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: Aug 31, 2018
To: "Elizabeth G. Raymond" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1452

RE: Manuscript Number ONG-18-1452

Systematic Review of Efficacy of Misoprostol Alone for First Trimester Medical Abortion

Dear Dr. Raymond:

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 Sep 21, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: For the review titled "Systematic review of efficacy of misoprostol alone for first trimester medical abortion", I have the following comments and queries:

1. Thanks for submission of your work.

2. This is an important women's health care issue.

3. The search and review seems to have been performed with sufficient rigor.

4. Contacting authors to clarify data is a strength of the study.

5. The meaning of the sentence in lines 105 to 106 is a bit unclear. Perhaps you could elaborate on specifically which errors were corrected.

6. Some of the statistical analyses may be too complicated for our readers to follow, and this section is difficult to get through.

7. It's somewhat concerning that 43% of the total number of cases studied came from retrospective case series in two anonymous Latin American countries.

8. Other concerns include the fact that the study population was very heterogeneous, and a multitude of misoprostol regimens were used.

9. A strength of the quality of the data is the fact that 92% of the population came from studies in which ultrasound was "routinely" used to determine gestational age.

10. The inclusion criteria seem to be too broad. Perhaps including only subjects who had a pre-treatment ultrasound, and used misoprostol 800 mcg vaginally would have been a better population to study.

11. Data regarding the association between complete abortion and both the number of doses of misoprostol used and waiting 4 to 7 days after medical treatment before performing surgery is very useful.

12. Overall, the manuscript is somewhat difficult to read. A significant issue, in this regard, is the constant need to describe the proportion of your study population included in each analysis.

13. There is very little data regarding side effects. This is especially important for women taking up to four doses of medication. Of note, data regarding satisfaction is given.

Reviewer #2:

1. Lines 54-55. Can the authors also include efficacy for the approved 70 days?

2. Line 107. Can the authors define what "surgical completion" is? Does this include retained products of conception? How was this evaluated in the studies included?

3. Line 298: What other advantages are there of using miso alone for medication abortion other than the price of mifepristone and the ease of accessing miso?

Reviewer #3:

1. This is a systematic review of efficacy of misoprostol alone for first trimester abortions, ultimately including 43 studies, consisting of 55 groups, with the primary outcome of proportion of women who required surgical interventions to complete the abortion. In this current climate, this systematic review is valuable. The description of the strategy, analytic method, and assessment of bias were very clearly delineated throughout the paper. One point I had trouble clarifying after multiple reads of the paper, is if women who hadn't completed the abortion after additional contingent doses were directly compared to women who hadn't completed the abortion and immediately had surgical intervention. I think further clarification of the section between lines 168 and 189 would be helpful -- basically, I was looking for the definition of "failure" and was having a hard time with that. When was surgical intervention used for possible retained POCs versus continuation of a "viable" pregnancy?

2. A small point, but in the abstract objective portion its stated that secondary outcomes include hospitalizations and transfusions. Those numbers were very small and in the conclusion, it states the reported incidence of "serious complications" requiring hospitalization or transfusion was only 0.2% (lines 246 and 247). I suggest replacing hospitalization and transfusions with serious complications in the abstract.

3. The completion rate of abortion with misoprostol alone is significantly less than with mifepristone (acknowledged in your paper). I feel the language used in lines 295 to 296 of misoprostol alone "should" be offered to be strong. I suggest rewording or restructuring the paragraph to state in settings where mifepristone is difficult to obtain, too costly, or prohibited, single agent misoprostol could be an option for women seeking abortion in the first trimester. It's not an equal treatment option, so the language around that should be clear.

Thank you for your work!

Reviewer #4:

To the Authors:

This is a systematic review of the efficacy of misoprostol alone for first trimester medical abortion. The purpose of the review is to summarize available data on the effectiveness and safety of medical abortion with misoprostol alone in the first trimester of pregnancy. In many settings, medical abortion with a combination of mifepristone and misoprostol is standard of care, with success rates greater than 95%; however, mifepristone is not available in some countries and it is expensive. The authors report that medical abortion with misoprostol alone results in surgical intervention in 21.3% of cases, with an ongoing pregnancy rate of 6.6%.

