OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Jun 25, 2020
To: "Maria Isabel Rodriguez" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1084

RE: Manuscript Number ONG-20-1084

Management of postpartum hemorrhage with a novel agent for uterine tamponade: an early feasibility study

Dear Dr. Rodriguez:

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

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

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Jul 25, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This paper describes a limited proof of concept study to evaluate the use of the Mini-sponge tamponade device in the treatment of post-partum hemorrhage. The investigators modified the existing device (designed for use in trauma) to be used in uterus. IRB approvals were received from all institutions and patient written consent was obtained.

Abstract
1. Lines 75-76: States here that resolution of bleeding occurred "within seconds" but no data on this outcome are presented in the paper. Sound conclusion statement.

Introduction:
2. Describes the clinical issue and why this device might play an important role. Clearly states the objective of the study.

Method:
3. Line 142: Just to clarify the study was conducted from May 20-June 12, 2019. So 827 women presented to Labor and Delivery during this 24 day period? Also the hospital where the study was conducted was not specified.

4. Lines 159-163: Was ease of placement assessed by a survey? If yes, can details about the survey be provided (number of questions, response format).

5. Lines 159-163: How was blood loss estimated (visual inspection, quantitative?)

6. Was any thought given to assess the patient's experience with the device (for example pain or discomfort)? Is this something that should be assessed going forward?

Experience:
7. Line 204: What is "active HIV"? It might be more useful to comment on viral load status or use of anti-retroviral medications in this subgroup.

8. No data on "time to hemostasis" are provided in this section.

Discussion:
9. Was there any contingency planning in the event that the device removal was difficult or incomplete (for example - what if the removal strand were to break off?)

10. Lines 245-246: Who did the investigators share their prototype modification suggestions with - the device manufacturer?

References:
11. The references seem complete.

Table
12. Consider adding "time to hemostasis" to this table.

FIGURES:
13. The addition of the figures is helpful.

Reviewer #2: Thanks for the opportunity to read this -- it's an interesting concept, and could possibly work for PPH. As it stands, this manuscript describes a small series of women who received this novel treatment in response to a diagnosed PPH. The study obviously lacks case numbers and a control group, and so it is very preliminary data. General conclusions regarding ease of placement and removal seem reasonable, even if data on individual providers' "learning" curves are not clear within the Results or Table, and no statistical analyses seem to have been performed. However, it's hard to conclude much regarding efficacy (or safety) with just nine subjects and no control group.

Other thoughts:

- QBL may be preferable to EBL in a scientific study evaluating a PPH intervention.

- Did the authors consider weighing the sponge packs before/after use to see how much blood was soaked up by the device?

- Is the device stopping bleeding or just absorbing the PPH blood until the atonic uterus finally contracts with oxytocin and massage?

- Why was the postpartum CBC drawn on PPD 4-6? One day postpartum might be easier to interpret.

- Also, if this cohort really involved PPH diagnoses prior to device use, then why didn't any subject experience a substantial drop in Hgb from pre-delivery to post-delivery? Example: if case 9 really lost 1.2 liters of blood, it would seem odd for her Hgb to only drop 1 mg/dL ... even if the postpartum draw was up to 6 days later.

Thanks again, and good luck with further study of this device.

Reviewer #3: This feasibility study assesses the usability and preliminary efficacy of a novel device developed to treat postpartum hemorrhage known as the Mini-sponge PPH Device. The authors report on the results of 9 women with estimated blood loss in excess of 500 mL who had the device successfully placed. Placement resulted in "immediate" cessation of bleeding with no need for additional treatment and no adverse events were reported. Based on these results, the authors conclude that further evaluation of the device and comparison to other available products is warranted.

These initial study results are certainly interesting. However, there are some bothersome aspects to the study design, even if this is just an initial feasibility or proof-of-concept study. First and foremost, the definition of PPH is 500 mL based on visual estimation alone (at least from what I can gather). We know this to be a very fallible definition, since providers are notoriously inaccurate when visually estimating blood loss, particularly in the absence of specific training or adjunctive information. It is also not specified that a diagnosis of atony in addition to EBL >500 was requisite for device placement, although I would presume this to be true. Secondly, the relatively expeditious placement of the device (EBL 500-625 mL in the majority of cases) does beg the question of whether additional treatment was really warranted or if self-resolution could explain some of the rapid improvement in bleeding in these patients. And finally, the flexible definition of PPH utilized in the study is mildly problematic. The methods say eligibility requirement was EBL GREATER than 500 mL at delivery, but at least 3 women only had an EBL equal to 500 mL at the time of placement. Not to mention, the definition of PPH has evolved based on ACOG criteria, which deserves some acknowledgement in the manuscript.

While these design limitations would definitely need to be addressed and remedied before a more rigorous evaluation could be undertaken, these preliminary results nonetheless demonstrate that further testing of this device is appropriate, safe and warranted given the potential to improve PPH treatment.

Specific Comments:

Title: "Device" seems more appropriate/descriptive than "agent".

Precis: I would suggest a more specific description of the device rather than just "mini-sponges". Perhaps "a novel mini-sponge tamponade device" or something along those lines.

Introduction: The PPH definition was updated by ACOG in 2017. The reference here is from 1993. I'd suggest a more contemporaneous reference and mention of the ACOG definition.

