

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)*
- Email correspondence between the editorial office and the authors*

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

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: Oct 26, 2018
To: "Katherine Whitehouse" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1806

RE: Manuscript Number ONG-18-1806

Effects of prophylactic oxytocin on bleeding outcomes in women undergoing dilation and evacuation: a randomized, double-blinded, placebo-controlled trial

Dear Dr. Whitehouse:

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 Nov 16, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

In this manuscript, the authors present an RCT investigating the effect of oxytocin on hemorrhage interventions following a D&E. The author state no such like study has been done in the past and my quick review endorses this view. Arguing against the use of oxytocin in this context is that there may not be receptors to induce the effect seen at term. Nevertheless, anecdotally surgeons have used oxytocin in this setting and thus the impetus for the study. The study appears to be well done. Cohort allocation concealment was ensured insofar as the study drug was indistinguishable from placebo. The randomization sequence was pretty good although the "varying block sizes" could be more specific (what was the block size range?). I have the following specific questions/comments:

- 1) The primary outcome is odd. It would seem much easier to have used a continuous variable such as blood loss particularly given the lengths used in this study to estimate that blood loss. The "frequency of interventions" seems unnecessarily imprecise. More explanation about this choice of primary outcome would be helpful - beyond just admitting this is a limitation. This choice of outcome made an otherwise apparently successful intervention a bust. Given the trouble with this outcome your power analysis might be off leading to the conflicted conclusion identified relative to the past retrospective study. The whole impetus of the study seems odd relative to the past analysis.
 - 2) The cost comments in the introduction seem out of place insofar as they are mentioned nowhere else and this outcome isn't assessed as part of the study.
 - 3) When were study surgeons instructed on the algorithm of interventions? Were the interventions and the order used agreed upon by all the study surgeons before the study? Are there any data on how obedient the surgeons were to the algorithm?
 - 4) The paragraph starting on line 253 details several studies that are unsupportive of using oxytocin in this context. Given the 2x greater blood loss seen in this trial across cohorts why wouldn't the 730 women studied retrospectively (by the authors) have a similar finding? For that matter anecdote would have seemingly led more than 19% of surgeons to identify oxytocin's benefit. Some comment should be devoted to trying to explain this matter.
 - 5) Any comment on the features of those women who declined to participate in the study?
- Overall, reasonable study but odd outcome that rendered a negative result. Relative to the existing literature, this study may only deepen the mystery as to what is the best practice in this context.

REVIEWER #2:

In this well-done RCT, Whitehouse and colleagues demonstrate that prophylactic IV oxytocin for D&Es 18-24 weeks significantly reduces MBL and other relevant clinical outcomes, even if they failed to achieve statistical significance for their primary outcome of decreased interventions to control excess bleeding.

Abstract. No edits, clear and concise.

Introduction: The authors succinctly describe the scant literature that exists in this area, and the limitations of that research, making a compelling case for the importance and value of testing their hypothesis.

Methods: I commend the researchers on using trainees on this project, as I have worked at centers that exclude trainees on RCTs in abortion research, which leads to results which are not generalizable outside of high-volume surgical sites staffed by very experienced providers. Also, the methods for collecting MBL is very robust and clearly explained.

Line 172-177: This information does not relate to how MBL was collected, and it should be separated to an additional paragraph. The 2nd half of line 177 and 178 should be in the same paragraph as lines 169-172 about MBL collection.

Results:

Line 211: I would replace "population" with "sample"

Line 226-7: Can you run any significance testing on those that required interventions beyond uterine massage?

Tables & Figures:

Table 1: You can remove the p-value

Discussion: Some of the exclusions listed in the methods restricted those patients at the highest risk of hemorrhage, likely leading to bias towards the null. The intervention would likely have even more of an effect if used in high risk patients or in a research sample that included higher risk patients.

