

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Feb 05, 2019
To: "Roxane C Handal-Orefice"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2

RE: Manuscript Number ONG-19-2

Labor Induction: Oral versus Vaginal Misoprostol and Cesarean Delivery Risk

Dear Dr. Handal-Orefice:

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

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

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

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective single institution study (Boston University Medical Center) comparing vaginal Misoprostol at 25 mcg 2013-2014 to Oral Misoprostol 50mcg

primary outcome measures was cesarean delivery, Secondary outcomes included median time to vaginal delivery, indications for cesarean section, tachysystole, obstetric hemorrhage

(500cc blood loss for vaginal delivery and 1000 cc of blood loss for cesarean section), composite neonatal morbidity

1. Given historical comparisons and the inevitability of practice changes did the overall cesarean rate change during those two years
2. Please describe the difference in pharmacokinetics of oral vs vaginal
3. The cohort was predominantly overweight or obese, with 77% of women in each group having a BMI ≥ 28 at the time of delivery ($p=1.00$). Why did you use 28.
4. "The years were evaluated in immediate succession when there was minimal other change in general obstetric management. Interrogation for differences in the patient population revealed no significant difference." Please be more specific. Was there any difference between cesarean rates each year? How many faculty changed over? Demographics of patients different and how did you interrogate this? Can you explain the change to oral from a systems standpoint. What prompted this change?
5. Clearly there are more failed IOL in Oral group: Do you have a protocol for failed labor or failed induction, how were these decisions made?
6. Is the decision to perform a cesarean left to an individual physician. Were all patients part of the same teaching service team or were there private and public patients with several different physicians making decisions. Are there guidelines for Failed IOL and for active phase arrest that all providers use
7. Can you explain why oral Misoprostol might not be as efficacious Pharmacokinetics?

Reviewer #2:

Methods:

1. Was was the definition for failure to progress? Was a standard definition used in the review process? In addition to looking for the diagnosis in the indication section in the operative note, was the chart reviewed to confirm the predetermined definition if one was developed?
2. Similarly, were the fetal tracings reviewed in cases of non-reassuring fetal heart rate tracing as the indication for the cesarean section?
3. Who determined the initial bishop score? Was the cervical exam performed by interns? Residents? Nurses? non-ob residents?
4. The study objectives state that "the purpose of this study was to determine... in a primarily overweight population. The sensitivity analysis was restricted to patients with a BMI of ≥ 25 . The mean BMI in the groups were 32.6 and 33.8. Did you analyze the for any differences in between subjects with BMIs in the overweight category vs the obese category?

Results:

5. Was there a difference in the time to achieve the active phase of labor between groups? Duration of the first or second stage of labor?
6. In the failed induction groups were there any differences in those achieving the active phase of labor or achieving the second stage of labor?
7. What was the longer hospital stay attributed to in the oral group? Was it due to the increase in cesarean deliveries, longer labor length or both?

Discussion:

8. Line 203: is there any literature evidence to support the comment that a shorter timing of vaginal administration may have resulted in a quicker labor course?
9. Another limitation for a time/epoch study is the change in residents or attendings during the two time periods, please comment.

Reviewer #3: This is a retrospective cohort comparing cesarean delivery risk before and after introduction of oral misoprostol for labor induction. In a single center labor induction with vaginal misoprostol 25 ug was replaced with 50 ug oral misoprostol.

1. The authors state that during each study period the respective dose and route of misoprostol were used exclusively, please offer an explanation as to why so many more charts were reviewed in order to obtain the vaginal misoprostol charts vs the oral misoprostol charts 410 vs 262. How did this crossover happen? Were providers banned from using vaginal misoprostol?
2. Were other forms of induction were allowed during this time such as Foley other prostaglandins etc? A tremendous risk of selection bias.
3. What other changes were made during this time that may have accounted for the increased risk? It is mentioned that there was more delay between placements in the group with vaginal misoprostol. Did acuity change? Staffing or total deliveries?
4. Although significance wasn't quite reached, please comment on the risk of hemorrhage between groups as it was quite close.
5. Also comment on biologic plausibility of why the difference, including first pass metabolism.

STATISTICAL EDITOR'S COMMENTS:

1. Table 2: Since the number of vaginal exams can only have integer values, should cite as median(range or IQR) and test non-parametrically.
2. Table 3: Need units for BMI. Should separate the primary outcome of interest from the secondary ones. The adjusted ORs may have insufficient counts of events to allow for use of 5 or 4 covariates. Why was vaginal delivery < 24 hours

adjusted using only 2 covariates. Suggest including the coefficients of 7.6 and 7.5 hours in the table adjacent to their respective CIs, and citing the p-values as a footnote, rather than p-values adjacent to the p-values and the coefficients as a footnote. The number of women with BMI < 25 kg/m² is very small and hence the testing of CD among BMI ≥ 25 kg/m² essentially recapitulates the findings for all women in the study.

3. Table 4: Was LOS rounded to nearest integer? If so, should cite as median(range or IQR) and test non-parametrically. Several of the comparisons have small counts and there is little power to generalize the NS findings.

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, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

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

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

3. 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. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

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

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis,

writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

8. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

9. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

10. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

11. 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.

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

"Figure 1: Please upload as a figure file on Editorial Manager."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

13. 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/ifaauth.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.

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

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

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

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.