Date: Jul 06, 2018
To: "Oscar A Viteri" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1103

RE: Manuscript Number ONG-18-1103

Torsemide for the Prevention of Persistent Postpartum Hypertension in Preeclamptic Women: The TROPHY Randomized Clinical Trial

Dear Dr. Viteri:

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 Jul 27, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors conducted a randomized controlled trial to determine whether administration of torsemide for 5 days following delivery decreased the rate of persistent postpartum hypertension in women with either preeclampsia or chronic HTN with superimposed preeclampsia. This is an interesting topic and perspective, since we don't normally think of treatment as a means to prevent persistent postpartum hypertension (but rather as a way to manage hypertension when it occurs). The study findings were negative: torsemide did not significantly decrease hypertension, either during hospitalization or at 7-10 or 6 weeks postpartum. Comments and questions follow.

1. Abstract. Overall this is a faithful summary of the manuscript. The conclusion is somewhat confusing however. The authors write that they failed to reject their hypothesis of no difference. The reader will probably want to know that 5 days of torsemide for women with preeclampsia did not have a significant effect on the rate of postpartum hypertension.

2. Introduction.
a. In the 1st paragraph, lines 4-7, the authors cite 6 references about management of postpartum hypertension. There appear to be others on the reference list. Are there really a "paucity of studies" as much as lack of consistent benefit across trials?
b. The authors also write that women with postpartum hypertension are at risk for CV disease and kidney failure later in life. Is the suggestion that 5 days of torsemide will have an impact on long-term health?
c. In the last paragraph, the authors write that torsemide is the only category B loop diuretic. The FDA no longer uses letter categories, but even if it did, these are postpartum patients. Why is this mentioned?
d. As not all women with preeclampsia require medication to treat hypertension postpartum, what is the rationale for treating in the absence of hypertension?

3. Methods.
a. Under participants, the authors explain that they included all women with any degree of hypertension and proteinuria equivalent to 0.3 mg/dL (which are not severe features) and that in the absence of proteinuria, they included women with severe hypertension and (not or) criteria for severe features. What about women with blood pressure elevation that was not severe but other features of severe preeclampsia?
b. The protocol was to monitor blood pressure every 4 hours in the absence of severe elevation. What was the protocol for severe hypertension, and did all women with severely elevated blood pressure receive medication immediately? Did all women with severe preeclampsia receive magnesium sulfate for seizure prophylaxis?
c. By what mechanism would 5 days of torsemide affect the secondary outcomes of hypertension at 7-10 days or 6 weeks?

4. Results.
a. Might provide additional information about blood pressure values.
b. Please clarify the role of the Bayesian analysis. The disparate description of the findings is somewhat confusing.
c. Figure 2 (just 2 bars) is not necessary.
d. Tables. Might provide a column of p-values for comparisons or include a statement that there were no significant differences between groups.
e. Would try to address response to torsemide in the context of whether women did or did not require additional antihypertensive medication and whether they did or did not receive magnesium sulfate.
f. In Table 3, please address whether women with hypertension at 7-10 days or at 6 weeks had (or did not have) chronic hypertension. Please also address whether women were discharged from the hospital on other medication to control blood pressure

5. Discussion.
a. The opening (summary) statement is confusing as written. The authors write that they failed to reject their hypothesis of no difference. Suggest rephrasing to clearly state that in their randomized trial, 5 days of torsemide for women with preeclampsia did not have a significant effect on the rate of postpartum hypertension, regardless of disease severity. Please explain how Bayesian analysis could realistically outweigh this.
b. In the last sentence, the authors write that trials with longer duration of treatment are warranted. However, they had explained that the main limitation of their study was that women were hospitalized for less than 3 days. How would a longer duration of treatment address this?

Reviewer #2: The authors present a double blind, randomized control trial of torsemide for the prevention of persistent postpartum hypertension in women diagnosed with preeclampsia. This is an important study, as persistent postpartum hypertension is associated with adverse and costly outcomes. In this study, women with preeclampsia (without severe features, with severe features, and superimposed) women were randomized to receive either placebo or torsemide for 5 days.