Methods: This needs some revision. More specific details need to be clarified and added.
--Lines 142-144 mention the exclusion criteria. However, figure 3 has some additional exclusion criteria including active labor and GA that are not mentioned. These criteria need to be concordant and comprehensive.
--I assume this study was performed somewhere in Zambia, but this is not specifically mentioned. In hospital(s) was the study performed? Were there multiple centers?
--Presumably eligibility was "greater than or equal to" 500 mL, not just greater than 500 mL as stated in line 147. Also I assume atony was a requisite requirement for device placement but that is not stated here.
--How much blood does each sponge hold? Are there estimates that can be made for additional blood loss to the device based on how much of the device is retained in the uterus? Can uterine volume by ultrasound be correlated to blood retained in the sponges?
--Presumably estimation of blood loss was just based on visual estimation by the provider? Was any training done for providers to improve their blood loss estimation? This is so important given that visual estimation is known to be fairly inaccurate.

Experience:
--How was cervical dilation measured? By ultrasound? Manual examination by the physician?
--How was complete fill of the uterus defined?
--When was the IM pit given in relation to delivery? Is that routinely given for PPH prophylaxis in all deliveries? How long from IM pit administration to device placement?
--The methods and abstract both mention survey results about ease of placement, but that is not explicitly mentioned here.
--Were any of the sponges expelled prematurely?

Discussion:
--Line 241: What do the authors mean by complicated? Does that just mean a second attempt was required? Is time to placement data available for other balloon tamponade devices?
--What modifications do the authors recommend? This doesn't need to be exhaustive, but to mention and not expound seems like a missed opportunity.

Figure 3: Can the reason for exclusion be detailed in the figure i.e. number of women excluded for each reason?

STATISTICAL EDITOR COMMENTS:

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

Reviewer #4: Abstract, lines 200, 209, 214 : A sample of 9 women is too few to estimate SDa with any precision. Should simply cite either a mean or median with range of values, not a SD.

lines 205-206: Should provide the demographic profiles in Table as on-line material. The treated cohort (n = 9) is too small to allow sufficient statistical power for robust comparisons, so would simply be for qualitative comparisons, not for generalizable conclusions.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

35. “mini sponges” doesn’t really capture the essence of the device you have modified here. Can you enhance this a bit? You have 25 words available in the precis. Maybe “mini-sponge tamponade device”?

76. Please provide specific data rather than “within seconds” if available. As you have the seconds for placements, you likely have it for cessation of bleeding. Do you have any data about other outcomes? Cessation of bleeding could be transient, of course, so it may be more compelling to give information about whether there was any recurrence after initial cessation.

100. Please note that ACOG uses a different definition. The one you cite if from 1993. Please edit.
ACOG Practice Bulletin 183, 2017: Maternal hemorrhage, defined as a cumulative blood loss of greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process, remains the leading cause of maternal mortality worldwide.

112. As you cite time to placement after ID of PPH as a criticism of balloons, make sure you cite similar data for the minisponges. In my experience, the actual placement of the balloon doesn’t take long and you should compare like with like. It’s the identification of the need for the device that is the bulk of the 30 minutes referenced, not the physical act of placing it.

118. Can you better define the population studied included in “traumatic non compressible bleeding”? Is this resulting from trauma like a gun shot wound or MVA or is this intraoperative bleeding and surgical trauma?

123. I need a bit more explanation, as might other readers. Do these sponges absorb the blood and expand and exert their tamponade effect simply by being saturated and expanded in volume so they exert an outward tamponade effect? Is there some hemostatic agent on the sponges? You’ve adapted the device for the uterus but wound cavities and uteri come in different shapes and sizes. Is this a one-size-fits all device?

129. By “routine vaginal examination” do you mean without needing a speculum?

136. Please be consistent in use of capitalization for your device name. If it is a brand name, you can reference it once by it’s brand name and then it should likely be capitalized. If it is a descriptive name, no caps are needed.

147. Was this EBL anytime in the first 24 hours, as you have defined PPH above? One reviewer comments on preference for QBL instead of EBL. As this may be a common concern by readers, please include a statement that QBL is not used in your hospitals. Some readers may not understand the limitations of low resourced birthing centers compared to US centers.

150. Was US used to guide placement of the device or just to confirm adequate uterine fill? Do you have an US image of a uterus with the device in place?

152. Please use United States -English spelling rather than European-English spelling throughout the paper. (Hemorrhage instead of haemorrhage; cesarean instead of caesarean; labor not labour).

157. Please indicate that this 6 day post discharge visit is atypical for your routine OB patients, if that is the case.

164. Somewhere in this paragraph tell us how many mini sponges are within the pouch? Although it seems unlikely, if the pouch breaks, and sponges extruded, the clinician may need to count sponges to make sure they are all present and accounted for.

177. What sort of monitoring for ongoing bleeding happens after sponge deployment? Is there still use of fundal massage in the post partum period with a sponge in place. Presumably, although it should be noted, uterotonics have been used during the treatment of the PPH and before the minisponge device is deployed. Do you continue w/ uterotonics after the sponges are in place? Throughout your section on the experience, please note the statistician’s comments.

214. Please give decision to placement time as well as mean time to place the device. Is your time to place the device started with after the device was opened and in the hands of the investigator?