Overall, the study makes a very compelling case for the use of prophylactic oxytocin, even if the intervention did not significantly decrease the rate of interventions used for control of bleeding. All other bleeding outcomes showed improvement with the use of oxytocin without any impact on the patient experience. Throughout my training and early career, I have continuously heard about the uncertain use of oxytocin prior to term due to concerns about oxytocin receptors expression, but this study provides strong evidence on the benefit of oxytocin for D&Es, starting at 18 weeks.

REVIEWER #3:

1. A randomised study involving the Universities of Hawaii and Washington; the data does not give the numbers of patients recruited to the study by each centre. It involves women undergoing D&E at 18-24 weeks or evacuation of cases of fetal death either under general anaesthesia or deep sedation. Sixty minutes before surgery and 60 minutes after surgery patients were questioned about pain and satisfaction with the procedure. The object of the study was to determine whether the administration of oxytocin 30 units in 500 mL or placebo given over 15 minutes at the start of the surgical procedure (i) influenced the need for interventions to control present or anticipated excess bleeding, (ii) reduced excess blood loss (>500 mL and >1000 mL), (iii) reduced the need for blood transfusion and (iv) reduced serious injury or death. The duration of the surgery was also recorded.

2. Obtaining consent for the study This appears to have been obtained following admission on the day for surgery. This suggests the patients had little time to contemplate the request and the possibility of some degree of coercion could have existed. It would be reassuring to know that potential patients/participants of the study had been given written information relating to the study at least 24 hours in advance of their giving consent, a frequent requirement by Ethical Review Boards except for emergency procedures.

3. Inclusion of cases of intrauterine fetal demise Since a coagulopathy can develop in such cases this inclusion potentially compromises the study. Table 1 indicates only 5 cases were recruited so excluding these from the analyses would reduce an unnecessary potential confounding factor. According to Table 4, 2 of 3 (67%) cases of intrauterine fetal death treated with placebo received an intervention to control bleeding.

4. Decision to intervene was based on clinical judgment and signs of impending haemorrhage As observed in the Discussion, this subjective decision has the potential to compromise outcome analyses. It would therefore be reassuring to know that these subjective decisions were similar across both study sites. The figures provided in Table 4 suggest they were not equivalent. A similar analysis for procedure times across the two study sites would also be worthy of recording for reassurance.

5. Post procedure patient satisfaction Since patients' recovery from general anaesthesia or deep sedation is variable, how confident were the researchers full recovery had occurred before enquiry into patient satisfaction was recorded?

STATISTICAL EDITOR'S COMMENTS:

1. lines 39-41: Need to state the primary outcome first.
2. lines 223-225: 15/19 should be cited as proportion with CIs, since the sample is relatively small.
3. Table 1: Since this is an RCT, there is no need to statistically compare the cohorts, any differences should be due to random chance. Need units of BMI.
4. Table 2, lines 190-193: Need to clearly demarcate the primary outcome from the secondary ones. The differences in uterotonic medication and intrauterine tamponade should be tested with Fisher's test, not chi-square. The blood loss distributions are highly skewed. Rather than testing with student's t, should use a non-parametric stats test. Were procedure durations normally distributed? If not, should cite as median(range) and test non-parametrically. Should clarify in this table and others, when Fisher's test was used.
5. Table 3: Were the VAS pain scores and Likert scores normally distributed? If not, and given the sample sizes, should cite as median(range) and test non-parametrically.
6. Table 4: Need units for BMI. Many of the comparisons require Fisher's test. The small sample sizes invalidate use of student's t, should use non-parametric testing

ASSOCIATE EDITOR - GYN:

- 1) Please report out results using RR and 95% CI (rather than p-values) - as suggested by STAT editor
- 2) The Discussion would benefit from a reflection on the study design parameters - ie sample size calculations - and how the findings/conclusions here might have differed with a larger group. Also, since oxytocin is a widely used drug with few reasons not to use it, and secondary outcomes appearing to favor its usage, what should be its role in this population?