Major Issues, Study Design:
1) The authors define the primary outcome as postpartum hypertension >150/100 on two occasions at least 4 hours apart by day 5 or by the time of hospital discharge. Functionally, the majority of women would have been evaluated at 2-4 days postpartum (typical length of stay for vaginal and cesarean deliveries). Therefore, the authors are assessing the "outcome" before the intervention is complete. This also led to different lengths of exposure to the intervention based on mode of delivery and different outcome assessment based on mode of delivery.

2) The inclusion of women with chronic hypertension is problematic. Women with chronic hypertension by definition have high blood pressure that is not affected by delivery (whereas preeclampsia is expected to resolve with delivery). Therefore, in 25% of women included in the study, the primary outcome of persistent postpartum hypertension may just be a reflection of their underlying disease. Additionally, this outcome will be strongly impacted by antihypertensive use in this population.

Minor issues, Methods:

1) The definition of preeclampsia with severe features was unclear. It reads as though both severe-range blood pressures and serum laboratory abnormalities were required.

2) Per ACOG Task Force on Hypertension, severe range blood pressure elevations alone are not sufficient for the diagnosis of superimposed preeclampsia in chronic hypertension.

3) How was the dose & duration of torsemide selected?

4) Justify your choice of powering to a 50% reduction in postpartum hypertension.

Minor issues, Results

1) In table 1 and table 2, the number of women with chronic hypertension should be the same as the number of women with superimposed preeclampsia (percentages are different)

2) The authors report length of stay in hours. However, as mode of delivery is most strongly associated with length of stay, a more appropriate measure would be % of women who remained in hospital longer than expected or % of women who remained in hospital longer than expected due to persistent hypertension.

3) I would like to see the outcome of discharged on antihypertensives. I assume "acute antihypertensives" are IV antihypertensives.

Discussion

1) I think instead of the null hypothesis not being "disproven" it could not be "rejected."

Introduction
No issues

Abstract
No comment

Reviewer #3:

1. In patients on antihypertensive medication, were the medications continued postpartum?

2. The treating physician could decide how to treat severe hypertension postpartum. I assume some patients got acute treatment but some patients likely got started on antihypertensive medication and continued throughout the study period. How many in each group were placed on oral medication for the duration of the postpartum period?

3. Were the characteristics of the patients who showed up postpartum similar to the ones that did not?

STATISTICAL EDITOR'S COMMENTS:

1. lines 10-13, pg 4: Need to identify how many had BP measured in hospital on PP day 5 vs discharge day, for each cohort.

2. lines 4-5, pg 11 and lines 8-12, pg 11: Need to clarify for the reader that the sample size and primary outcome were based on a 50% reduction in rate of persistent post partum HTN. The other criteria (at least a 10% reduction in the rate) was achieved, but that was not the how the hypothesis was stated.

3. Fig 1, lines 18-20, pg 11: Should include in the flow diagram the number of women who did not comply in each study arm.

4. Table 3: For the CI of RR for HTN at 7-10 days, I cannot replicate the results, but rather RR = 1.1 (0.6-2.1); Need to identify whether any of these were significant and note that if NS, cannot generalize the results, since study design did not power for these outcomes.

ASSOCIATE EDITOR'S COMMENTS:

We would welcome a revised manuscript responsive to the above comments. We are asking that the Bayesian analysis be offloaded to Supplemental Digital Content and that you allude to it in only the briefest way in the actual manuscript.

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:
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2. 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.

3. This manuscript appears to have been presented at SMFM. Please disclose the name, dates, and location of this meeting on your title page.

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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 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 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.

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 appendixes).

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

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 edit your acknowledgments or provide more information in accordance with 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 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).

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College 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. 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 a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

16. The Journal's Production Editor had the following comments about the figures in your manuscript:

"Figure 1: Were the exclusion criteria not mutually exclusive? Please upload as a separate figure file on Editorial Manager.
Figure 2: Please include a y-axis and upload the original figure file to Editorial Manager (eps, tiff, jpeg). Items pasted into Word often lose resolution.
Figure 3: Please consider including a y-axis and upload the original figure file to Editorial Manager (eps, tiff, jpeg). Items pasted into Word often lose resolution."

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.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (http://cjs.cadmus.com/da/index.asp) for more direction on digital art preparation.

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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 Jul 27, 2018, 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

If you would like your personal information to be removed from the database, please contact the publication office.

Dear Editors,

Thank you for allowing us to review our manuscript. Please see below the answers to the Reviewer's queries. Should you require any additional information, please do not hesitate to contact me.

