plus foley arm.

Methods

1. What are the criteria/contraindication for oral misoprostol?

2. Have the authors excluded women with previous cesarean delivery from the study? Please emphasize this issue.

3. Can the authors give more details about how they decided to give another dose of misoprostol? Who are the "qualifying patients"? (page 6 line 109)

4. What was the definition for "failed induction"? (page 6 line 129) as well, what is the definition for "labor dystocia"? (table 3)

5. The bulb inflated with 30 ml of saline may be expelled shortly after placement and may not be so effective when placed in women with 2 cm cervical dilation.

Results

6. Can the authors provide data about the gestational age at delivery for both of the groups?

7. Was there a difference in the time to achieve the active phase of labor between groups? What was the duration of the first or second stage of labor?

8. The authors state that "women in the oral misoprostol plus foley study arm were less likely to require oxytocin" (page 11 line 222). Can the authors provide more information as to how they determined who needed oxytocin?

9. 756 of the foleys expelled less than 12 hours from placement. Can the authors describe the bishop score of those women? I'm wondering if most of them had dilated cervix at induction start.

10. Can the authors provide a multiple logistic regression analysis to confirm that induction with misoprostol and foley is associated with a higher incidence of chorioamnionitis?

Discussion

11. Can the authors describe what is the "biologic plausibility" and provide a reference? (page 14 line 275)

12. A more thorough review of the weaknesses of the study would be helpful.

Reviewer #3:

This is a very well written large trial, well designed to evaluate whether induction of labor in term gravidas with cervix ≤2cm and intact membranes using oral misoprostol preceded by transcervical Foley bulb placement results in a significantly increased vaginal delivery rate compared with using oral misoprostol alone.

Objective is well aligned throughout with excellent definitions of primary and secondary outcomes

Single-center- Parkland- cluster-randomized trial (30 subjects in each cluster) and 34 clusters in each group. The two groups Oral Misoprostol (only-n=1110) 100 mcg 4 hours apart for two doses with the vs the same dosing of Oral Misprostol with a foley catheter (30cc ballon) (n=1117).

Introduction:line 74,75 You state there is safety and efficacy data for oral Misoprostol/ Please discuss "Oral or Vaginal Misoprostol for Labor Induction and Cesarean Delivery Risk Compared with vaginal misoprostol,Oral misoprostol may be associated with increased risk of cesarean delivery and longer time to vaginal delivery. (Obstet Gynecol 2019;134:10-6)

Methods: Was the foley bulb used with rupture of membranes? please state in Methods

Amniotomy was performed when feasible, with intrauterine pressure catheter and fetal scalp monitors placed/ What was the percent of IUPC in each group?

Consider the following points to address in the Discussion

Effacement is traditionally used to describe a favorable or unfavorable cervix. Can you discuss why effacement was not considered as a criteria

A 30% difference in chorioamnionitis , a secondary outcome is crazy high, Please address the following if you have the data and if you don't have the data it should be part of the discussion surrounding your findings and your findings should be tempered by lack of data for traditional risk factors. My read of the supplemental data is that this was largely centered in the nulliparous group receiving a foley bulb and Miso and that the Foley bulb and Miso had a less favorable cervix.?? Please address the traditional risk factors that are associated with Chorioamnionitis 1. Length of time of ROM between groups especially since the foley-bulb + Miso had a longer IOL, was there more IUPC use in this group? GBS in both groups

This finding of a 30% chorioamnionitis needs to be addressed with traditional risk factors and a sub analysis of this group to better understand their characteristic and how they are different. Was the foley bulb an innocent bystander?

STATISTICAL EDITOR COMMENTS:

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

lines 51-52: Should include the corresponding rates of chorioamnionitis, in order to put the aRR in context.

Table 1: Since the groups were randomized, there is no need to show stats tests comparing the baseline characteristics. Any difference should be due to random chance. If some characteristics were known a priori to be important determinants, then the randomization should incorporate an appropriate block design.

Table 3, lines 44-46,49-51, 157-171 : Since the sample size was based on detection of a 5% increase in vaginal delivery, should state the actual change in % (0.3%) in vaginal deliveries (with CIs), then cite the adjusted figure. The columns of p-values are not necessary, since CIs are included with the RRs and aRRs. Although many of the maternal and neonatal outcomes have NS differences, most rates are very low and there is little power to generalize the NS findings, especially for the adverse neonatal outcomes.

Supplemental Table 2: No need for p-values, since have included CIs.

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 relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

35. Does <=2cm refer to dilation or length?

40. Not sure what you mean by "randomized by week"? As I read further, I see that you randomized the intervention based on a per week, not per patient basis. Is that your "cluster"? Perhaps you could describe this a bit more clearly in the abstract? Something like the following starting on line 39.

"We randomized cervical ripening method by week of admission to labor and delivery, with each week group described as a cluster. Inclusion criteria included term gestation, cervix < 2cm dilated, intact membranes and an indication for induction. The study arms were 100 µg oral 30 minutes after transcervical Foley placement misoprostol or 100 µg oral misoprostol. "

44." Increase in vaginal delivery rate."

45. In your methods, please describe the interim analysis. Were there stopping rules? When was it done?

47. 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. Change similar word choice throughout.

47. 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.
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.
For instance, please give the absolute rates of chorio on line 51.

This is true for the abstract as well as the manuscript, tables and figures.

Please state if you used "intention to treat" analysis.

56. Please temper the statement about chorio abit. The aOR is not large and the lower bound approaches 1. Perhaps 'did result in a modest increased rate of chorioamnionitis…". In fact, from Table 3, the RR is 30% but its from an 14% to 18% Do you really think that is clinically relevant? Seems honestly like not a big deal.