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

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

2. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the January 2018 issue). Please note:

- a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.
- b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.
- c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.
- d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; <http://www.icmje.org>):

* Substantial contributions to the conception or design of the work;

OR

the acquisition, analysis, or interpretation of data for the work;

AND

* Drafting the work or revising it critically for important intellectual content;

AND

* Final approval of the version to be published;

AND

* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The author agreement form is available online at <http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

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

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: 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.

6. 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).

7. 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.

8. 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.

9. 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.

10. 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.

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

"Figure 1: Note that this is a box. Please update manuscript to reflect this change."

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.

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 Nov 16, 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

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



November 23, 2018

Dr. Nancy Chescheir
Editor-in-chief
Obstetrics & Gynecology

Dear Dr. Chescheir,

Thank you for your time spent in reviewing our manuscript #ONG-18-1806, "Effects of prophylactic oxytocin on bleeding outcomes in women undergoing dilation and evacuation: a randomized, double-blinded, placebo-controlled trial" by Katherine Whitehouse, Mary Tschann, Reni Soon, James Davis, Elizabeth Micks, Jennifer Salcedo, Michael Savala, and Bliss Kaneshiro.

Per the suggestion of your reviewers and editors, we have made a number of changes to the manuscript and corresponding tables and figures. Please see the below point-by-point response to the reviewer comments and explanation of changes made.

Thank you for your consideration and I look forward to hearing from you again soon.

Sincerely,

Kate Whitehouse, DO, MS

Response to reviewers' comments on ONG-18-1806, "Effects of prophylactic oxytocin on bleeding outcomes in women undergoing dilation and evacuation: a randomized, double-blinded, placebo-controlled trial"

REVIEWER #1:

1) In this manuscript, the authors present an RCT investigating the effect of oxytocin on hemorrhage interventions following a D&E. The authors state no such like study has been done in the past and my quick review endorses this view. Arguing against the use of oxytocin in this context is that there may not be receptors to induce the effect seen at term. Nevertheless, anecdotally surgeons have used oxytocin in this setting and thus the impetus for the study. The study appears to be well done. Cohort allocation concealment was ensured insofar as the study drug was indistinguishable from placebo. The randomization sequence was pretty good although the "varying block sizes" could be more specific (what was the block size range?). I have the following specific questions/comments:

The primary outcome is odd. It would seem much easier to have used a continuous variable such as blood loss particularly given the lengths used in this study to estimate that blood loss. The "frequency of interventions" seems unnecessarily imprecise. More explanation about this choice of primary outcome would be helpful - beyond just admitting this is a limitation. This choice of outcome made an otherwise apparently successful intervention a bust. Given the trouble with this outcome your power analysis might be off leading to the conflicted conclusion identified relative to the past retrospective study. The whole impetus of the study seems odd relative to the past analysis.

Response:

We provided the following additional justification as to why we chose this primary outcome. In addition, we added information about block sizes.

Old text

"The study sample size was based on our primary outcome, the rate of intervention to control blood loss. In a study by Micks et al., investigators found the baseline need for intervention to be 16% when skilled abortion providers performed D&E procedures.¹⁷"

"A researcher not directly involved in the study prepared a computer-generated random number scheme in varying block sizes specific to each site and placed them in sequentially numbered sealed, opaque envelopes."

New text:

"Our primary outcome was the rate of interventions to control blood loss. We believed this outcome was more clinically relevant than blood loss because it is unclear what amount of blood loss is clinically meaningful in the D&E

population. We felt that measuring the need for additional interventions would allow a comparison of the clinical consequences of use or nonuse of prophylactic oxytocin. Our rationale for study sample size was based on a study by Micks et al. in which investigators used the same primary outcome and found a baseline need for intervention of 16% when skilled abortion providers performed D&E procedures.¹⁷

“A researcher not directly involved in the study prepared a computer-generated random number scheme specific to each site in random varying block sizes of four, six, and eight, and placed them in sequentially numbered sealed, opaque envelopes.”

