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: Oct 03, 2019
To: "Mitchell D. Creinin" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1640

RE: Manuscript Number ONG-19-1640

A Randomized, Placebo-Controlled, Trial of Mifepristone Antagonization with High-Dose Progesterone to Prevent Medical Abortion

Dear Dr. Creinin:

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 Oct 24, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Summary: This RCT terminated prior to completion presents valuable information pertaining the potential risks associated with offering "reversal" of medication abortion - namely the significant risk of hemorrhage. While this article presents important information, I recommend that the authors temper their editorial tone in the discussion section. The data speaks for itself and using more editorial language may take away from the weight of the data. That said, the commentary embedded in the discussion is important. I recommend submitting a complementary Perspectives piece that discusses the dangers of legislative interference in the patient-provider relationship, especially around medical management around politically charged procedures. Alternatively, perhaps the authors or journal could reach out to individuals to write such a complementary piece.

Title page:
1. N/A

Abstract:
1. Lines 39-40: That the study stopped after enrolling 12 participants should go in the results section.
2. Line 51: Why did the 2 participants withdraw?

Introduction:
1. Line 68: Please include mifepristone method of action for those less familiar with this medication.
2. Line 85: Please specify what is meant by "high-dose progesterone" - what dosing?
3. Line 87: While I appreciate not wanting to legitimize these studies, it would be helpful to present what these papers report regarding the "outcomes".

Methods:
1. Lines 103: Please explain why you excluded those with peanut allergies.
2. Lines 138-9: Please explain what is meant by "safety evaluations".

Results:
1. Was there no monitoring of HCG levels post-enrollment? Why not?

Discussion:
1. Line 217: Please clarify, the study was powered to look for difference between PG and placebo, but was unable to do

so because of stopping enrollment.
2. Line 227-8: Please provide some background on the typical EBL with med ab or changes in Hgb pre- and post-med ab.
3. Line 230: With these small numbers, can you say that the risk of hemorrhage is "inherent"? Consider "potential dangers" or another phrase that is a bit less definitive in light of the small sample.
4. Paragraph starting line 242: The two ideas conveyed in this paragraph are not clearly linked. Consider breaking up into 2 paragraphs or link these two points more readily.
5. Paragraphs (2) starting at line 262: I entirely agree with your points here. However, I fear that the editorial nature of some comments in these paragraphs will allow some readers to question the objectivity of your science and the conclusions that you make based on your findings. I recommend using more dispassionate language in these paragraphs. (As an aside, I question whether legislators really view existing case reports as "medical gospel" - do they really care about the "scientific basis" of these laws?!)

Reviewer #2: Thank you for the opportunity to review Creinin et al's RCT for medication abortion reversal. This is a valuable contribution to the literature secondary to recent legislative mandates that have been based on harmful claims by unethical researchers. Publication is important as it highlights how a well designed study looks and how there may be risks to patients. I have the following minor comments and some suggested literature to consider incorporating.

1. For reference #1 please use updated citation from Guttmacher published after your submission

2. Although you highlight legislation in response to prior evidence in the discussion I would like to see a sentence highlighting this in the introduction. You may also want to consider referencing here or in the discussion the AJOG viewpoint by Bhatti et al for readers to better understand the landscape of med ab reversal attempts.

3. Intro- lines 84-87- please also highlight varying dosages of progesterone administered in these series.

4. Methods- line 120-122- please clarify that this was the recommended dosing regimen as the series reported on varying regimens. he also makes a recommendation about IM dosing which you may want to acknowledge here or in discussion.

5. Discussion- line 248-- I believe Delgado recommend treatment through the end of first tri

6. Discussion- lines 254-6-- recommend adding in Grossman's systematic review and highlighting that continuing pregnancies after one mife dose ranged from 8-46% for up to 56 days. Delgado's claim for mife reversal rate is 48% for up to 66 days.

7. Discussion- may also want to consider incorporating literature by Raymond et al (Gynuity) has generally not shown concerns for same day ENG implant but has for DMPA if you want to go into unexplored areas with respect to progestin dosings. This being said i don't know if its needed but something to consider and may be of help to the readers.

Reviewer #3: Thank you for your submission.

Specific comments:

Abstract: well written and reflects the study and stoppage well. I would include in your objectives one line on WHY are you asking this question.

Introduction: your rational and the scientific background are well described.

Methods:
Were women offered any compensation for participation, a this is a large ask (2 medications, blood draws and a delay of 2 weeks)?

Results:
Your results are well described, and the details about the bleeding complications are good to have included.

Discussion: your discussion is appropriate and thorough.