Sincerely,

Oscar A. Viteri, MD

REVIEWER COMMENTS:

Reviewer #1: The authors conducted a randomized controlled trial to determine whether administration of torsemide for 5 days following delivery decreased the rate of persistent postpartum hypertension in women with either preeclampsia or chronic HTN with superimposed preeclampsia. This is an interesting topic and perspective, since we don't normally think of treatment as a means to prevent persistent postpartum hypertension (but rather as a way to manage hypertension when it occurs). The study findings were negative: torsemide did not significantly decrease hypertension, either during hospitalization or at 7-10 or 6 weeks postpartum. Comments and questions follow.

1. Abstract. Overall this is a faithful summary of the manuscript. The conclusion is somewhat confusing however. The authors write that they failed to reject their hypothesis of no difference. The reader will probably want to know that 5 days of torsemide for women with preeclampsia did not have a significant effect on the rate of postpartum hypertension.
Thank you for the suggestion. The conclusion has been rewritten as proposed.

2. Introduction.
a. In the 1st paragraph, lines 4-7, the authors cite 6 references about management of postpartum hypertension. There appear to be others on the reference list. Are there really a "paucity of studies" as much as lack of consistent benefit across trials?
The statement has been revised on line 148.

b. The authors also write that women with postpartum hypertension are at risk for CV disease and kidney failure later in life. Is the suggestion that 5 days of torsemide will have an impact on long-term health?
Thank you. Certainly not. However, our study provides preliminary data for future larger, longer trials that might impact these outcomes.

c. In the last paragraph, the authors write that torsemide is the only category B loop diuretic. The FDA no longer uses letter categories, but even if it did, these are postpartum patients. Why is this mentioned?
We concur. Please note this has been removed from the manuscript.

d. As not all women with preeclampsia require medication to treat hypertension postpartum, what is the rationale for treating in the absence of hypertension?
The rationale for a postpartum prophylactic medical intervention in women with preeclampsia originates from the high rate of persistent puerperal hypertension that characterizes the disease (50% in prior literature, which was equivalent to our findings). In addition, the rationale for the use of torsemide is explained in lines 155-162.

3. Methods.
a. Under participants, the authors explain that they included all women with any degree of hypertension and proteinuria equivalent to 0.3 mg/dL (which are not severe features) and that in the absence of proteinuria, they included women with severe hypertension and (not or) criteria for severe features. What about women with blood pressure elevation that was not severe but other features of severe preeclampsia?
They were also considered preeclampsia with severe features. We have amended line 202 to reflect this change.

b. The protocol was to monitor blood pressure every 4 hours in the absence of severe elevation. What was the protocol for severe hypertension, and did all women with severely elevated blood pressure receive medication immediately? Did all women with severe preeclampsia receive magnesium sulfate for seizure prophylaxis?
The protocol used at our institution follows current ACOG recommendations for the emergent management of acute-onset, severe hypertension. However, the decision to start emergent antihypertensives and to use magnesium sulfate was left to the discretion of the treating physician (combination of private and academic practices). The proportion of women who received acute antihypertensives is depicted in table 4 and of those receiving magnesium sulfate in table 3. We have also added a statement to better clarify this in lines 222-224.

c. By what mechanism would 5 days of torsemide affect the secondary outcomes of hypertension at 7-10 days or 6 weeks?
It is well established that increases in blood pressure immediately after delivery is bimodal (usually days 3 and 6) and is secondary, in part, to fluid shifts occurring postpartum. Purportedly, torsemide for 5 days may affect blood pressure within 7-10 days by having removed excess fluid accumulated during pregnancy.

4. Results.
a. Might provide additional information about blood pressure values.
Thank you for the suggestion we have referenced a new figure depicting systolic and diastolic blood pressures trends between the study groups (Figure 3).

b. Please clarify the role of the Bayesian analysis. The disparate description of the findings is somewhat confusing.
Bayesian analyses answer a different question that frequentist analyses. While the frequentist analysis focuses on rejecting the null hypothesis of no difference on the primary outcome between the two treatment groups given the observed data, Bayesian

analyses answer a more clinically relevant question, i.e, what is the probability of a true treatment effect given the observed data. For this study, the probability of a true benefit from torsemide in reducing the primary outcome was 92%. More importantly, these analyses indicate a probability of 78% of torsemide reducing the primary outcome by at least 10%. We have added a more thorough description of the Bayesian analyses on a supplementary digital content appendix uploaded with this revision.