79. I recognize that I'm being very picky here, but please bear with me. You use "cervical ripening and labor induction" here. Do you actually mean both? Do you use miso for labor induction (for instance, instead of oxytocin) or do you ripen the cervix with miso, then with evidence of cervical ripening or membrane rupture, switch to oxytocin for the actual induction portion of labor? If the miso is used only for cervical ripening, then you should refer to it that way throughout your paper. On line 119-120, you indicate that in fact the miso or miso+foley were for cervical ripening, followed by induction with oxytocin. As such, yours is a study of cervical ripening for women undergoing induction, not a study of the overall induction.

83. In the abstract, you state that you are studying women < 2cm. Here you say 2cm or less. Which is it?

95. This implies that prior to the study, women could have undergone cervical ripening with miso alone or miso+ Foley. Is that true? If you had not previously included the option of Foley + Miso, were women actually counseled about this as an option before you started this study so that this was not a novel intervention at Parkland?

152. Apgar is a woman's name, not an acronym. Please correct the capitalization.

188. What is your total delivery volume at Parkland? Back of the envelope calculation—generous induction rates for indications at term is about 30% , your delivery volume would be about 53,000 during that time frame to have almost 16,000 "eligible" women. What number does the 15,835 actually represent? As I read through the next few lines, the vast majority of these "eligible" women were not eligible.

190. The Green Journal uses the reVITALize definitions, adopted by ACOG. Please use these definitions. For instance, the correct terminology for PROM is prelabor rupture of the membranes.

194. Were the clusters block randomized? A little unusual to get exactly the same number without blocking.

197. Why was Foley not attempted in 6%? In discussion, please explain the 15% failure to place in those attempted rate. That seems quite high.

198. If I understand this correctly, could this be rewritten: Misoprostol was administered in 1,026 (92%) of the misoprostol-alone group and 859 (77%) of the misoprostol plus Foley group.

197-199: In your discussion, the relatively high rate of non compliance with the protocol (as I read it, you had 1117 women randomized to Miso + Foley of whom only 859 (77%) got the full intervention. This is a significant limitation—your Miso alone arm had a 92% compliance. This difference will need to be discussed.

215-216. Please provide the statistical data to support saying these are other than numerically different.

222. Would you consider "were marginally less likely…."?

223: Please refer back to earlier comments about giving absolute numbers, crude OR's and then aOR's. Was the only adjustment done for cluster?

225. Perhaps clearer as "Time (reported as mean hours +/- SE) to delivery at first induction trial was lower among women in the oral misoprostol plus Foley arm [give unadjusted data]. This difference did not remain significant after adjusting for clustering [give adjusted data].."

236-239. Could you note data for the subgroups for chorio and time to delivery since these were different in the entire cohort?

246. This is one place where the absolute numbers are important. Clinically relevant? Could difference in cervical exam at onset be related to this, rather than use of Foley?

247. Are you trying to say here that your standardized protocol without Foley results in a 78% success rate so why add something else? Is it worth highlighting that the Miso + Foley arm had a modestly shortened Time to Delivery and lower use of oxytocin than the other arm so that from an L&D perspective, this approach may use fewer resources without other differences?

253. In supplemental data, please provide the search terms and data bases used for this literature review.

Table 3: please embolden the statistically significant findings for ease of reading.

276. "Classic definition" is interesting. From the latest version of Williams Obstetrics text, I note the following : "Traditionally, a temperature ≥38°C (100.4°F) accompanying ruptured membranes has implied infection. At Parkland Hospital, we still adhere to this criterion." From the ACOG Committee Opinion #72 "For the purposes of this Committee Opinion, the diagnosis of suspected intraamniotic infection is made when the maternal temperature is greater than or equal to 39.0°C or when the maternal temperature is 38.0–38.9°C and one additional clinical risk factor is present.

For the purposes of this Committee Opinion, isolated maternal fever is defined as any maternal temperature between 38.0°C and 38.9°C with no additional risk factors present, and with or without persistent temperature elevation". As such, your definition in your paper meets neither of the definitions for chorio and fits most closely with the definition of an isolated maternal fever. You don't require ROM in your study, which appears to be a requirement based on the Williams' text, citing specifically what is used at Parkland. Please comment.

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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

5. Please submit a completed CONSORT checklist with your revision.

6. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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.

8. 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.

9. 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).

10. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

11. 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 limit for Original Research articles is 300 words. Please provide a word count.

12. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

13. 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.

14. 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.

15. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

16. 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%").

17. 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.

18. 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

19. Figure 1: Please upload as a figure file to Editorial Manager.

20. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

21. 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.

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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 30 days from the date of this letter. If we have not heard from you by Jul 18, 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

_____

UT Southwestern
Medical Center

Department of Obstetrics and Gynecology

July 16, 2020
Nancy C. Chescheir
Obstetrics and Gynecology

Dear Editor:

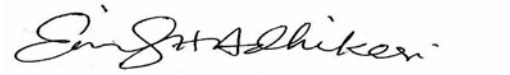
Please find enclosed the revised manuscript ONG-S-20-01676 entitled, "A cluster randomized trial of Foley bulb added to an oral misoprostol induction protocol". Thank you for the opportunity to revise this manuscript for your review. We provide a point-by-point response to reviewer comments in the pages that follow.

This report is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted, and any discrepancies from the study as planned have been explained.

This manuscript has not been published elsewhere. All authors have sufficiently participated in the design of this study and in authorship of the manuscript, and the authors below approved the final submitted manuscript. The senior author, Dr. Kenneth Leveno, passed away this Spring 2020, although he was intimately involved with design and implementation of the study as well as writing the original manuscript. Please advise if the journal does not allow his name to be listed as an author.

The authors report no conflicts of interest. The Institutional Review Board for the University of Texas Southwestern Medical Center approved this study. The authors report no conflicts of interest.

Thank you for considering this manuscript for publication.