2) The cost comments in the introduction seem out of place insofar as they are mentioned nowhere else and this outcome isn't assessed as part of the study.

Response:

We have removed the segments that mention cost.

Old text:

“Unnecessary use of oxytocin could raise abortion-related healthcare costs both directly, via the price of the medication, and indirectly, via the cost of treating related adverse events or side effects. Given the increased cost and the lack of evidence supporting routine use...”

New text:

“Given the lack of evidence supporting routine use of oxytocin to prevent excess bleeding during D&E...”

3) When were study surgeons instructed on the algorithm of interventions? Were the interventions and the order used agreed upon by all the study surgeons before the study? Are there any data on how obedient the surgeons were to the algorithm?

Response:

Surgeons did agree upon and were trained on the intervention algorithm before recruiting participants. Surgeons overall adhered to the algorithm; as described in Table 4: 19 participants required an intervention, 15/19 received only uterine massage (first step in the algorithm), 3/19 received massage + uterotonic medication (second step in algorithm), and 1/19 required intrauterine tamponade in addition to massage and uterotonic medication. One participant received only a uterotonic medication. We have updated the text to clarify this per below.

Old text:

“We instructed providers to follow an algorithm (Figure 1) when intervening to control excess blood loss; we noted deviations from the algorithm or contraindications to mediations when applicable.”

“In accordance with our algorithm (Figure 1), surgeons most frequently used uterine massage to intervene for bleeding...”

New text:

“Surgeons taking part in the study agreed upon and were trained at study initiation to use an evidence based algorithm (Box 1) when intervening to control excess blood loss...”

“Overall, surgeons adhered to the intervention algorithm (Box 1), most frequently using uterine massage to intervene for bleeding, followed by uterotonics, and in one case, intrauterine tamponade. One participant received just a uterotonic, without massage.”

4) The paragraph starting on line 253 details several studies that are unsupportive of using oxytocin in this context. Given the 2x greater blood loss seen in this trial across cohorts why wouldn't the 730 women studied retrospectively (by the authors) have a similar finding? For that matter anecdote would have seemingly led more than 19% of surgeons to identify oxytocin's benefit. Some comment should be devoted to trying to explain this matter.

Response:

We have provided a justification for the discrepancy between the findings in the two studies as below.

Old text:

“In that study, we were unable to identify an association between prophylactic oxytocin use and excessive blood loss or other complications.”

New text:

“In that study, we were unable to identify an association between prophylactic oxytocin use and excessive blood loss or other complications, however blood loss was not actually measured and, as previously mentioned, surgeons typically underestimate blood loss.”

5) Any comment on the features of those women who declined to participate in the study?

Response:

We did not capture demographic data on women who declined to participate in our study.

REVIEWER #2:

In this well-done RCT, Whitehouse and colleagues demonstrate that prophylactic IV oxytocin for D&Es 18-24 weeks significantly reduces MBL and other relevant clinical outcomes, even if they failed to achieve statistical significance for their primary outcome of decreased interventions to control excess bleeding.

Abstract. No edits, clear and concise.

Introduction: The authors succinctly describe the scant literature that exists in this area, and the limitations of that research, making a compelling case for the importance and value of testing their hypothesis.

Methods: I commend the researchers on using trainees on this project, as I have worked at centers that exclude trainees on RCTs in abortion research, which leads to results which are not generalizable outside of high-volume surgical sites staffed by very experienced providers. Also, the methods for collecting MBL is very robust and clearly explained.

6) Line 172-177: This information does not relate to how MBL was collected, and it should be separated to an additional paragraph. The 2nd half of line 177 and 178 should be in the same paragraph as lines 169-172 about MBL collection.