219. I don’t understand this. If the pouch is within the uterus, how are sponges in the vagina?

220. How did you calculate volume of sponges? Do you use antibiotics in women with sponge placement?

230. What was the information gleaned from the visit/phone call at day 6 post discharge?

Discussion: Please describe endpoints of an RCT that would be appropriate. In your hospital, what are the alternatives available to this device? Do you have the balloon device? If you were going to do an RCT, what would be your comparison arm? Would a non-inferiority trial be adequate? Can you comment on cost?

The third panel of figure 2 is not necessary. Please include a sonographic image of a distended uterus w/ device in place.

EDITORIAL OFFICE COMMENTS:

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

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

4. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, "see Table 1 in Smith et al" (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission for modifications of material — the material will be reprinted in its original form.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

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

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 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. Provide a short title of no more than 45 characters, 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 limit for Procedures and Instruments is 200 words. Please provide a word count.

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

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. Figures:

Figure 1: Is this figure original to this manuscript? If not, please upload a letter of permission granting use in print and online formats.

Figure 2: Is this figure original to this manuscript? If not, please upload a letter of permission granting use in print and online formats. Additionally, please update the legend to indicate what is happening in each image.

Figure 3: No comments.

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:
* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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

***Again, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from

you by Jul 25, 2020, we will assume you wish to withdraw the manuscript from further consideration.***.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

Response to Reviewers

Thank you for your review of our work. We respond below on a point by point basis to the questions raised by the reviewers. Our response is in bold for ease of reference.

Reviewer #1: This paper describes a limited proof of concept study to evaluate the use of the Mini-sponge tamponade device in the treatment of post-partum hemorrhage. The investigators modified the existing device (designed for use in trauma) to be used in uterus. IRB approvals were received from all institutions and patient written consent was obtained.

Abstract

1. Lines 75-76: States here that resolution of bleeding occurred "within seconds" but no data on this outcome are presented in the paper.

We have added language to the Results to reflect this finding and modified the abstract.
Abstract: "In a pilot study, we successfully placed the mini-sponge device into nine women experiencing postpartum hemorrhage following a vaginal birth with resolution of bleeding within a minute."
Results: "For all participants, bleeding stopped in less than a minute."

Method:

3. Line 142: Just to clarify the study was conducted from May 20-June 12, 2019.
So 827 women presented to Labor and Delivery during this 24 day period? Also the hospital where the study was conducted was not specified.

Thank you. The study period and number of women who presented are corrected. We have added that the University Teaching Hospital in Lusaka, Zambia was the study site (Line 143).

4. Lines 159-163: Was ease of placement assessed by a survey? If yes, can details about the survey be provided (number of questions, response format).

This information was filled out by the placing provider as they filled out the participant form. It was a categorical variable. We have added the below detail to the Experience section.
"Ease of placement was assessed by asking the physician whether the placement was easy, moderately difficult, or hard."

5. Lines 159-163: How was blood loss estimated (visual inspection, quantitative?)

The following text has been added : "Blood loss was assessed by visual inspection."

6. Was any thought given to assess the patient's experience with the device (for example pain or discomfort)? Is this something that should be assessed going forward?

Thank you for this suggestion. This is something we plan to formally assess moving forward. All women had unmedicated vaginal births. We asked women informally if they experienced pain with placement, or had any cramping with the device, or if they wanted oral anti-inflammatory tablets. We will formally evaluate this in the next phase.

Experience:

7. Line 204: What is "active HIV"? It might be more useful to comment on viral load status or use of anti-retroviral medications in this subgroup.

We appreciate the point. We did not have information on viral load status or use of ARV, and would aim to include that information in subsequent studies. We have modified this language to indicate that: "Almost half of the women [44% (4/9)] were living with HIV."

8. No data on "time to hemostasis" are provided in this section.
We have added the following information, line 223 "For all participants, bleeding stopped in less than a minute."

Discussion:
9. Was there any contingency planning in the event that the device removal was difficult or incomplete (for example - what if the removal strand were to break off?)
This is an important point, and a concern that was discussed throughout all stages of prototype development. All materials were picked for their tensile strength, and tested to verify that the bags would not break even under extreme circumstances. Plans for a difficult removal included: grasp bag with forceps (ring, Bozeman, placental) under direct ultrasound guidance, or manual removal.

10. Lines 245-246: Who did the investigators share their prototype modification suggestions with - the device manufacturer?
We have edited these lines to indicate who the suggestions were made to.
"Investigators involved in the testing of this initial prototype suggested to the manufacturer several modifications of the design to improve use characteristics."
References:
11. The references seem complete.
Thank you.

Table
12. Consider adding "time to hemostasis" to this table.
We have added time to hemostasis in the text. For all subjects, it was less than one minute.
FIGURES:
13. The addition of the figures is helpful.
We appreciate your review and feedback.

Reviewer #2: Thanks for the opportunity to read this -- it's an interesting concept, and could possibly work for PPH. As it stands, this manuscript describes a small series of women who received this novel treatment in response to a diagnosed PPH. The study obviously lacks case numbers and a control group, and so it is very preliminary data. General conclusions regarding ease of placement and removal seem reasonable, even if data on individual providers' "learning" curves are not clear within the Results or Table, and no statistical analyses seem to have been performed. However, it's hard to conclude much regarding efficacy (or safety) with just nine subjects and no control group.

Other thoughts:

- QBL may be preferable to EBL in a scientific study evaluating a PPH intervention.
This is an important point. For future studies, we will use QBL. QBL was not routinely used at our study site. For this limited, proof of concept study, we relied on EBL.
- Did the authors consider weighing the sponge packs before/after use to see how much blood was soaked up by the device?
Thank you for this suggestion, we will incorporate it in future studies.