c. Figure 2 (just 2 bars) is not necessary.
Figure 2 has been removed.

d. Tables. Might provide a column of p-values for comparisons or include a statement that there were no significant differences between groups.
Since this is a randomized trial, any difference in baseline variables at randomization would be due to chance and is not appropriate to give p-values for these. For outcomes, as noted by the RR, all CI crossed one and therefore results were not statistically significant.

e. Would try to address response to torsemide in the context of whether women did or did not require additional antihypertensive medication and whether they did or did not receive magnesium sulfate.
Unfortunately, only 7 women in the torsemide group and 6 in the placebo group actually received acute antihypertensive medications (table 4). However, 20 (34%) women in the placebo group and 19 (32%) in the torsemide group were discharged with either de novo or increased doses antihypertensive medications in the puerperium (lines 293-295). The proportion of those who received magnesium sulfate per study group is depicted in table 3.

f. In Table 3, please address whether women with hypertension at 7-10 days or at 6 weeks had (or did not have) chronic hypertension
Please note table 3 (now Table 4) has been amended to answer your query.
Please also address whether women were discharged from the hospital on other medication to control blood pressure
Please see response for e.

5. Discussion.
a. The opening (summary) statement is confusing as written. The authors write that they failed to reject their hypothesis of no difference. Suggest rephrasing to clearly state that in their randomized trial, 5 days of torsemide for women with preeclampsia did not have a significant effect on the rate of postpartum hypertension, regardless of disease severity. Please explain how Bayesian analysis could realistically outweigh this.

Please note the opening statement as well as the conclusion in abstract has been rewritten taking in accordance to yours and other Reviewer's suggestions. Bayesian analyses provide different and more clinically relevant information than frequentist p-values. Specifically, with Bayesian analyses we can calculate the probability of a true treatment effect given the data (which is not possible with frequentist analyses). Here, the probability of torsemide reducing the rate of persistent postpartum hypertension by

at least 10% is 78%. This probability of a clinically important reduction may be large enough to indicate benefit from this medication.

b. In the last sentence, the authors write that trials with longer duration of treatment are warranted. However, they had explained that the main limitation of their study was that women were hospitalized for less than 3 days. How would a longer duration of treatment address this?
We believe that larger trials with longer duration of treatment to analyze the effect of torsemide at 6 weeks postpartum (not only at discharge or 5 days) would be clinically relevant.

Reviewer #2: The authors present a double blind, randomized control trial of torsemide for the prevention of persistent postpartum hypertension in women diagnosed with preeclampsia. This is an important study, as persistent postpartum hypertension is associated with adverse and costly outcomes. In this study, women with preeclampsia (without severe features, with severe features, and superimposed) women were randomized to receive either placebo or torsemide for 5 days.

Major Issues, Study Design:
1) The authors define the primary outcome as postpartum hypertension >150/100 on two occasions at least 4 hours apart by day 5 or by the time of hospital discharge. Functionally, the majority of women would have been evaluated at 2-4 days postpartum (typical length of stay for vaginal and cesarean deliveries). Therefore, the authors are assessing the "outcome" before the intervention is complete. This also led to different lengths of exposure to the intervention based on mode of delivery and different outcome assessment based on mode of delivery.
Thank you for your comment. Indeed, we were powered to 5 days based on prior published data. Due to the pragmatic nature of this study (we have no control over the time of discharge), we created two secondary outcome time points in addition to the primary outcome: 7-10 days postpartum and 6 weeks postpartum.

2) The inclusion of women with chronic hypertension is problematic. Women with chronic hypertension by definition have high blood pressure that is not affected by delivery (whereas preeclampsia is expected to resolve with delivery). Therefore, in 25% of women included in the study, the primary outcome of persistent postpartum hypertension may just be a reflection of their underlying disease. Additionally, this outcome will be strongly impacted by antihypertensive use in this population.
We agree that this outcome is likely impacted by the preexisting use of antihypertensives in women with chronic hypertension, however the magnitude of this effect is unknown (particularly in the setting of superimposed preeclampsia). However, as the current ACOG Task Force for Hypertension in Pregnancy states: “In women with preeclampsia or superimposed preeclampsia, BP usually decreases within 48 hours following delivery, but the BP increases again 3-6 days postpartum”, we elected to only exclude those with chronic hypertension without superimposed preeclampsia.