Response:

We have reordered the text per your suggestion

Old text:

"We performed a measured blood loss (MBL) in the following fashion: a strainer was used to separate products of conception and blood so that volume of blood could be measured; gauze and sponges were weighed to determine additional blood loss. Staff gave women 15 mg of intravenous ketorolac or 500 mg of oral naproxen, unless contraindications existed, and administered additional pain medications or anti-emetics as needed to achieve optimal patient comfort. Approximately 60 minutes after procedure completion, study staff assessed overall patient satisfaction with the abortion experience and postoperative pain scores, as well as weighed any used pads and other blood-soiled materials to quantify postoperative bleeding."

New text:

"We performed a measured blood loss (MBL) in the following fashion: a strainer was used to separate products of conception and blood so that volume of blood could be measured; gauze and sponges were weighed to determine additional blood loss. **Postoperatively, we weighed any used pads and other blood-soiled materials to quantify bleeding up until the time of discharge.**

Staff gave women 15 mg of intravenous ketorolac or 500 mg of oral naproxen, unless contraindications existed, and administered additional pain

medications or anti-emetics as needed to achieve optimal patient comfort. Approximately 60 minutes after procedure completion, study staff assessed overall patient satisfaction with the abortion experience and postoperative pain scores.”

Results

7) Line 211: I would replace "population" with "sample"

Response:

We have made this wording change.

Old text:

“and cervical laceration were the only complications occurring in our population...”

New text:

“and cervical laceration were the only complications occurring in our sample...”

8) Line 226-7: Can you run any significance testing on those that required interventions beyond uterine massage?

Response:

Please see Table 4 for 95% confidence intervals on interventions beyond uterine massage.

Tables & Figures:

9) Table 1: You can remove the p-value

Response:

We have removed the column with p-values in Table 1 and made a comment about the only significant finding in the Results section as below.

Old text:

“Baseline and demographic characteristics were similar between groups (Table 1).”

New text:

“Baseline and demographic characteristics were similar between groups (Table 1) aside from a three-day difference in gestational age ($p=0.05$).”

10) Discussion: Some of the exclusions listed in the methods restricted those patients at the highest risk of hemorrhage, likely leading to bias towards the null. The intervention would likely have even more of an effect if used in high risk patients or in a research sample that included higher risk patients.

Response:

To the discussion, we have added the below text to lines...to comment on our exclusion of those at highest risk for hemorrhage.

New text:

“While our study excluded women at an increased risk for hemorrhage due to coagulopathy, anticoagulant use, chorioamnionitis, or suspected placenta accreta, we did include those with fetal demise. It is unclear how prophylactic oxytocin use would affect the subpopulation we excluded.”

REVIEWER #3:

11) A randomised study involving the Universities of Hawaii and Washington; the data does not give the numbers of patients recruited to the study by each centre. It involves women undergoing D&E at 18-24 weeks or evacuation of cases of fetal death either under general anaesthesia or deep sedation. Sixty minutes before surgery and 60 minutes after surgery patients were questioned about pain and satisfaction with the procedure. The object of the study was to determine whether the administration of oxytocin 30 units in 500 mL or placebo given over 15 minutes at the start of the surgical procedure (i) influenced the need for interventions to control present or anticipated excess bleeding, (ii) reduced excess blood loss (>500 mL and >1000 mL), (iii) reduced the need for blood transfusion and (iv) reduced serious injury or death. The duration of the surgery was also recorded.

Response:

In Table 1, we provide the numbers of women recruited to each study site:

Site		
University of Hawaii	56 (68.3)	56 (71.8)
University of Washington	26 (31.7)	22 (28.2)

12) Obtaining consent for the study: This appears to have been obtained following admission on the day for surgery. This suggests the patients had little time to contemplate the request and the possibility of some degree of coercion could have existed. It would be reassuring to know that potential patients/participants of the study had been given written information relating to the study at least 24 hours in advance of their giving consent, a frequent requirement by Ethical Review Boards except for emergency procedures.

Response:

Recruitment and consent took place either the day before the procedure at the preoperative visit or on the day of the procedure, consistent with other abortion and non-abortion related studies at both participating institutions. In both the states of Hawaii and Washington, there was no mandatory waiting period between decision to abortion and the abortion procedure. Participants were provided ample time to ask questions and were offered a copy of the study

consent/information sheet. We obtained ethical review approval at both at the University of Washington and the Queens Medical Center in Hawaii for recruitment to take place at either time.