- Is the device stopping bleeding or just absorbing the PPH blood until the atonic uterus finally contracts with oxytocin and massage?
In this initial study, we sought to determine whether device could be safely deployed and removed. Given the ethical concerns when testing an investigational device in a low resource setting, it was appropriate to test it in combination with existing therapies available. In future, larger studies we will need to parse this out further.

- Why was the postpartum CBC drawn on PPD 4-6? One day postpartum might be easier to interpret.
We agree. There were multiple logistical challenges in obtaining labs. For future studies, we plan to utilize direct point of care testing and obtain the CBC at 24 hours postpartum.

- Also, if this cohort really involved PPH diagnoses prior to device use, then why didn't any subject experience a substantial drop in Hgb from pre-delivery to post-delivery? Example: if case 9 really lost 1.2 liters of blood, it would seem odd for her Hgb to only drop 1 mg/dL ... even if the postpartum draw was up to 6 days later.
Thank you- we have modified the text to reflect that participant 9 obtained a blood transfusion postpartum.
“Line 229 Participant 9 received a blood transfusion postpartum, given her baseline anemia and EBL of 1200 ml.”

Reviewer #3: This feasibility study assesses the usability and preliminary efficacy of a novel device developed to treat postpartum hemorrhage known as the Mini-sponge PPH Device. The authors report on the results of 9 women with estimated blood loss in excess of 500 mL who had the device successfully placed. Placement resulted in "immediate" cessation of bleeding with no need for additional treatment and no adverse events were reported. Based on these results, the authors conclude that further evaluation of the device and comparison to other available products is warranted.

These initial study results are certainly interesting. However, there are some bothersome aspects to the study design, even if this is just an initial feasibility or proof-of-concept study. First and foremost, the definition of PPH is 500 mL based on visual estimation alone (at least from what I can gather). We know this to be a very fallible definition, since providers are notoriously inaccurate when visually estimating blood loss, particularly in the absence of specific training or adjunctive information. It is also not specified that a diagnosis of atony in addition to EBL >500

was requisite for device placement, although I would presume this to be true. Secondly, the relatively expeditious placement of the device (EBL 500-625 mL in the majority of cases) does beg the question of whether additional treatment was really warranted or if self-resolution could explain some of the rapid improvement in bleeding in these patients. And finally, the flexible definition of PPH
utilized in the study is mildly problematic. The methods say eligibility requirement was EBL GREATER than 500 mL at delivery, but at least 3 women only had an EBL equal to 500 mL at the time of placement. Not to mention, the definition of PPH has evolved based on ACOG criteria, which deserves some acknowledgement in the manuscript.

While these design limitations would definitely need to be addressed and remedied before a more rigorous evaluation could be undertaken, these preliminary results nonetheless demonstrate that further testing of this device is appropriate, safe and warranted given the potential to improve PPH treatment.

Specific Comments:

Title: "Device" seems more appropriate/descriptive than "agent".
Thank you, we have modified the title as suggested.
“Management of postpartum hemorrhage with a novel device for uterine tamponade: an early feasibility study”

Precis: I would suggest a more specific description of the device rather than just "mini-sponges". Perhaps "a novel mini-sponge tamponade device" or something along those lines.
We have modified the Precis as suggested.
“Preliminary testing suggests that a novel mini-sponge tamponade device may be feasible for use in treatment of postpartum hemorrhage.”

Introduction: The PPH definition was updated by ACOG in 2017. The reference here is from 1993. I'd suggest a more contemporaneous reference and mention of the ACOG definition.
Thank you, we have added additional text to reflect that a range of definitions are in use world wide. ACOG’s definition of 1000 ml following a vaginal birth is the standard for births in the US. The WHO guidelines for PPH, updated in 2012, maintain the definition of 500 ml following a vaginal birth. The lower threshold for identifying PPH was important to use in an outside US setting. We agree that diagnosis of PPH early is critical to preventing morbidity and mortality, and these risks are higher in a lower resource setting such as Zambia.
We have corrected the reference cited in the introduction to reflect it is WHO guidance, and added this text to the Discussion to address the reviewer’s point.

“It is important to note that a range of definitions for PPH are used globally. We used the World Health Organization’s definition of PPH being blood loss of 500 ml or greater, given that our study setting was in Zambia.[1] Early diagnosis and swift management of PPH is essential to reducing maternal morbidity and mortality,

particularly in low resource settings where the risks to maternal health are high.[1] The American College of Obstetricians and Gynecologists updated their PPH guidance to reflect a new definition of PPH as greater than or equal to 1000 ml of blood loss or any bleeding that causes hemodynamic stability.[18] Our use of the lower threshold for diagnosing PPH effects the generalizability of our results. Future studies will include a larger number of cases to assess the device's effect in managing more cases with severe PPH."

We have also revised the text to reflect the reviewer's point that our criteria was equal to or greater than 500 ml EBL.

Methods: This needs some revision. More specific details need to be clarified and added.
--Lines 142-144 mention the exclusion criteria. However, figure 3 has some additional exclusion criteria including active labor and GA that are not mentioned. These criteria need to be concordant and comprehensive.
Thank you for catching this error. We have removed gestational age from Figure 3, and in both the figure and narrative clarified that the exclusion criteria was cervical dilation less than 2.5 cm. We have added text to clarify that inability to consent due to active labor was also an exclusion criteria.