The review is done well and includes 55 trial groups from 38 published studies and one abstract whose authors also provided data for review, totaling 13,220 evaluable women. Limitations include that 43% of these evaluable women came from just two very large retrospective case series. Overall the paper is well-written. I have a few specific suggestions and concerns.

1. Results and Table 1: The data presented in lines 172-174 do not match the numbers in Table 1.

2. Results: The Authors appropriately attempt to answer the question about misoprostol route, dosing, timing, number of doses, etc associated with less need for surgical intervention. However, the unadjusted data in a cluttered Table 3 do not clearly reflect the dominance of the two large retrospective case series from Latin/South America that the Authors

describe in the text. Consider revising Table 3 with adjusted rates and/or by removing characteristics (such as publication date) that are not theoretically associated with surgical intervention. Lines 254-257 of Discussion may be better located in Results; this sentence supports your Conclusions more than the rest of the review does.

3. Discussion and Conclusions: It is not appropriate to conclude that misoprostol as a single agent "should" be an option for medical abortion when the review shows an ongoing pregnancy rate of 6.6% and surgical intervention rate of 21.3%. How do the Authors conclude that misoprostol alone is effective, when as they state, misoprostol alone is "clearly less effective" than standard regimens that include mifepristone? At what intervention or ongoing pregnancy rate would the Authors consider the regimen ineffective? Missing from this conclusion is any mention of the teratogenic effects of misoprostol, particularly in the context of repeated high doses. It may be appropriate to conclude from this review that a regimen of multiple doses of 800 mcg misoprostol "could" be offered as an option to women, especially if mifepristone is not available.

STATISTICAL EDITOR COMMENTS:

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

lines 44-46: For consistency, should include CIs for the proportions 0.2% and 86%.

lines 149-153: The studies cited were of variable quality, ranging from case series to cohort studies or RCTs. What were the analysis results if the case series were eliminated?

Methods: In addition to adjustment of OR for "clustering by paper", since there were so many characteristics (dose, number of doses, route of administration, geographic region, max GA, timing of surgery etc), what were the results of adjustment for each of those factors on the outcome of surgical completion?

Table 1, fig 2A, Supplemental Appendix: 27 of the trial groups were comprised of 3-100 women and it appears that those smaller groups contributed most to the higher proportion needing surgical completion. Were the smaller groups also the case series groups? What were the results if those with the smallest samples were eliminated from the analysis? It also appears from the supplemental material that the higher rates of loss to follow-up were concentrated among the larger studies.

Tables 2, 3 and 4: Need to include columns for crude OR to contrast with aORs.

EDITOR COMMENTS:

1. Please cites lines 197-201 (Across trial groups…subject who).

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

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

- Cover letter: Please provide an update about the in-press reference with your revision. Per the Instructions for Authors, "Unpublished data, personal communications, statistical programs, papers presented at meetings and symposia, abstracts, letters, and manuscripts submitted for publication cannot be listed in the references. Information from such sources may be cited, if necessary, in the text with the sources given in parentheses.
Manuscripts accepted by peer-reviewed publications but not yet published (“in press”) are not acceptable as references."

- Title page: The journal does not permit statements about anonymous funders. Please name the funder.

- The objective for the abstract should be a simple "to" statement without background.

- The Journal style does not include the use of the virgule (/) except in numeric expressions. Please edit here and in all instances.

- I agree w/ other reviewers that "should" is a bit strong. Perhaps "Could be offered...if mifipristone is unavailable or contraindicated".

- Can you state primary and secondary outcomes here?

- Could you move the search strategy information noted here in red to a box for easier reading?

- Mcg misopristol should be changed to "dose of misopristol" here and throughout.

- Please give parallel units of time. <=91 days =13 weeks; 14 weeks=98 days.

- It's not clear as written that the "one study" is in addition to the 38, so its confusing when you come up with 39 later. Could you say, "An additional study is included which has to date been published only in abstract form, but the authors....

- Could you state more clearly here the best approach: dose, route, moistent or note, repeat doses.

- If mifipristone is unavailable or contraidicated-as noted in abstract comments.

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

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

6. 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.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with the following guidelines:

* All financial support of the study must be acknowledged. The journal does not permit states about anonymous donors. All funders must be named.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your signature on the journal's author agreement form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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: Reviews, 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. Figure 1 and 2 may be resubmitted as-is.

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 21, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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