13) Inclusion of cases of intrauterine fetal demise: Since a coagulopathy can develop in such cases this inclusion potentially compromises the study. Table 1 indicates only 5 cases were recruited so excluding these from the analyses would reduce an unnecessary potential confounding factor. According to Table 4, 2 of 3 (67%) cases of intrauterine fetal death treated with placebo received an intervention to control bleeding.

Response:

Based on your suggestion, we performed a secondary analysis wherein we removed the five subjects with fetal demise in our sample and recalculated the comparisons of the outcomes for interventions, blood loss, hemorrhage, and procedure duration. There were no significant changes to our results when this subpopulation was removed. The data reported in the manuscript still includes the participants with fetal demise.

14) Decision to intervene was based on clinical judgment and signs of impending haemorrhage: As observed in the Discussion, this subjective decision has the potential to compromise outcome analyses. It would therefore be reassuring to know that these subjective decisions were similar across both study sites. The figures provided in Table 4 suggest they were not equivalent. A similar analysis for procedure times across the two study sites would also be worthy of recording for reassurance.

Response:

In comparing the two sites, there was no difference in procedure duration with a mean time in minutes of 12.9 SD 4.7 in placebo group and 13.8 SD 6.9 in oxytocin group ($p=0.4$). There were more interventions performed at the Hawaii site (18/112) than the Washington site (1/48), $p=0.03$, however the median total measured blood loss was also higher in Hawaii 218.6 (45.1-1593.0) mL vs. 161.4 (48.3-1715.3) mL, $p=0.04$. As addressed in our response to comment #3, providers at both sites overall adhered to our intervention algorithm. We feel that there should be no differences between sites due to randomization of treatment groups.

15) Post procedure patient satisfaction: Since patients' recovery from general anaesthesia or deep sedation is variable, how confident were the researchers full recovery had occurred before enquiry into patient satisfaction was recorded?

Response:

We assessed pain and satisfaction one hour after the procedure was complete. If participants were not ready to be assessed, the study staff would approach them again later. Furthermore, the half-life of the IV medications

typically used in these procedures is about 1-2 hours.

STATISTICAL EDITOR'S COMMENTS:

16) Lines 39-41: Need to state the primary outcome first.

Response:

We have updated the Précis per the below text at lines 39-41.

Old text:

"Prophylactic oxytocin use during surgical abortion at 18-24 weeks' gestation decreases blood loss and rate of hemorrhage but not rate of interventions for bleeding."

New text:

"Prophylactic oxytocin use during surgical abortion at 18-24 weeks' gestation **did not affect rate of interventions for bleeding**, but decreased blood loss and rate of hemorrhage."

17) Lines 223-225 (Table 4): 15/19 should be cited as proportion with CIs, since the sample is relatively small.

Response:

We now provide a confidence interval for this proportion.

Old text:

"Uterine massage was sufficient to control bleeding in approximately eighty percent (15/19) of the instances that providers needed to perform an intervention."

New text:

"Uterine massage was sufficient to control bleeding in approximately eighty percent (15/19, **95% CI 0.6 to 0.9**) of the instances that providers needed to perform an intervention."

18) Table 1: Since this is an RCT, there is no need to statistically compare the cohorts, any differences should be due to random chance. Need units of BMI.

Response:

We have removed the p-value column from Table 1 and added the units of kg/m² to BMI.

19) Table 2, lines 190-193: Need to clearly demarcate the primary outcome from the secondary ones. The differences in uterotonic medication and intrauterine tamponade should be tested with Fisher's test, not chi-square. The blood loss distributions are highly skewed. Rather than testing with student's t, should use a

non-parametric stats test. Were procedure durations normally distributed? If not, should cite as median (range) and test non-parametrically. Should clarify in this table and others, when Fisher's test was used.