--I assume this study was performed somewhere in Zambia, but this is not specifically mentioned. In hospital(s) was the study performed? Were there multiple centers?
We have added language to indicate that the study was conducted at a single site, the University Teaching Hospital in Lusaka, Zambia.
--Presumably eligibility was "greater than or equal to" 500 mL, not just greater than 500 mL as stated in line 147. Also I assume atony was a requisite requirement for device placement but that is not stated here.
Thank you for these points. We have modified the language.
"We followed all enrolled women throughout their labor and delivery; eligibility for device placement was an estimated blood loss equal to or greater than 500 ml due to atony after a vaginal delivery."

--How much blood does each sponge hold? Are there estimates that can be made for additional blood loss to the device based on how much of the device is retained in the uterus? Can uterine volume by ultrasound be correlated to blood retained in the sponges? Presumably estimation of blood loss was just based on visual estimation by the provider? Was any training done for providers to improve their blood loss estimation? This is so important given that visual estimation is known to be fairly inaccurate.
Each device could absorb a maximum of 1200 ml of blood. We had the ability to place a second device if needed, but this was not required in our case series.
We have added language that estimation of blood loss was based on visual inspection by the providers, all experienced obstetrician gynecologists. We agree that visual estimate of blood

loss is challenging, and have added this as a limitation. In future studies, we plan to use QBL and obtain sponge weights.

Experience:
--How was cervical dilation measured? By ultrasound? Manual examination by the physician?
We have added text to clarify.
Line 154, "Cervical dilation was assessed by manual exam."
--How was complete fill of the uterus defined?
We have added text to clarify.
Complete fill of the uterus was defined by inability to place further sponges within the uterus (physical exam) and ultrasound documentation.
--When was the IM pit given in relation to delivery? Is that routinely given for PPH prophylaxis in all deliveries? How long from IM pit administration to device placement?

IM Pitocin was given within five minutes following placental expulsion. It is routinely given for PPH prophylaxis when it is available. The time varied, and was not recorded unfortunately, for time from IM Pitocin administration to device placement.
--The methods and abstract both mention survey results about ease of placement, but that is not explicitly mentioned here.
We have added that information as requested.
"Placement of the device was rated as moderately difficult to easy by providers."

--Were any of the sponges expelled prematurely?
We have added in this detail.
Line 239, "No sponges were prematurely expelled."

Discussion:
--Line 241: What do the authors mean by complicated? Does that just mean a second attempt was required? Is time to placement data available for other balloon tamponade devices?
Thank you, we have clarified the text.
"**A previous multi country study has demonstrated that over half (52.1%) of all uterine balloon placements were complicated, most commonly due to balloon displacement, or they required a second attempt at placement. [9]"**

--What modifications do the authors recommend? This doesn't need to be exhaustive, but to mention and not expound seems like a missed opportunity.
Thank you for the suggestion.
We have added the following text:
"Investigators involved in the testing of this initial prototype suggested to the manufacturer several modifications of the design to improve use characteristics, including reducing the dose of sponge delivered and reducing pressure needed to deploy the sponges."

Figure 3: Can the reason for exclusion be detailed in the figure i.e. number of women excluded for each reason?

Regrettably we did not capture this data separately, and acknowledge this was an oversight.

STATISTICAL EDITOR COMMENTS:

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

Reviewer #4: Abstract, lines 200, 209, 214 : A sample of 9 women is too few to estimate SD with any precision. Should simply cite either a mean or median with range of values, not a SD.
Thank you for this feedback, we have made the suggested changes.

lines 205-206: Should provide the demographic profiles in Table as on-line material. The treated cohort (n = 9) is too small to allow sufficient statistical power for robust comparisons, so would simply be for qualitative comparisons, not for generalizable conclusions.
We are happy for Table 1 to be an online, supplementary Table if that is the Editor's preference.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.
Thank you, we have reviewed the formatting carefully.

Numbers below refer to line numbers.

35. "mini sponges" doesn't really capture the essence of the device you have modified here. Can you enhance this a bit? You have 25 words available in the precis. Maybe "mini-sponge tamponade device"?
We appreciate the suggestion and have modified the Precis as follows: "Preliminary testing suggests that a mini-sponge tamponade device may be feasible for use in treatment of postpartum hemorrhage."

76. Please provide specific data rather than "within seconds" if available. As you have the seconds for placements, you likely have it for cessation of bleeding. Do you have any data about other outcomes? Cessation of bleeding could be transient, of course, so it may be more compelling to give information about whether there was any recurrence after initial cessation.

We have provided additional information as requested.

100. Please note that ACOG uses a different definition. The one you cite if from 1993. Please edit.
ACOG Practice Bulletin 183, 2017: Maternal hemorrhage, defined as a cumulative blood loss of greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process, remains the leading cause of maternal mortality worldwide.