Minor issues, Methods:

1) The definition of preeclampsia with severe features was unclear. It reads as though both severe-range blood pressures and serum laboratory abnormalities were required.
Please note the definition has been revised.

2) Per ACOG Task Force on Hypertension, severe range blood pressure elevations alone are not sufficient for the diagnosis of superimposed preeclampsia in chronic hypertension.
We agree. This statement has also been revised in lines 193 and 202.

3) How was the dose & duration of torsemide selected?
The selected dose of torsemide is equivalent to commonly used doses of furosemide in cases of severe edema (i.e. 40-60 mg per day divided in 2 doses). As discussed in lines 155-162, it is believed that preeclamptic women mobilize an excess of 6-8 liters of fluid from the extravascular to the intravascular space in a relatively short period of time. In addition, since the incidence of immediate puerperal hypertension is bimodal (days 3-6 postpartum), 5 days of treatment with torsemide were considered an appropriate choice.

4) Justify your choice of powering to a 50% reduction in postpartum hypertension.
The study was powered to a 50% reduction due to feasibility.

Minor issues, Results

1) In table 1 and table 2, the number of women with chronic hypertension should be the same as the number of women with superimposed preeclampsia (percentages are different)
Thank you. We have corrected the typo. Please note the new order of tables.

2) The authors report length of stay in hours. However, as mode of delivery is most strongly associated with length of stay, a more appropriate measure would be % of women who remained in hospital longer than expected or % of women who remained in hospital longer than expected due to persistent hypertension.
Thank you. We have added a post-hoc analysis to answer this query on line 299.

3) I would like to see the outcome of discharged on antihypertensives. I assume "acute antihypertensives" are IV antihypertensives.
The latter assumption is correct. Please note that 20 (34%) women in the placebo group and 19 (32%) in the torsemide group were discharged with either de novo or increased doses antihypertensive medications in the puerperium. We have added this analysis on lines 292-295.

Discussion

1) I think instead of the null hypothesis not being "disproven" it could not be "rejected."

We agree. Please note that the discussion has been re-written to a more accurate statement on lines 312-314.

Introduction
No issues

Abstract
No comment

Reviewer #3:

1. In patients on antihypertensive medication, were the medications continued postpartum?
Thank you for your question. The use of medications postpartum was left to the discretion of treating physicians. We report this data now on lines 292-295.

2. The treating physician could decide how to treat severe hypertension postpartum. I assume some patients got acute treatment but some patients likely got started on antihypertensive medication and continued throughout the study period. How many in each group were placed on oral medication for the duration of the postpartum period?
Thank you for the question. Please note that 20 (34%) women in the placebo group and 19 (32%) in the torsemide group were discharged with either de novo or increased doses antihypertensive medications in the puerperium. We have added this analysis on lines 292-295.

3. Were the characteristics of the patients who showed up postpartum similar to the ones that did not?
Yes. Given randomization, baseline characteristics for both groups were similar. Any differences would be due to chance.

STATISTICAL EDITOR'S COMMENTS:

1. lines 10-13, pg 4: Need to identify how many had BP measured in hospital on PP day 5 vs discharge day, for each cohort.
Thank you. We did not create a specific variable for blood pressure at discharge since the duration of stay was unpredictable and beyond the investigator's control. However, we have added a statement in the results section on lines 285-288 showing the percentage of women who had their blood pressure taken on day 5 for each cohort as requested.

2. lines 4-5, pg 11 and lines 8-12, pg 11: Need to clarify for the reader that the sample size and primary outcome were based on a 50% reduction in rate of persistent post partum HTN. The other criteria (at least a 10% reduction in the rate) was achieved, but that was not the how the hypothesis was stated.

Please note a statement to this effect was added to lines 357-360.

3. Fig 1, lines 18-20, pg 11: Should include in the flow diagram the number of women who did not comply in each study arm.
Please note that we have included a new table with the pill compliance breakdown for each cohort (table 1). We feel this is more illustrative.