Response:

We have added an additional row, shaded in color, below the primary outcome and other outcomes listed in Table 2 to better demarcate. We have reported the aforementioned variables now as medians (IQRs) with 95% CIs in the tables (and throughout text) and explained how we calculated these values in our methods section.

Old text:

"We analyzed data with R software version 3.0.3. We compared intervention rates between treatment and placebo groups using a chi-square test. Measured blood loss, procedure length, pain and satisfaction scores, and continuous demographic variables were compared using a student's t-test. Complications and categorical demographic variables were compared using a chi-square test and Fisher's Exact Test when applicable."

New text:

"We analyzed data with R software version 3.0.3 and SAS (Statistical Analysis System) software version 9.4. We compared differences in proportions and 95% confidence intervals (CIs) for bleeding interventions between treatment and placebo groups using the Fleiss method. Median measured blood loss, procedure length, pain and satisfaction scores and their 95% confidence intervals (CIs) were calculated for both groups using the Hodges Lehmann procedure and assessed for normality. Continuous demographic variables were compared using a student's t-test. We compared the proportions of complications and other categorical outcomes and corresponding 95% CIs using the Fleiss method. Categorical demographic variables were compared using a chi-square test or Fisher's Exact Test as applicable."

20) Table 3: Were the VAS pain scores and Likert scores normally distributed? If not, and given the sample sizes, should cite as median (range) and test non-parametrically.

Response:

No, these were not normally distributed. Please see updated Table 3 for medians (IQRs) and CIs.

21) Table 4: Need units for BMI. Many of the comparisons require Fisher's test. The small sample sizes invalidate use of student's t, should use non-parametric testing

Response:

BMI units were added as kg/m². In addition, we have reassessed statistical significance using 95% CIs. See updated Table 4.

ASSOCIATE EDITOR - GYN:

22) Please report out results using RR and 95% CI (rather than p-values) - as suggested by STAT editor.

Response:

We have reported 95% CIs in our tables and throughout the manuscript.

23) The Discussion would benefit from a reflection on the study design parameters - ie sample size calculations - and how the findings/conclusions here might have differed with a larger group. Also, since oxytocin is a widely used drug with few reasons not to use it, and secondary outcomes appearing to favor its usage, what should be its role in this population?

Response:

We have updated the Discussion with these points per the below.

Old text:

“Our primary outcome, rate of interventions to control excess bleeding, was a limitation of our study due to its potentially subjective nature. However, in order to standardize interventions, we provided surgeons with an algorithm for management of excess bleeding

“Providers should not only have these medications accessible to treat hemorrhage, but consider using oxytocin prophylactically for those at an elevated risk for hemorrhage which includes those at 18 to 24 weeks of gestation.”

New text:

“Our primary outcome, rate of interventions to control excess bleeding, was a limitation of our study due to its potentially subjective nature **with sample size calculation based on limited evidence¹⁷**. In order to standardize interventions, we **did** provide surgeons with an algorithm for management of excess bleeding...”

“Finally, our sample size of 160 women may have limited our ability to detect and draw conclusions about more rare complications such as uterine perforation or drug reactions...”

“In their clinical guideline on management of postabortion hemorrhage, the Society of Family Planning (SFP) provides an algorithm to identify and classify women at risk for hemorrhage.² For those at moderate risk, including those at advanced gestational age, SFP recommends that “uterotonic medications be readily accessible.”² Based on the results of our study, providers consider using oxytocin prophylactically at 18 to 24 weeks of gestation to reduce blood loss and the risk for hemorrhage.

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

"Figure 1: Note that this is a box. Please update manuscript to reflect this change."

Response:

We have changed Figure 1 to Box 1 on the box itself and as referenced throughout the manuscript.