Reviewer #4: Thank you for a thoughtfully designed RCT investigating the efficacy and safety of oral progesterone to "reverse" medication abortion. Although you had to terminate your protocol early due to safety concerns, this in and of itself is a significant finding and provides evidence to support the belief that it is unsafe to reverse a medication abortion. I appreciate that you did have a higher continuing pregnancy rate in the arm that was randomized to progesterone, and while this is not statistically significant due to lack of power, my concern is that this data can still be used to promote medication abortion "reversal" protocols, and be used as evidence that might actually support the mandated provision of misinformation of doctors to patients.

I note that 2/3 hemorrhages (and the one requiring a transfusion) occurred in the placebo group and not the progesterone arm. I would like to see language in your manuscript addressing whether you can determine if the progesterone treatment helped prevent hemorrhage.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:
lines 54-55, 164- 166, 193-194, 194-196, and Table 1: Two issues with use of this stats comparison: (1) the groups were randomized, so any stats difference could be attributed to random chance and (2) the groups ended up with such small samples that there was insufficient power to discern any difference. Should just report the summaries, as in Table 1 and not do any stats comparisons.

Could report the overall and subset rates of bleeding (table 2), but would need to include CIs and include a caveat in Discussion re: power and small sample sizes.

EDITOR COMMENTS:

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

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

- you have 2 definitions of study exit, here and on line 47-48. Please clarify in a succinct fashion

- As noted by reviewers, the statistical comparisons between the groups should be deleted due to very small sample sizes. Just make this part descriptive. The key finding of hemorrhage w/o miso in both groups is of course the finding of greatest importance.

- Perhaps edit to avoid "generally" twice in same sentence: something like " however, efficacy is about 80% in pregnancies less than 49 days of gestation"

- Perhaps edit to" In women treated with combination mifepristone and misoprostol, approximately 0.3% at 7 weeks...." (in some cases you use days and in other weeks--that's OK if that's what your references cited but if you can make this in the same units that might be clearer)

- opted

- Consider putting sentence line 74-76 in next paragraph as they seem to be closely related.

- some scientists? Most scientists? As written it seems like you are saying "all" scientists. Given that you on line 80 you say that this theory has been questioned by "investigators". On line 81 could you add '...may antagonize the effects of mifepristone alone and reverse the abortifacient effect"?

- Perhaps for clarity: "After women presented for first trimester abortion abortion and completed the counseling and gave consent for surgical abortion, a study coordinator (?) discussed the trial with them. Inclusion criteria included: ... Exclusion criteria were:....

- Sentence not in parallel construction: "Screening visit included recording demographic information, soliciting baseline pregnancy symptoms and obtaining study consent" might be clearer.

- subjects for whom....

- why was this important? If they answered yes was it an exclusion?

- Eligible or enrolled subjects?

- starting when?

- Can you provide their data? Not sure I understand this completely. Here you say they were exited from the study but secondary outcomes included expulsion rates over 2 weeks.....seems like you included them.

- why didn't you have a dsmb and stopping rules?

- reporting or finding instead of claiming.

- do you mean would choose to continue the pregnancy or would have an ongoing viable gestation?

- Very clear data sharing statement. Please do not forget to update your clinicaltrials.gov site.

- Do you have hemoglobin or hematocrit data for all 3? Any assessment of quantity of blood loss or physiologic effects such as tachycardia, like the 3rd case?

- this is the 3rd subject with bleeding isn't it?

- of whom

- We do no allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms “trend” or “tendency” or “marginally different”) unless there is a statistical difference. Please edit here and throughout. You cannot make the statement that they were twice as high, implying a difference, given the underpowered nature of your results.

- Line 203 indicates that there were not changes from baseline.

- This is written as a double negative..previous studies did not...for women who did not.... Please edit for clarity.

- This is where any objective measure of degree of bleeding for all 3 women would be helpful.

- I would delete highlighted.

- Very strong statement perhaps

- Delete semicolon and add colon: as such, it does not capture...

- avoid comparisons here

- if progesterone does reverse the abortifacient effect of mifepristone alone, what is the ideal treatment length, dose and route of administration?

- You set these up as 2 opposing questions so the "second" one should be phrased as a question.

- does cause? Usually causes? May cause?

- will spontaneously have an early pregnancy loss. information about correlation of heart rate w/ SAB rate is out of place and unncessary. Your paper isn't looking at predictors of pregnancy loss.

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

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

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

4. 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.

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

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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

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

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

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

10. 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.

11. 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.

12. 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.

13. 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%").

14. Line 271: To support your priority claim (that this is the first study), please include the details of your systematic search of the literature. That search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If you cannot provide the search details, the journal cannot allow you to assert that this is the "first" study.

15. 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.

16. Figures 1-3 should be resubmitted with the revision.

17. 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.

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

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 24, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Nancy C. Chescheir, MD
Editor-in-Chief

The Editors of Obstetrics & Gynecology
2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals