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University of Texas Southwestern Medical Center
[redacted]

RE: Manuscript Number ONG-20-1385

A cluster randomized trial of the effects of transcervical Foley bulb on a standardized misoprostol induction protocol

REVIEWER COMMENTS:

Reviewer #1:

Overall - this is a huge trial, and while it does not demonstrate superiority of one induction method over another, it gives good data on how inductions can be practiced and the outcomes seen in this particular hospital.

Abstract:

1. Line 43 - The sample size calculation does not belong in the abstract.
Instead, you could briefly describe your clusters.
According to the Editorial Office for Obstetrics and Gynecology, the sample size justification is a necessary part of the abstract and follows the example provided.

2. Line 49 - would say "vaginal delivery" rather than "primary outcome" so we don't have to go back and remember what it is.
We have modified this line to say "vaginal delivery at the first induction attempt"

3. Line 51 - would include the absolute risks of chorio in addition to relative risks.
We have added the absolute risks to the abstract text.

4. Line 82 - why do they hypothesize that adding foley would increase vaginal delivery rates? As they say, prior studies on combined and separate cervical ripening regimens support some increased time to delivery with combined methods, but no difference in vaginal delivery rates. In addition, their institution has a low cesarean delivery rate, so hard to understand why adding foley would change this.
The intent of cervical ripening and induction is to achieve vaginal delivery, but few prior studies have actually attempted to detect a difference in vaginal delivery rates. Because studies have shown promise in reducing time to delivery and because the technique is commonly used, there is a need for rigorous, systematic study and we begin with clinical equipoise.

5. Line 86 - This paragraph is confusing, and information about the education and clustering should be put below, when the randomization information is shared. The IRB/CONSORT guidelines can go at the very end of the Methods section.
The statement about education was moved to the third paragraph under Methods section. We believe the importance of emphasizing IRB approval and adherence to CONSORT guidelines in the first paragraph of the Methods is in keeping with other published trials in this journal (see Ref 7 and 17).

6. Line 93 - this is confusing - during the trial, were women informed of both options (miso +/- foley)? Could they decline the proposed method?

All women were informed of the methods of induction in use at our hospital. When a recommendation for induction of labor is made by medical staff, women have the autonomy to accept or refuse the recommendation. We do not have information on the number of women who did not accept the medical recommendation for induction, but because we do not perform elective induction of labor, this number is likely to be very small.

7. Line 123 - This is very interesting. Did they get more cervical ripening after the rest period? I realize that these women were randomized, and thus should be included, but I think their induction is so different, that it is very difficult to include them. Since it was a cluster randomized trial, rather than randomizing individual women, I wonder if they can be excluded.

Women who were allowed a period of rest were given additional cervical ripening and induction agents according to established protocols. Misoprostol plus Foley was limited to the first induction attempt, but a woman could be eligible for oral misoprostol or oxytocin according to our established protocols on the second induction attempt. Because this was an intent-to-treat analysis, we included all women in the trial according to the induction method assigned at randomization. The majority of women (97% in each study arm) delivered at this initial induction (Table 2), and 3% of each arm had more than one attempt at induction. This did not affect the outcome of the trial.

8. Line 162 - I still don't understand why a 5% increase in vaginal delivery rate was expected. I guess this doesn't invalidate the results, but it is not surprising to me that there was no difference.

A 5% increase in vaginal delivery rate was felt to be clinically relevant, feasible, and detectable at our high-volume maternity hospital.

9. Line 188 - women in spontaneous labor were not "eligible" for the trial.

The word "eligible" was moved to the end of this sentence to better reflect eligibility criteria.

10. Line 219 - the text should include the percentages, not the RR.

We have provided both absolute risks, as well as crude and adjusted RR as requested by the Editors.

11. Line 225 - since time to delivery has been shown to be different with combined methods, and we know nulliparous women have longer inductions (and thus are more likely to benefit from a combined method), time to delivery should be reported separatedly for nulliparous women.

Presented below are data on time to delivery stratified by nulliparity:
The interaction test was not significant for the interaction of induction method and time to delivery when stratified by parity or initial cervical dilation, and so the overall effect size is presented.

Time to delivery (first induction), h	*Misoprostol plus Foley*	*Misoprostol*	*Difference in means (95% CI)*
Parity			-0.89 (-1.63– -0.14)
Nulliparous	21.5 ± 8.7	22.0 ± 9.1	
Multiparous	12.7 ± 7.2	14.1 ± 7.3	
Cervical dilation			-0.16 (-92, 0.60)
Closed	22.6 ± 8.3	23.5 ± 9.4	
1 cm	17.5 ± 8.8	17.6 ± 8.6	
2 cm	13.0 ± 7.4	13.0 ± 6.7	

These data are added to the Appendix.

12. Line 223 - if you are going to talk about chorio, we need to know what the absolute risks are
We have added absolute risks to this sentence.

13. Line 266 - OK, if this is why you looked at vaginal delivery rates, I'd put this earlier (in the introduction).
This text was moved to the Introduction, at the beginning of the third paragraph (line 88).

14. Line 252 - I think it is also worth mentioning that your study had a very high rate of vaginal birth, especially compared with the FOR MOMI trial that had a much higher CD rate. RCT data on induction methods and length of labor is very dependent on local practice and we know there is huge variation in CD Rates at different hospitals, which is why studies of induction methods at a single hospital may not truly reflect expected vaginal delivery rates at other hospitals.
In addition, I think rate of vaginal delivery is dependent on overall labor induction management, not just cervical ripening agent.
We agree, and believe this underscores the fact that our findings from a single institution with a) high delivery volume and b) standardized labor management are particularly relevant. While the practices in other hospitals may vary, clinicians can still take from this study an understanding that the Foley bulb does not improve vaginal delivery rates above those accomplished with a standardized oral misoprostol regimen.