Daniel Mosier

From: Kate Whitehouse [REDACTED]
Sent: Thursday, December 6, 2018 9:43 AM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-1806R1
Attachments: Salcedo - Dec 5 2018 - 4-55 PM.pdf; MTDisclosure.docx; agreementformMT.pdf; Kaneshiro Disclosures.docx; Kaneshiro disclosure green journal.pdf

Dear Daniel,

That is great news that the editors have approved it!

Attached are additional authorship forms and disclosures. Now the only one missing is Dr Savala. I will follow up again with him

Thanks very much,
Kate Whitehouse

On Thu, Dec 6, 2018 at 2:25 PM Daniel Mosier <dmosier@greenjournal.org> wrote:

Dr. Whitehouse,

Thank you very much for sending us your revisions in a timely manner. The editors have reviewed this version, and approve of the changes you have made throughout.

Before we move on to the next stage of the process, I'm currently awaiting four of the author agreement forms from your co-authors: Tschann, Salcedo, Savala, Kaneshiro. Once those forms are received, we can begin the first stages of production.

Please let us know if you have any questions or concerns.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

Obstetrics & Gynecology

Tel: 202-314-2342

From: Kate Whitehouse [REDACTED]
Sent: Saturday, December 1, 2018 9:25 AM
To: Daniel Mosier <dmosier@greenjournal.org>
Subject: Re: Manuscript Revisions: ONG-18-1806R1

Dear Daniel,

Thanks for getting this back to me. I put answers to the queries below in red and worked off the document you sent to make the edits as suggested. Hope this is what you were looking for!

On Fri, Nov 30, 2018 at 8:13 PM Daniel Mosier <dmosier@greenjournal.org> wrote:

Dear Dr. Whitehouse,

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.

Yes, all look ok.

- 1.
2. LINE 4: With the exception of Katherine Whitehouse, please provide completed author agreement forms for all authors using the latest version of our author agreement form, which can be found at <http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.

I have reminded my co-authors

- 1.
2. Since the first version of the manuscript, you have changed the method for analyzing differences in proportions to Fleiss Kappa, whose nomenclature will be confusing to our readers. Please use a more traditional comparison of proportions, which will still show a NS change (compared to their a priori threshold of 15% difference), but it will be more straightforward for our readership. e.g., difference = 9.4% (95% CI = -.8% to 20%)

Made updates to abstract, text, and tables. Please do let me know if I have not done this as you had envisioned.

- 1.
2. Please make clear the distinction between their primary vs secondary outcomes.

I have done this in the abstract

- 1.
2. For consistency, the changes in frequencies of hemorrhage should likewise be expressed as differences in proportions. Those were statistically significantly different, but secondary outcomes and not subject to their 15% difference threshold. Also, the EBLs should be rounded to nearest whole mL.

Completed throughout document.

- 1.
2. After completing queries 3-5, please modify the Tables and text to conform to the Abstract.

Completed.

- 1.
2. LINE 5: Please ask the following authors to respond to the authorship confirmation email we sent. We sent an email from em@greenjournal.org. The message contains a link that needs to be clicked on. We emailed the authors at the email addresses below– are these the correct addresses?

a. Michael Savala: [REDACTED]

I have reminded Michael Savala

1.
 - a.
2. LINE 205: For articles submitted to O&G after July 1, 2018, we require a data sharing statement for RCTs. Your answers may be different from what I've listed here. If so, please edit the responses accordingly.

I agree with the answers you supplied.

- 1.

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 **Tuesday, December 4th**.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

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Web: <http://www.greenjournal.org>

From: [REDACTED]
To: [Stephanie Casway](#)
Subject: Re: O&G Figure Revision: 18-1806
Date: Thursday, November 29, 2018 4:51:19 PM

This looks good to me

Thanks

Kate Whitehouse

On Thu, Nov 29, 2018 at 6:51 PM Stephanie Casway <SCasway@greenjournal.org> wrote:

Good Afternoon Dr. Whitehouse,

Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please review the figure and legend CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes made 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 Monday, 12/3. Thank you for your help.

Best wishes,

Stephanie Casway, MA
Production Editor

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