4. Table 3: For the CI of RR for HTN at 7-10 days, I cannot replicate the results, but rather RR = 1.1 (0.6-2.1); Need to identify whether any of these were significant and note that if NS, cannot generalize the results, since study design did not power for these outcomes.
Thank you. We concur. This variable has been reviewed and updated. We acknowledged that this study is not powered to ascertain differences in this as well as other rare outcomes in line 350.

ASSOCIATE EDITOR'S COMMENTS:

We would welcome a revised manuscript responsive to the above comments. We are asking that the Bayesian analysis be offloaded to Supplemental Digital Content and that you allude to it in only the briefest way in the actual manuscript.
A supplement addressing our Bayesian analysis has been uploaded as requested.

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.
OPT-IN

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

2. 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.

3. This manuscript appears to have been presented at SMFM. Please disclose the name, dates, and location of this meeting on your title page.
SMFM presentation of this study has been disclosed as requested.

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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 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 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.

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 appendixes).

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

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 edit your acknowledgments or provide more information in accordance with 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 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).
Funding for this study was added as requested.

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College 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. 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 a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

16. The Journal's Production Editor had the following comments about the figures in your manuscript:

"Figure 1: Were the exclusion criteria not mutually exclusive? Please upload as a separate figure file on Editorial Manager.
Figure 2: Please include a y-axis and upload the original figure file to Editorial Manager (eps, tiff, jpeg). Items pasted into Word often lose resolution.
Figure 3: Please consider including a y-axis and upload the original figure file to Editorial Manager (eps, tiff, jpeg). Items pasted into Word often lose resolution."

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.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (http://cjs.cadmus.com/da/index.asp) for more direction on digital art preparation.

17. To ensure a quality experience for those viewing supplemental digital content, the journal's publisher suggests that authors submit supplemental digital files no larger than 10 MB each. The exceptions to this rule are audio or video files, which are acceptable up to 100 MB. When submitting text files or tables as supplemental digital content with your revisions, please do not submit PDFs.

***

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 Jul 27, 2018, 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

If you would like your personal information to be removed from the database, please contact the publication office.

Daniel Mosier

From: Oscar Viteri [redacted]
Sent: Thursday, August 9, 2018 10:39 PM
To: Daniel Mosier
Cc: Sibai, Bahaeddine M
Subject: Re: Manuscript Revisions: ONG-18-1103R1
Attachments: 18-1103 Legend.docx; 18-1103R1 ms (8-9-18v4).docx; TrophyBayesianAnalysesSupp8.9.18.docx

Dear Mr. Mosier,

Thank you for your email. Please see answers to the Editor's queries below:

1. LINE 98: Why would edema result from mobilization of fluid from the extravascular to the intravascular space?

- We appreciate this important observation. Indeed, edema occurs as a result of mobilization from intravascular to extravascular space and not viceversa and is a manifestation of fluid retained/accumulated in preeclampsia. We have removed this from the sentence.

1. FIGURE 2: This figure should be moved to supplemental digital content. Please rename the figure “Appendix 2,” and rename Figure 3 “Figure 2.” Please also update the in-text citations and figure legend.

- Figure has been moved to Appendix 2. References to this figure have been updated throughout the manuscript as well as figure legends. Please also note attached the updated Supplement as we expanded on the results of our Bayesian analysis. We also reference to Appendix 2 here. Please let us know if you would agree with this change.
- Citations have been updated throughout the manuscript.

We appreciate your time and assistance in this matter. If you have any additional questions, please do not hesitate to contact us.

Respectfully,

Oscar Viteri MD

On Thu, Aug 9, 2018 at 10:31 AM Daniel Mosier <dmosier@greenjournal.org> wrote:

> Dr. Viteri,
>
> Thank you for responding to the queries in a timely manner. The Editor on your manuscript has a few follow-up questions for you and your co-authors:
>
> 1. LINE 98: Why would edema result from mobilization of fluid from the extravascular to the intravascular space?
> 2. FIGURE 2: This figure should be moved to supplemental digital content. Please rename the figure “Appendix 2,” and rename Figure 3 “Figure 2.” Please also update the in-text citations and figure legend.

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the “Accept all Changes” function in Microsoft Word.

Please let me know if you have any other questions or concerns.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

Obstetrics & Gynecology

Tel: 202-314-2342

From: Oscar Viteri [redacted]
Sent: Wednesday, August 8, 2018 6:45 PM
To: Daniel Mosier <dmosier@greenjournal.org>
Subject: Re: Manuscript Revisions: ONG-18-1103R1

Dear Ms. Mosier,

Thank you for your email. Please see answers to queries below and word document with track changes attached.