15. Line 272 - . I looked at the table for the chorio rates - 18% vs. 14%. Those rates seem high. How do they compare with the literature? Do you think they are generalizable?
We have added the following text to the discussion (3rd paragraph):

Ten Eikelder, et al. reported rates of maternal intrapartum infection, defined as temperature of ≥37.8C during labor, in 13.1% of women induced with oral misoprostol compared with 12.8% of women induced with transcervical Foley catheter (RR 1.02, 95% CI 0.81-1.30).[11] Chung, et al. reported rates of chorioamnionitis (similarly defined as temperature of at least 38.0C at any time during the course of labor) were 6% with vaginal misoprostol alone, 9% with Foley catheter alone, and 21% with combined vaginal misoprostol and Foley catheter (p=0.07).[26] Carbone, et al. report no significant difference in rates of chorioamnionitis (not defined in their study) with Foley plus vaginal misoprostol (9%) compared with vaginal misoprostol alone (12%).7 In a 2015 meta-analysis, Chen, et al. describes a relative risk of chorioamnionitis (defined as temperature of at least 38.0C during labor) of 2.07 (95% CI 1.04-4.13) associated with combined use of Foley plus oral or vaginal misoprostol, compared with misoprostol alone.[10] We used a definition of chorioamnionitis that was easily defined, measurable, and has been used for quality assurance purposes at our institution for decades. Importantly, the definition was the same for both study arms, making the relative risk a clinically meaningful outcome. The complexity of newer definitions and risks of under-treatment of intrapartum infection in our high-volume, high-risk obstetric population cannot be overstated.[27] Our findings may not be generalizable to other institutions that use a different definition of chorioamnionitis.

16. Line 278 - I think that you can at least state the reasons you may be overcalling chorio without inadvertently "overstating" it. If you are going to use increased chorio as in important finding that

should inform other hospitals' choice of labor induction method, it needs to be clear that these rates are higher than what they may see at their own institutions and thus may not be generalizable.

We have modified the text in the third paragraph of the discussion to better reflect this comment, see previous response.

17. Line 294 - I understand the desire for standardized labor induction protocols, but here I think you show that it doesn't so much matter which one you choose. If you don't get much benefit with addition of foley, and you can get a high vaginal delivery rate without it, then it makes sense to skip it - I think you can say that.

We have added a line to the last paragraph: "Using a standardized labor induction protocol achieved a high rate (77%) of vaginal delivery without the added use of Foley catheter."

Reviewer #2:

This is a cluster-randomized study of 2227 women, comparing the rate of vaginal delivery among women undergoing labor induction using oral misoprostol and transcervical foley bulb placement and misoprostol alone. The authors found that the rate of vaginal delivery, which was the primary outcome, was similar between the groups and that risk of chorioamnionitis was 30% higher in the misoprostol plus foley arm.

Methods

1. What are the criteria/contraindication for oral misoprostol?

Our misoprostol protocol states:
Misoprostol may be used as a method of labor stimulation in patients > 36 weeks gestation, no prior uterine scar, with clear fluid if membranes are ruptured, and with no IUGR. Misoprostol may be used to induce labor for any complication with membranes intact other than IUGR. Misoprostol should not be given to women experiencing 4 or more painful contractions per 10 min.

2. Have the authors excluded women with previous cesarean delivery from the study? Please emphasize this issue.

We have added the following line to the Inclusion/Exclusion criteria: "Contraindications to misoprostol included prior uterine scar and meconium-stained amniotic fluid at initial assessment."

3. Can the authors give more details about how they decided to give another dose of misoprostol? Who are the "qualifying patients"? (page 6 line 109)

A second dose can be administered four hours after the first in women without evidence of labor and with reassuring fetal status. This line was added to the methods.

4. What was the definition for "failed induction"? (page 6 line 129) as well, what is the definition for "labor dystocia"? (table 3)

As described in this paragraph, the term "failed induction" was specific to the first induction trial of this study. This term refers to the label ascribed patients for whom the decision is made to stop the induction and allow a period of rest overnight in the hospital when no evidence of labor is documented after 12 to 24 hours of induction with reassuring fetal status and no evidence of severe hypertension. This occurred with 3% of patients in each group (Table 2).

The term labor dystocia in Table 3 may include clinical indications such as labor arrest or cephalopelvic disproportion as documented in the medical record by the clinical teams.

5. The bulb inflated with 30 ml of saline may be expelled shortly after placement and may not be so effective when placed in women with 2 cm cervical dilation.

We acknowledge this is possible, although the Median duration of Foley bulb (reported as median hours [Q1,Q3]) in the misoprostol plus Foley arm was 5.3 hours [4.6,8.3]. We did not overfill the balloon because the FDA recommendation for the device is to fill with 30cc.

Results

6. Can the authors provide data about the gestational age at delivery for both of the groups?

Median gestational age at delivery [Q1,Q3] was 39 weeks [38,40] for both groups. This was added to Table 1.

7. Was there a difference in the time to achieve the active phase of labor between groups? What was the duration of the first or second stage of labor?

We do not have data on time to active phase of labor, but we can report there was no difference in duration of first or second stage of labor. We have added the following data to Table 2: Obstetric Characteristics.

Outcome	Foley+	Miso	P-value
n	1117	1110	
Delivered on first induction	1088	1075	
Length of first stage of labor, hours	14.8 [9.8, 21.7]	15.2 [10.0, 21.8]	0.40
Length of second stage of labor, hours	0.3 [0.2, 0.7]	0.3 [0.2, 0.7]	0.44

Data reported as median [1st quartile, 3rd quartile]

8. The authors state that "women in the oral misoprostol plus foley study arm were less likely to require oxytocin" (page 11 line 222). Can the authors provide more information as to how they determined who needed oxytocin?

To achieve progressive cervical dilation and fetal descent, our practice is titration of intravenous oxytocin for labor induction to a contraction pattern of 3 to 5 contractions in 10 minutes, or at least 200 Montevideo Units if intrauterine pressure catheter is in place. Our standard practice is to administer oxytocin beginning 4 hours after the last dose of misoprostol in women with an indication for labor induction who have not established this contraction pattern.