Thank you, Reviewer 3 also raised this point. We have added the proper citation to our definition (WHO Guidelines 2012), and added text to the Discussion about why we chose the WHO definition, and how it varies from ACOG's US definition. Given the location was outside of the US, and in a lower resource setting, it was thought to be most appropriate to use a more conservative, international definition of PPH when testing an investigational device.
Discussion, lines 266-276

"It is important to note that a range of definitions for PPH are used globally. We used the World Health Organization's definition of PPH being blood loss of 500 ml or greater, given that our study setting was in Zambia.[1] Early diagnosis and swift management of PPH is essential to reducing maternal morbidity and mortality, particularly in low resource settings where the risks to maternal health are high.[1] The American College of Obstetricians and Gynecologists updated their PPH guidance to reflect a new definition of PPH as greater than or equal to 1000 ml of blood loss or any bleeding that causes hemodynamic stability.[18] Our use of the lower threshold for diagnosing PPH effects the generalizability of our results. Future studies will include a larger number of cases to assess the device's effect in managing more cases with severe PPH."

112. As you cite time to placement after ID of PPH as a criticism of balloons, make sure you cite similar data for the minisponges. In my experience, the actual placement of the balloon doesn't take long and you should compare like with like. It's the identification of the need for the device that is the bulk of the 30 minutes referenced, not the physical act of placing it.
Thank you, this is an important point. We did not collect data on time after ID of PPH to placement of device. We will be sure to do so in future studies. We have edited the discussion to reflect this point.

"This rapid placement time, even with first use, reflects an important comparative advantage of the mini-sponge device; it is known that reducing time from diagnosis to placement of all uterine tamponade balloons reduces morbidity (9). A previous multi

country study has demonstrated that over half (52.1%) of all condom balloon placements were complicated, most commonly due to balloon displacement, or they required a second attempt at placement. [9]"

118. Can you better define the population studied included in "traumatic non compressible bleeding"? Is this resulting from trauma like a gun shot wound or MVA or is this intraoperative bleeding and surgical trauma?
We have added additional text to explain this. The published evidence comes from the battlefield. It has been used for intraoperative bleeding (large liver lacerations) but that is unpublished data, so we do not cite it.
"Data from its use in battlefield or trauma settings indicate that the mini-sponge device is simple to deploy with minimal training and experience. The types of injuries treated in trauma settings include penetrating injuries from shrapnel, gunshots or motor vehicle accidents."

123. I need a bit more explanation, as might other readers. Do these sponges absorb the blood and expand and exert their tamponade effect simply by being saturated and expanded in volume so they exert an outward tamponade effect? Is there some hemostatic agent on the sponges? You've adapted the device for the uterus but wound cavities and uteri come in different shapes and sizes. Is this a one-size-fits all device?
We have added additional explanation to address this point.

"The compressed sponges, when inserted into a wound or uterine cavity conform to the unique shape of that space, allowing them to effectively treat a wide range of types of bleeding. They do not have a fixed shape such as other uterine balloon tamponade devices.[15] In a bleeding wound, the mini-sponges rapidly absorb blood, which causes the sponges to expand and exert outward pressure. The sponges have been observed to remain expanded and maintaining pressure for greater than 24 hours.[16] The mini-sponges are distinct from routine laparotomy sponges, which when saturated, become smaller in size. The effect is not due to a hemostatic agent, but simply holding and maintaining pressure."

129. By "routine vaginal examination" do you mean without needing a speculum?
We have clarified that we mean digital or manual exam.

136. Please be consistent in use of capitalization for your device name. If it is a brand name, you can reference it once by it's brand name and then it should likely be capitalized. If it is a descriptive name, no caps are needed.
Thank you, we are using a descriptive name and have adjusted the capitalization.

147. Was this EBL anytime in the first 24 hours, as you have defined PPH above? One reviewer comments on preference for QBL instead of EBL. As this may be a common concern by readers,

please include a statement that QBL is not used in your hospitals. Some readers may not understand the limitations of low resourced birthing centers compared to US centers.
Thank you, we have clarified that this was EBL anytime in the first 24 hours, although all cases occurred within 30 minutes of vaginal birth. We have added detail on QBL.

150. Was US used to guide placement of the device or just to confirm adequate uterine fill? Do you have an US image of a uterus with the device in place?

It was just used for verifying placement.

152. Please use United States -English spelling rather than European-English spelling throughout the paper. (Hemorrhage instead of haemorrhage; cesarean instead of caesarean; labor not labour).

Apologies, we have made this correction.
157. Please indicate that this 6 day post discharge visit is atypical for your routine OB patients, if that is the case.
We amended the methods as requested.
"We followed participants receiving the device from delivery until hospital discharge. For the purpose of the study only, we asked participants to return for follow up approximately 6 days post discharge, this was not a standard time for a visit."

164. Somewhere in this paragraph tell us how many mini sponges are within the pouch? Although it seems unlikely, if the pouch breaks, and sponges extruded, the clinician may need to count sponges to make sure they are all present and accounted for.
We have added the following language to address this point.
"Approximately 400 mini-sponges are contained within each pouch. A removal strand is attached to the pouch to facilitate post-treatment removal by means of gentle traction, without additional procedures. The pouch was inspected upon removal to confirm that it was intact, and that all sponges had been removed. In the unlikely event that a pouch broke, the sponges would be visible on ultrasound and removed by suction or forceps."
And
"All dressings were visually inspected - sponge pouch was intact in all cases."

177. What sort of monitoring for ongoing bleeding happens after sponge deployment? Is there still use of fundal massage in the post partum period with a sponge in place. Presumably, although it should be noted, uterotonics have been used during the treatment of the PPH and before the minisponge device is deployed. Do you continue w/ uterotonics after the sponges are in place? Throughout your section on the experience, please note the statistician's comments.
We have added language to the Experience section to indicate how we monitored for ongoing bleeding and to reflect that ongoing uterotonics was at the discretion of the clinical time. The device was used as an adjunct to their standard clinical management.
"Women were monitored by visual , physical (fundal height and massage), and ultrasound to confirm that the bleeding had stopped and did not recur over the first 24 hours postpartum."