Thank you for the opportunity to submit our study to Obstetrics & Gynecology. If you need any additional information, please do not hesitate to contact me.

Sincerely,

Oscar Viteri MD

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.

Thank you. We agree with changes as proposed.

2. LINE 73: Do you mean post-partum? If yes, please change throughout

We have updated an changed throughout.

3. LINE 157: Please here and everywhere in manuscript, replace with "antihypertensive medications"

We have updated and replaced as suggested.

4. LINE 186: Supplementary text was provided with your manuscript. Was this information intended for publication? If so, cite in the text as Appendix 1.

We have cited as requested.

5. LINE 253: We prefer to avoid statements that suggest the study is the first of its kind, so this was deleted.

We concur.

6. TABLE 1: Please delete this Table and in the text simply list median and range for both groups

Table 1 has been removed and compliance median (IQR) is listed in main text under results.

On Tue, Aug 7, 2018 at 2:14 PM Daniel Mosier <dmosier@greenjournal.org> wrote:

> Dear Dr. Viteri,
>
> Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.

2. LINE 73: Do you mean post-partum? If yes, please change throughout

3. LINE 157: Please here and everywhere in manuscript, replace with "antihypertensive medications"

4. LINE 186: Supplementary text was provided with your manuscript. Was this information intended for publication? If so, cite in the text as Appendix 1.

5. LINE 253: We prefer to avoid statements that suggest the study is the first of its kind, so this was deleted.

6. TABLE 1: Please delete this Table and in the text simply list median and range for both groups

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the “Accept all Changes” function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Thursday, August 9th.**

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

Obstetrics & Gynecology

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Web: http://www.greenjournal.org

From: [redacted]
To: Stephanie Casway
Subject: Re: O&G Figure Revision: 18-1103
Date: Wednesday, August 8, 2018 3:58:48 PM

Hello Ms. Casway,

i can acknowledge how this can be confusing. Though these were consented, they were not randomized for those various reasons. Therefore, I think it would be prudent to remove them from the flow diagram to avoid reader's confusion.

I appreciate your assistance.

Oscar

On Wed, Aug 8, 2018 at 7:59 AM Stephanie Casway <SCasway@greenjournal.org> wrote:

> Good Morning Dr. Viteri,
>
> Thank you so much for your reply. We will definitely update the exclusion box to remove the 48 women who were not excluded. I am a little confused as to where these 48 women should go on the flowchart. Are these the same women that were not invited to participate (n=48)? Or, maybe we add an asterisk to one of the boxes and explain why these 48 women were not excluded in the legend?
>
> Thanks so much for your help!
>
> **From:** Oscar Viteri [redacted]
> **Sent:** Tuesday, August 7, 2018 9:11 PM
> **To:** Stephanie Casway <SCasway@greenjournal.org>
> **Subject:** Re: O&G Figure Revision: 18-1103
>
> Good evening Ms. Casway,
>
> Thank you for your email. Figures and legends look good and accurate.
>
> In regards to your query, indeed 47 women declined consent. Of the remaining 48, they all consented but between informed consent and actual randomization they either no longer met inclusion criteria for various reasons (i.e. developed renal failure, received another diuretic, etc. N = 17), or the randomization process took too long and medications could not be provided within the established timeframe (i.e. 24 h, N = 31). Therefore, these patients were not excluded.

Hope this explanation is helpful. If you have any additional questions please do not hesitate to contact me.

Sincerely,

Oscar A. Viteri

On Tue, Aug 7, 2018 at 12:48 PM Stephanie Casway <SCasway@greenjournal.org> wrote:

> Good Afternoon Dr. Viteri,
>
> Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes. In addition, please see our query below.
>
> AQ1: In Figure 1, the values in the exclusion box add up to more than 95. Are these values not mutually exclusive, or should something else be edtied?
>
> PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article's publication.
>
> To avoid a delay, I would be grateful to receive a reply no later than Thursday, 8/9. Thank you for your help.
>
> Best wishes,
>
> Stephanie Casway, MA
> Production Editor
>
> *Obstetrics & Gynecology*
> American College of Obstetricians and Gynecologists

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