We have added the following text to the methods:

Four hours after the last dose of oral misoprostol, a standardized intravenous oxytocin protocol was initiated in women who did not demonstrate a contraction pattern of 3 to 5 contractions in 10 minutes. Amniotomy was performed when feasible, with intrauterine pressure catheter and fetal scalp monitors placed, and oxytocin titrated to a goal of 200 Montevideo units in 10 minutes according to protocol.

9. 756 of the foleys expelled less than 12 hours from placement. Can the authors describe the bishop score of those women? I'm wondering if most of them had dilated cervix at induction start.

We routinely record initial cervical dilation at induction start, which is shown in Table 2 for each of the groups. We do not routinely record a complete Bishop score.

10. Can the authors provide a multiple logistic regression analysis to confirm that induction with misoprostol and foley is associated with a higher incidence of chorioamnionitis?

As this is a randomized trial, and demographic factors appear to be evenly distributed, this suggests that the randomization process "worked". According to CONSORT guidance, the decision to adjust should not be determined by whether baseline differences are statistically significant. We do not plan to perform post hoc adjustments in the primary or secondary outcomes per se. However, we did present a stratified analysis of the primary and select secondary outcomes according to parity (a priori) and initial cervical dilation (post hoc) which do not demonstrate increased chorioamnionitis associated with oral misoprostol plus Foley in specific subgroups.

Discussion

11. Can the authors describe what is the "biologic plausibility" and provide a reference? (page 14 line 275)

The concept of biologic plausibility we refer to in this sentence has to do with the idea that with a transcervical foreign body (Foley bulb) placed in direct contact with the amniotic membranes and leading directly from the vagina into the cervix, bacteria have direct access to the membranes. We are not aware of a specific study comparing bacteria or inflammatory cell quantities in the amniotic membranes of women with and without Foley bulb. We have removed this portion of the sentence to avoid confusion.

12. A more thorough review of the weaknesses of the study would be helpful.

We have addressed additional comments in the discussion with regard to limitations of the study:

Limitations of this study include the finding that more women allocated to the oral misoprostol plus Foley arm began induction with a cervical dilation of 2cm. Because time "zero" of induction was considered the time of initial induction agent (either Foley or oral misoprostol), providers who attempted transcervical Foley placement may have been more likely to determine that the cervix was dilated, rather than closed, if placement was successful. Despite this potential bias, there was no difference in vaginal delivery when data were stratified by initial cervical dilation. Additionally, the Foley placement success rate was 85%; when considering the success rate among women who had Foley placement attempted, the success rate was 945/1053 (90%). In the majority of cases, failure to successfully place transcervical Foley occurred because the cervix was not dilated. Although 90% success may be suboptimal for a standardized induction protocol, we consider this "real world" success rate reasonable for attempted mechanical cervical ripening in women with an unfavorable cervix.

Reviewer #3:

This is a very well written large trial, well designed to evaluate whether induction of labor in term gravidas with cervix ≤2cm and intact membranes using oral misoprostol preceded by transcervical Foley bulb placement results in a significantly increased vaginal delivery rate compared with using oral misoprostol alone.

Objective is well aligned throughout with excellent definitions of primary and secondary outcomes

Single-center- Parkland- cluster-randomized trial (30 subjects in each cluster) and 34 clusters in each group. The two groups Oral Misoprostol (only-n=1110) 100 mcg 4 hours apart for two doses with the vs the same dosing of Oral Misprostol with a foley catheter (30cc ballon) (n=1117).

1. Introduction:line 74,75 You state there is safety and efficacy data for oral Misoprostol/ Please discuss "Oral or Vaginal Misoprostol for Labor Induction and Cesarean Delivery Risk Compared with vaginal misoprostol,Oral misoprostol may be associated with increased risk of cesarean delivery and longer time to vaginal delivery. (Obstet Gynecol 2019;134:10-6)

In the abovementioned study, the comparison is that of vaginal versus oral misoprostol, with use of Foley catheter in a proportion of the patients in each group, compared retrospectively. In this study the authors found that significantly more women who received oral (32%) compared with vaginal (21%) misoprostol underwent cesarean delivery. Compare this study to findings from our prospective, cluster-randomized trial is comparing apples to oranges. Efficacy of oral misoprostol as part of a standardized induction protocol is demonstrated in the consistent vaginal delivery rates (77 and 78%) for both study arms. This same oral misoprostol protocol has been in place at our institution since 2001, and we have previously demonstrated safety and efficacy with this protocol (Reference 12).

2. Methods: Was the foley bulb used with rupture of membranes? please state in Methods

Please see the second paragraph of methods: "Eligible participants included women at 37 weeks' gestation or greater with a living, singleton, nonanomalous fetus in cephalic presentation, with intact membranes,…"

3. Amniotomy was performed when feasible, with intrauterine pressure catheter and fetal scalp monitors placed/ What was the percent of IUPC in each group?

We have added the following data to Table 2. Obstetric Characteristics and in the Results section.

Outcome n	Foley+ 1117	Miso 1110	P-value
Internal monitors	851 (76%)	858 (77%)	0.53

Consider the following points to address in the Discussion

4. Effacement is traditionally used to describe a favorable or unfavorable cervix. Can you discuss why effacement was not considered as a criteria

We do not routinely use effacement as a determining factor for induction at our institution. Therefore, a woman with a cervical dilation of 1cm with 75% effacement was eligible, but a woman with cervical dilation of 3cm and 0% effacement was not eligible for this study.