214. Please give decision to placement time as well as mean time to place the device. Is your time to place the device started with after the device was opened and in the hands of the investigator?
Unfortunately we do not have time to decision to time to placement. We will capture that in future studies.

219. I don't understand this. If the pouch is within the uterus, how are sponges in the vagina?
We have added language to clarify that the pouch was too large- it filled both the uterus and extended into the vagina.

220. How did you calculate volume of sponges? Do you use antibiotics in women with sponge placement?
We measured volume by obtaining 2 measurements in one plane, and a third measurement in a perpendicular plane, as done with gestational sac or follicular measurements. Antibiotics were used at the discretion of the clinical team, but were made available by the research team if desired (antibiotics are frequently not available at the study site). All women received a dose of IV cefazolin.
Information is added in Lines 240-250.

230. What was the information gleaned from the visit/phone call at day 6 post discharge?

"Participants were asked to follow-up at six days postpartum, which was not a standard visit time. The purpose of this visit was to confirm safety of the device: that women did not have pain, evidence of infection or ongoing bleeding greater than normal lochia." Lines 260-265

Discussion: Please describe endpoints of an RCT that would be appropriate. In your hospital, what are the alternatives available to this device? Do you have the balloon device? If you were going to do an RCT, what would be your comparison arm? Would a non-inferiority trial be adequate? Can you comment on cost?
We have added additional information on what the next steps would be.
"The condom uterine balloon tamponade is available in Zambia, although not commonly used by practitioners at University Teaching Hospital. Following a pivotal study with a larger sample of cases, a comparative study between the mini-sponge PPH device and the condom uterine balloon tamponade is planned, with a primary outcome of time from diagnosis of PPH to cessation of bleeding."

AND
"This device is being developed to offer a low cost, easy to use product that is of similar or greater efficacy than the condom uterine balloon tamponade. It does not require electricity or additional equipment (e.g stetrile water, foley catheter) to place, which may facilitate its use in low- and high- resource settings."

The third panel of figure 2 is not necessary. Please include a sonographic image of a distended uterus w/ device in place.

We have included a potential Figure 4, that is an ultrasound image. As we are not certain it is of sufficient quality for publication, we leave the third panel of Figure 2 in place, and will allow the Editor to choose if it is suitable.

EDITORIAL OFFICE COMMENTS:

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

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

We have made this edit.
4. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.
We include written permission to use Figure 2. They were created for the manuscript, but it is anticipated they will be used in additional materials.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request;

please consult the publisher directly for more information. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, "see Table 1 in Smith et al" (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission
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When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
We include in our article and response that this device is being developed for global use, and the study was conducted outside of the United States.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 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.
Our title is 93 characters with spaces and includes type of study.

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).

All acknowledgments are aligned with journal standards.
9. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.
We have included this on the title page.
“Mini sponge device for uterine tamponade”

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 limit for Procedures and Instruments is 200 words. Please provide a word count.
The word count is 200 and is listed on the title page.

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.
The virgule symbol is only used when referring to data or measurements.
13. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.
We have made this change

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. Figures:

Figure 1: Is this figure original to this manuscript? If not, please upload a letter of permission granting use in print and online formats.
We have included this letter.
Figure 2: Is this figure original to this manuscript? If not, please upload a letter of permission granting use in print and online formats. Additionally, please update the legend to indicate what is happening in each image.
We have included this letter.

Figure 3: No comments.

Date: Aug 05, 2020
To: "Maria Isabel Rodriguez" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1084R1

RE: Manuscript Number ONG-20-1084R1

Management of postpartum hemorrhage with a novel tamponade device: an early feasibility study

Dear Dr. Rodriguez:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. The latest version of your manuscript is uploaded to your Author account in Editorial Manager (8-5-20v2). Please contact me by email if you cannot locate this file.

Please track your changes and leave the ones made by the Editorial Office. Your next version should be uploaded to Editorial Manager with a point-by-point reply letter to the comments below.

Your next version will be due by August 19.

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. Title: Please see the recommended change in title. This edit was made to conform to journal style.

3. Author Byline: Please add any academic degrees to the byline for each author you would like to include (no more than two per person).

4. The following co-authors will need to complete our electronic Copyright Transfer Agreement, which was sent to them by email through Editorial Manager (EM@greenjournal.org). Once the form is complete, please add their disclosures to the "Financial Disclosure" section.
- Mary Bullard
- Andrew D. Barofsky
- Tola Marts

5. Financial Disclosure: Please review the Financial Disclosure to confirm that the statements are correct.

6. Precis: I think it's relevant to add the suggested words to the precis.

7. Line 82-83: Please be sure these data are stated in the body of your paper. Statements and data that appear in the Abstract must also appear in the body text for consistency.

8. Line 96 (Length): The word limit for a procedures and instruments paper is 2000 and yours, without the references included is about 3400. I've made some suggestions for editing your paper as examples but I've not done so for the entire paper. Please use these examples to help guide you in the editing of your paper. The introduction should be about 1 page in length.