5. A 30% difference in chorioamnionitis , a secondary outcome is crazy high, Please address the following if you have the data and if you don't have the data it should be part of the discussion surrounding your findings and your findings should be tempered by lack of data for traditional risk factors. My read of the supplemental data is that this was largely centered in the nulliparous group receiving a foley bulb and Miso and that the Foley bulb and Miso had a less favorable cervix.?? Please address the traditional risk factors that are associated with Chorioamnionitis 1. Length of time of ROM between groups especially since the foley-bulb + Miso had a longer IOL, was there more IUPC use in this group? GBS in both groups
   This finding of a 30% chorioamnionitis needs to be addressed with traditional risk factors and a sub analysis of this group to better understand their characteristic and how they are different. Was the foley bulb an innocent bystander?

There were more women in the misoprostol plus Foley group with initial cervical dilation of 2cm (Table 2). Despite this perceived advantage, in the subgroup analysis, the Breslow-Day test was non-significant (p>0.10) for all subgroup comparisons, meaning the risk of chorioamnionitis was not different with regard to added Foley bulb when comparing within parity groups. Stated differently, the risk of chorioamnionitis associated with misoprostol plus Foley was not different for nulliparous versus multiparous women, and therefore the overall effect size for chorioamnionitis associated with misoprostol plus Foley after adjustment for clustering is presented in the Appendix 4 (aRR 1.28), and is similar to that shown in Table 4 (1.30).

There was no difference in time from rupture of membranes to delivery between groups: we have added this data to Table 2: Obstetric Characteristics.

Characteristic	*Foley*	*Miso*	*P-value*
n	*1117*	*1110*	
Time membrane rupture to delivery, hrs Median [Q1, Q3]	*5.2 [1.8, 10.1]*	*5.5 [2.1, 11.0]*	*0.15*

Our standard practice is to use intrauterine pressure catheter when titrating oxytocin. There was no difference in the frequency of IUPC between use, and this data is added to the manuscript (Table 2 and Results). See previous response with table above.

Our practice is to provide combined maternal plus neonatal antibiotic prophylaxis for prevention of early onset GBS, and this practice did not differ between groups.

STATISTICAL EDITOR COMMENTS:

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

1. lines 51-52: Should include the corresponding rates of chorioamnionitis, in order to put the aRR in context.

Rates were added as requested.

2. Table 1: Since the groups were randomized, there is no need to show stats tests comparing the baseline characteristics. Any difference should be due to random chance. If some characteristics were known a priori to be important determinants, then the randomization should incorporate an appropriate block design.

The column including p values was removed.

3. Table 3, lines 44-46,49-51, 157-171 : Since the sample size was based on detection of a 5% increase in vaginal delivery, should state the actual change in % (0.3%) in vaginal deliveries (with CIs), then cite the adjusted figure. The columns of p-values are not necessary, since CIs are included with the RRs and aRRs. Although many of the maternal and neonatal outcomes have NS differences, most rates are very low and there is little power to generalize the NS findings, especially for the adverse neonatal outcomes.

P values are removed.

4. Supplemental Table 2: No need for p-values, since have included CIs.

P values are removed.

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 relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

35. Does <=2cm refer to dilation or length?
Dilation. This is clarified as follows: "To evaluate whether induction of labor in term gravidas with cervical dilation ≤2cm…"

40. Not sure what you mean by "randomized by week"? As I read further, I see that you randomized the intervention based on a per week, not per patient basis. Is that your "cluster"? Perhaps you could describe this a bit more clearly in the abstract? Something like the following starting on line 39.

"We randomized cervical ripening method by week of admission to labor and delivery, with each week group described as a cluster. Inclusion criteria included term gestation, cervix < 2cm dilated, intact membranes and an indication for induction. The study arms were 100 µg oral 30 minutes after transcervical Foley placement misoprostol or 100 µg oral misoprostol. "
Thank you for the clarifying comments and suggestion. The corresponding paragraphs in both the abstract and the methods section have been amended to include the suggested language.

44." Increase in vaginal delivery rate."
We modify the text as suggested.

45. In your methods, please describe the interim analysis. Were there stopping rules? When was it done?
The following was added to the Sample size calculation section:

Stopping rules included 1) a statistically significant harmful impact of using foley bulb in combination with oral misoprostol; 2) a statistically significant increase in vaginal delivery with the combined method such that all women may benefit from it; or 3) demonstration of futility, meaning that further sampling would yield little additional useful information.

47. 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. Change similar word choice throughout.
This correction has been made throughout the text.

47. 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.
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.
For instance, please give the absolute rates of chorio on line 51.

This is true for the abstract as well as the manuscript, tables and figures.

We have added absolute values for variables as well as crude ORs followed by adjusted OR's for relevant variables in the abstract as well as the main body of the manuscript. We have removed p value columns as requested by another reviewer.

Please state if you used "intention to treat" analysis.
This line was added to abstract: "…analysis was by intention-to-treat."
Please see lines 172-173; "Primary and secondary outcomes were analyzed at an individual level and according to an intent-to-treat principle."

56. Please temper the statement about chorio abit. The aOR is not large and the lower bound approaches 1. Perhaps 'did result in a modest increased rate of chorioamnionitis…". In fact, from Table 3, the RR is 30% but its from an 14% to 18% Do you really think that is clinically relevant? Seems honestly like not a big deal.
We agree that a higher odds ratios suggests higher likelihood of causal association in an observational study, but with a large, prospective, cluster-randomized trial, an increase of 30% from 14% to 18% is meaningful.

79. I recognize that I'm being very picky here, but please bear with me. You use "cervical ripening and labor induction" here. Do you actually mean both? Do you use miso for labor induction (for instance, instead of oxytocin) or do you ripen the cervix with miso, then with evidence of cervical ripening or membrane rupture, switch to oxytocin for the actual induction portion of labor? If the miso is used only for cervical ripening, then you should refer to it that way throughout your paper. On line 119-120, you indicate that in fact the miso or miso+foley were for cervical ripening, followed by induction with oxytocin. As such, yours is a study of cervical ripening for women undergoing induction, not a study of the overall induction.
Thank you for pointing out the inconsistencies. We do use misoprostol not only for cervical ripening, but for the purpose of initiating the first stage of labor in nonlaboring women, as is consistent with other large studies (Ref 11). We have removed the language "following cervical ripening" in this section and replaced with "four hours after the last dose of oral misoprostol…"

83. In the abstract, you state that you are studying women < 2cm. Here you say 2cm or less. Which is it?
Forgive the typo, our study included all women with cervical dilation of 2cm or less. This is corrected in the abstract.

95. This implies that prior to the study, women could have undergone cervical ripening with miso alone or miso+ Foley. Is that true? If you had not previously included the option of Foley + Miso, were women actually counseled about this as an option before you started this study so that this was not a novel intervention at Parkland?

We used the combination of misoprostol and Foley catheter in select patients on a case-by-case basis prior to study initiation, but had not standardized the practice on our service. For this study, we standardized the process on a large scale to ensure consistency across the Labor and Delivery unit.

152. Apgar is a woman's name, not an acronym. Please correct the capitalization.
We have corrected these, thank you.

188. What is your total delivery volume at Parkland? Back of the envelope calculation—generous induction rates for indications at term is about 30% , your delivery volume would be about 53,000 during that time frame to have almost 16,000 "eligible" women. What number does the 15,835 actually represent? As I read through the next few lines, the vast majority of these "eligible" women were not eligible.
See the response to a previous reviewer's comment regarding "eligible" group, which includes 3,705 women rather than the total 15,835 women. We have corrected the first sentence in the results section to the following:

"From January 1, 2018 to May 13, 2019, a total of 15,835 women delivered live-born, singleton infants, including 10,057 women admitted in spontaneous labor, 2,073 women who presented with premature ruptured membranes, and 3,705 eligible women with intact membranes who underwent induction of labor (**Figure 1**)."

190. The Green Journal uses the reVITALize definitions, adopted by ACOG. Please use these definitions. For instance, the correct terminology for PROM is prelabor rupture of the membranes.
This term has been corrected according to reVITALize definitions.

194. Were the clusters block randomized? A little unusual to get exactly the same number without blocking.
Yes, correct. Clusters were block randomized, with block size varying randomly in week groups of 4, 6, 8, and 10.

We have added this line to the Methods, paragraph 3. We have also included this detail in the abstract (first sentence, methods).

197. Why was Foley not attempted in 6%? In discussion, please explain the 15% failure to place in those attempted rate. That seems quite high.
This was a pragmatic trial of a standardized induction practice implemented on a high-volume labor and delivery unit. We have clarified this detail in the Abstract and the first sentence of the Methods section.

For 6% of women who were eligible for Foley placement with oral misoprostol, the Foley was not placed according to protocol, and we do not have specific reasons documented in the medical record for all cases – meaning, the clinical teams likely overlooked these patients. However, we believe that a 94% success rate for a pragmatic induction trial is reasonable.

For 945 (15%) of all women randomized to the misoprostol plus Foley arm, placement of transcervical Foley was successful. In a per-protocol analysis, 945/1053 is 90% success in placement of transcervical Foley. In the majority of cases, failure to successfully place transcervical Foley occurred because the cervix was not dilated.

198. If I understand this correctly, could this be rewritten: Misoprostol was administered in 1,026 (92%) of the misoprostol-alone group and 859 (77%) of the misoprostol plus Foley group.
We have modified the sentence to add clarity and better reflect the flow in Figure 1:
"In the misoprostol plus Foley arm, misoprostol was administered in 1,026 (92%), and misoprostol plus successful Foley (as per protocol) in 859 (77%)."

197-199: In your discussion, the relatively high rate of non compliance with the protocol (as I read it, you had 1117 women randomized to Miso + Foley of whom only 859 (77%) got the full intervention. This is a significant limitation—your Miso alone arm had a 92% compliance. This difference will need to be discussed.
To clarify, the oral misoprostol plus Foley arm had 94% Foley attempted, and 92% receipt of oral misoprostol. The Foley placement success rate was 85%; when considering only women who had Foley placement attempted, the success rate was 945/1053 (90%). However, 77% of women received the combination per protocol of BOTH successful Foley placed, followed by oral misoprostol. The rate of per-protocol successful Foley placement followed by oral misoprostol in 77% of women allocated to this study arm reflects the facts that 1) not all attempts at Foley placement are successful, in women with an unfavorable cervix, and 2) women who underwent Foley placement attempt had an additional opportunity to be ineligible for oral misoprostol according to our induction protocol. For example, if evidence of labor was documented following Foley placement, a woman may no longer meet criteria for administration of oral misoprostol.
We have attempted to clarify this in the discussion.

215-216. Please provide the statistical data to support saying these are other than numerically different.
The data are shown in Table 2, and the p value is <0.001 for overall cervical dilation at induction start, see line 214 of original manuscript. The text below is modified to add clarity:

Initial cervical dilation at induction start (defined as time of initial induction agent, Foley or misoprostol, respectively) was significantly different among women in the two groups ($p<0.001$). Specifically within this group, the frequency of initial cervical dilation of 2 centimeters was higher among women in the oral misoprostol plus Foley study arm (31% vs 26%), and the frequency with a closed cervix was lower (25% vs 34%).

Another p for individual comparisons?

The p values for individual comparisons are presented below in the table, although we elect not to add this to the data in the manuscript text, as we presented the overall p value.

Measure	Foley+	Miso	P-value
Cervical dilation at induction start			<0.001
Closed	280 (25%)	373 (34%)	<0.001
1 cm	492 (44%)	450 (41%)	0.094
2 cm	345 (31%)	287 (26%)	0.009

222. Would you consider "were marginally less likely…."?

The text has been modified as suggested by a previous reviewer to provide absolute and relative risks with confidence intervals:

Compared to 84% of women receiving misoprostol alone who required oxytocin, 80% of women receiving oral misoprostol plus Foley required oxytocin prior to delivery (RR 0.96; 95% CI 0.92–0.99; aRR 0.96; 95% CI 0.92–0.99).