9. Line 98: First sentence can be deleted. Just start w/ "Post partum hemorrhage…". The references of course will need to be adjusted

I recommend adjusting the first two paragraphs this way:

Postpartum hemorrhage, defined by the World Health Organization as blood loss of 500 ml or more within 24 hours of birth, is responsible for a quarter of all maternal deaths globally. Although there are multiple strategies to prevent and treat it, uterine atony is responsible for the bulk of postpartum hemorrhage.

Uterine tamponade to treat atony has been attempted using sterile gauze, inflated Foley catheters, condom catheters and silicone obstetrical balloons. None of these are ideal, may be difficult to use without patient anesthesia, and may difficult to stock in low resourced settings.

Then spend some of your words on the description of the minisponge device (although this can be shortened some as well).

10. Line 122: Please note the recommended changes. You will need to adjust the references as my edit deleted reference 15.

11. Line 138: A lot of information stated here overlaps with what you've written in the later in the text. Please consolidate and edit for brevity. I would put all of this in the methods section and I would put all of it at the beginning of the methods section, followed by a description of the enrollment, etc of patients.

12. Line 147: Since your study is industry-funded, we require this paragraph to be included in your paper. Please add more details about how Obstetrx Inc. was involved or not involved in the study. (It's okay to repeat what is in the Financial Disclosure.) Please also edit this text so that the paragraph reflects YOUR reality.

13. Line 190: Please confirm this edit. This was from your response to reviewers letter.

14. Line 197: When was this question asked? Could you state when this occurred?

15. Line 233: What do you mean by "independent study team"? This needs to be clarified due to industry sponsorship.

16. Line 269: How soon after device placement would this be measured? Would all of the sponges been expanded by then? Given that you said they could expand to 400 cc and a lot was outside the uterus, will you adjust the size of the pouch in the future?

17. Line 310: Reference 18 does not point to an ACOG reference. Would you update the reference as needed?

18. Line 321: Can you tell us the cost here?

Best,
Randi Zung for Dr. Chescheir
Editorial Administrator
Obstetrics & Gynecology

_____

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.
We have reviewed the edits and agree.
2. Title: Please see the recommended change in title. This edit was made to conform to journal style.
Perfect, thank you.
3. Author Byline: Please add any academic degrees to the byline for each author you would like to include (no more than two per person).
Thank you, this is done.
4. The following co-authors will need to complete our electronic Copyright Transfer Agreement, which was sent to them by email through Editorial Manager (EM@greenjournal.org). Once the form is complete, please add their disclosures to the "Financial Disclosure" section.

- Mary Bullard
- Andrew D. Barofsky
- Tola Marts

I have again requested them to complete it.
5. Financial Disclosure: Please review the Financial Disclosure to confirm that the statements are correct.
We have reviewed and edited it.

6. Precis: I think it's relevant to add the suggested words to the precis.
We are ok with this addition.
7. Line 82-83: Please be sure these data are stated in the body of your paper. Statements and data that appear in the Abstract must also appear in the body text for consistency.
We have added this information to the methods.
8. Line 96 (Length): The word limit for a procedures and instruments paper is 2000 and yours, without the references included is about 3400. I've made some suggestions for editing your paper as examples but I've not done so for the entire paper. Please use these examples to help guide you in the editing of your paper. The introduction should be about 1 page in length.

We have cut the length of the manuscript to 2000 words and appreciate your edits.
9. Line 98: First sentence can be deleted. Just start w/ "Post partum hemorrhage…". The references of course will need to be adjusted

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Uterine tamponade to treat atony has been attempted using sterile gauze, inflated Foley catheters, condom catheters and silicone obstetrical balloons. None of these are ideal, may

be difficult to use without patient anesthesia, and may difficult to stock in low resourced settings.

Then spend some of your words on the description of the minisponge device (although this can be shortened some as well).

Thank you. We have incorporated these changes.
10. Line 122: Please note the recommended changes. You will need to adjust the references as my edit deleted reference 15.
We have updated the references.
11. Line 138: A lot of information stated here overlaps with what you've written in the later in the text. Please consolidate and edit for brevity. I would put all of this in the methods section and I would put all of it at the beginning of the methods section, followed by a description of the enrollment, etc of patients.
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12. Line 147: Since your study is industry-funded, we require this paragraph to be included in your paper. Please add more details about how Obstetrx Inc. was involved or not involved in the study. (It's okay to repeat what is in the Financial Disclosure.) Please also edit this text so that the paragraph reflects YOUR reality.
This has been done.
13. Line 190: Please confirm this edit. This was from your response to reviewers letter.
Correct.
14. Line 197: When was this question asked? Could you state when this occurred?
We have clarified that this was immediately following placement.
15. Line 233: What do you mean by "independent study team"? This needs to be clarified due to industry sponsorship.
We have clarified that the sponsor was not involved in data collection or analysis.
16. Line 269: How soon after device placement would this be measured? Would all of the sponges been expanded by then? Given that you said they could expand to 400 cc and a lot was outside the uterus, will you adjust the size of the pouch in the future?
We have added text to clarify that the measurement was immediately after placement, and directly prior to removal.
Reducing the size of the pouch and sponges delivered is a key update to the device. We reference this in the discussion.
17. Line 310: Reference 18 does not point to an ACOG reference. Would you update the reference as needed?
Oops. This has been updated!
18. Line 321: Can you tell us the cost here?

It is too early in device development to give a cost. The goal is a pricepoint at or below the condom uterine balloon tamponade. We reference that in the Discussion.