223: Please refer back to earlier comments about giving absolute numbers, crude OR's and then aOR's. Was the only adjustment done for cluster?

These absolute numbers have been included into the abstract and Results sections for all relevant variables in the text. The only adjustment was for clustering in the primary analysis.

225. Perhaps clearer as "Time (reported as mean hours +/- SE) to delivery at first induction trial was lower among women in the oral misoprostol plus Foley arm [give unadjusted data]. This difference did not remain significant after adjusting for clustering [give adjusted data].."
Text is modified to the following:

Time (reported as mean hours ± SE) to delivery at first induction trial was lower among women in the oral misoprostol plus Foley arm on unadjusted analysis (17.3 ± 9.2h vs 18.2 ± 9.2h, mean difference -0.82h, 95% CI -1.59–(-0.04)). The difference did not remain significant after adjustment for clustering (17.0 ± 0.3h vs 17.6 ± 0.3h, mean difference -0.58h, 95% CI -1.37–0.20).

Unadjusted analysis followed by adjusted analysis is now reflected in Table 3 as well.

236-239. Could you note data for the subgroups for chorio and time to delivery since these were different in the entire cohort?

See response to a previous comment by Reviewer#3 on the subgroup analysis. There is no difference in risk of chorioamnionitis with regard to subgroups of nulliparous or cervical dilation, so the overall effect size is presented.

There were more women in the misoprostol plus Foley group with initial cervical dilation of 2cm (Table 2). Despite this perceived advantage, in the subgroup analysis, the Breslow-Day test was non-significant ($p>0.10$) for all subgroup comparisons, meaning the risk of chorioamnionitis was not different with regard to Foley bulb when comparing within parity groups. Stated differently, the risk of chorioamnionitis associated with misoprostol plus Foley was not different for nulliparous versus multiparous women, and therefore the overall effect size for chorioamnionitis associated with misoprostol plus Foley after adjustment for clustering is presented in Appendix 4 (aRR 1.28), and is similar to that shown in Table 3 (1.30).

246. This is one place where the absolute numbers are important. Clinically relevant? Could difference in cervical exam at onset be related to this, rather than use of Foley?
We have added absolute numbers to this first paragraph of the discussion.

We address the differences in cervical exam at onset later in the discussion, although I am unclear on the specific question you refer to here.

247. Are you trying to say here that your standardized protocol without Foley results in a 78% success rate so why add something else? Is it worth highlighting that the Miso + Foley arm had a modestly shortened Time to Delivery and lower use of oxytocin than the other arm so that from an L&D perspective, this approach may use fewer resources without other differences?
We have added the following text to the first paragraph of the discussion:

Our standardized misoprostol labor induction protocol achieved a vaginal delivery rate of 77% in a population of women with indicated labor induction at a high-volume county hospital. There was no significant difference in time to delivery associated with adding Foley, although a marginal difference in need for oxytocin was demonstrated. Furthermore, induction with oral misoprostol plus Foley bulb was associated with 18% risk of clinical chorioamnionitis compared with 14% risk with oral misoprostol alone, a 30% increased risk despite no increase in vaginal delivery.

253. In supplemental data, please provide the search terms and data bases used for this literature review.
As this is not a systematic review, I am not clear that this is a required or desired element for this journal. We searched PubMed for the search terms "misoprostol" and "labor induction" to pull original studies, and reviewed all references from relevant systematic reviews for additional studies.

Table 3: please embolden the statistically significant findings for ease of reading.
We will follow guidance provided by the journal for all data preparation and in the revised submission.

276. "Classic definition" is interesting. From the latest version of Williams Obstetrics text, I note the following : "Traditionally, a temperature ≥38°C (100.4°F) accompanying ruptured membranes has implied infection. At Parkland Hospital, we still adhere to this criterion." From the ACOG Committee Opinion #72 "For the purposes of this Committee Opinion, the diagnosis of suspected intraamniotic infection is made when the maternal temperature is greater than or equal to 39.0°C or when the maternal temperature is 38.0–38.9°C and one additional clinical risk factor is present.

For the purposes of this Committee Opinion, isolated maternal fever is defined as any maternal temperature between 38.0°C and 38.9°C with no additional risk factors present, and with or without persistent temperature elevation". As such, your definition in your paper meets neither of the definitions for chorio and fits most closely with the definition of an isolated maternal fever. You don't require ROM in your study, which appears to be a requirement based on the Williams' text, citing specifically what is used at Parkland. Please comment.

Clinical chorioamnionitis as defined at our institution begins with maternal fever and clinical assessment. If the assessment by the clinical team is that maternal fever is due to suspected intrauterine infection – whether due to uterine irritability or tenderness, maternal or fetal tachycardia, malodorous discharge, leukocytosis, or other clinical findings of concern, antibiotics are administered. Not every isolated fever is due to chorioamnionitis and we consider other etiologies, particularly when no risk factors for chorioamnionitis exist. We do not have data on the timing of diagnosis of chorioamnionitis relative to

time of rupture of membranes, although we know there is no difference in time from rupture of membranes to delivery between the groups (see response to comment by Reviewer 3).
We have clarified the term "clinical chorioamnionitis" in the manuscript. Importantly, the definition was the same for both study arms, making the relative risk a clinically meaningful outcome.

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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:

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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. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

5. Please submit a completed CONSORT checklist with your revision.

6. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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.
For brevity, we have removed one Appendix table from the final manuscript submitted and have added pertinent text in the manuscript.

8. 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.
We have revised the title to meet word limit requirements.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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13. 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.

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