OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: Oct 15, 2020
To: "Holly B. Ende" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2385

RE: Manuscript Number ONG-20-2385

Risk factors for atonic postpartum hemorrhage: a systematic review and meta-analysis

Dear Dr. Ende:

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 14 days from the date of this letter. If we have not heard from you by Oct 29, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a very well written and organized systematic review examining risk factors for postpartum hemorrhage due to atony specifically. The authors provide a very detailed explanation of their search strategy and analytic method. They clearly state how they addressed bias and specific reasons for inclusion of study.

Introduction: Well written and described introduction section highlighting the need for further evaluation of atony PPH risk factors to improve prediction models.

Methods: The authors provide a very detailed explanation of their search strategy and analytic method. They clearly state how they addressed bias and specific reasons for inclusion of study. Perhaps further definition of some of the included risk factors should be included within the methods section to ensure it is clear by what is being included. For example, diabetes includes pre-gestational or GDM or both, andd placental disorders including accreta spectrum or previa/abruption only (some of this is included in appendix B, but more definition in methods would be helpful). Some further explanation of the various definitions used for prolonged labor may also be beneficial to readers.

Results: Figure 3 with combined Forest Plot images are very blurry and difficult to read, may be an uploading issue.

Discussion: You raise an interesting point about IVF as a potential effect modifier vs. risk factor-was there no data from the risk factors you examined looking at ART as risk factor for PPH? In lines 552 and 553, do you mean higher order perineal lacerations or cervical trauma? The wording here is slightly confusing.

Reviewer #2: Enda et al performed a metaanalysis and systematic review on risk factors for atonic postpartum hemorrhage. The objectives were to identify risk factors for the most common etiology of PPH, uterine atony to allow refinement of risk stratification tools.

Precis:

Abstract: Authors clearly define their objective. Methods for collection of data are clearly defined in the abstract. Results are clearly stated. Conclusions are appropriate for this manuscript.

Introduction:
Authors did a great job of providing background and developing the rationale for their study.

Recommend authors comment on how many patients with PPH have no risk factors.

Materials and Methods:
Study was registered with PROSPERO.

109-111 Recommend authors describe how they defined uterine atony for inclusion into this meta-anlysis.
Sources appears appropriate and complete.

138-139 How was the data collection form validated?

Data abstraction was performed by 2 reviewers on predesigned data abstraction form; differences were settled by a 3rd person arbitrator.

Recommend authors specify if there were restrictions based on sample size, to make sure that they avoided the overestimation of small studies.

Where estimates of effect size determined separately for randomized versus nonrandomized trials?

Methods to explore heterogeneity appear appropriate.

Results:
185-186 Recommend narrative summary of maternal age/history, pregnancy, labor and delivery rated risk factors be moved to an appendix; presenting table 2 with a shorter written summary focusing on the most pertinent result would be recommended in this section.

179-182 This belongs in methods section.

Discussion:
561-562 Recommend authors make sure readers understand that the risk factors were not found in this particular study with uterine atony as the outcome, but it is possible that they may predict other etiologies of PPH which were not studied in this particular study.

638-639 Please explain why articles that were not written in English were excluded.

656-658 I would caution the authors in making generalized statements about the risk assessment tools for PPH (from all cause) as their study only looked at risk factors for one etiology of PPH, uterine atony. Line 659-660 is an acceptable conclusion. Another limitation not highlighted by the authors is that from a clinical standpoint, the risk predictions tools that are currently in use are meant to capture all causes of PPH, not just those due to uterine atony. Overestimation of the potential risk of PPH, therefore, is acceptable with current risk stratification tools so as to minimize the risk of mis-classifying a patient as low risk. What this study does add, however, is the potential missed risk factors for uterine atony, as the authors point out.

Figures and Tables:
Appendix A: Please explain why other treatments for uterine atony such as tranexamic acid, intrauterine balloon, curettage, hysterectomy, selective artery embolization were excluded from MeSH search terms.

References: Appropriate for study.

Reviewer #3: This paper is a systematic review and meta-analysis to examine risk factors for atonic hemorrhage. It is an important clinical topic and germane to the readers of Obstetrics & Gynecology. The study is well designed, and the paper is well written.

Precis and abstract: good.

Introduction: clear statement of background, purpose, and aims.

Methods: Used PRISMA, with appropriate study registration. Appropriate search terms. Good attempt to standardize bias.

1. I recommend adding "English language" to inclusion criteria, since in the discussion it was mentioned that English language was an inclusion/exclusion factor.

2. I recommend adding Box 1's information to the methods section, since that information is needed to best understand the prose of the results section.

Results: clear, consistently presented.

Discussion: clear, backed up by presented data.

STATISTICAL EDITOR COMMENTS:

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

General and Fig 3: Most of the metrics used were aORs, while some were aRRs. So, without further information, the reader cannot be assured that the groups were equivalent, since they may have been adjusted for different baseline characteristics. Second, although there were some estimates of aRR, and for an infrequent event, RR and OR approximate the same values numerically, they do not give the reader context. For example, some of the statistically significant ORs were > 2. many were in the 1-2 range, so when the overall population prevalence is eg, 5%, that would mean that the allocation by that variable would be on the order of 3% vs 2% to yield OR ~ 1.5. So, the reader needs more context in terms of the absolute risk and risk differential. If the goal is to allow clinically useful prediction of those at risk, there needs to be information as to the number of false positives and false negatives. In other words, what are the trade-offs of any algorithm devised to optimally separate who will have the adverse outcome from those who will not?

As supplemental material, should provide a summary of the counts of adverse outcomes vs total N in the various groups being compared.

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. For instance, we don't use subheadings, as you've done for example in the results section.

Numbers below refer to line numbers.

27. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found. 31. The objective of the abstract should be a simple "To" statement without background information.

41. The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.

46. Do not begin a sentence with a numeral. Either spell out or edit your sentence to avoid the need to start w/ a number

49. Prior post partum hemorrhage? Of any sort? Or just from atony?
What is meant by "placental disorders"?

54. Rather than conclude with a statement of the goal of the review/meta-analysis, please write a conclusion to what you found.

63. Not all patients with PPH have substantial morbidity—they certainly can, but for some, there is no morbidity. Please edit.

65. I'm not clear what you mean by "early identification". Do you mean, identification of a hemorrhage? How does risk identification affect that? Hopefully, anyone delivering a baby will be able to identify a hemorrhage, risk factors or not. Isn't one of the reasons to identify those at elevated risks to try to mitigate those risks? Not just prepare for the hemorrhage when it occurs.

74. If there was a recent meta analysis, what gap are you filling with this one? You have not mentioned the machine learning studies of PPH that have been published recently.

Please shorten your introduction by about 1/3. Introductions should be about 1 page in length.

176. Please spell out OR, RR , rr, urr and indicate whether these are adjusted or crude.

192. P Values vs Effect Size and Confidence Intervals
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.
This is true for the abstract as well as the manuscript, tables and figures.

Please provide absolute values for variables, in addition to assessment of statistical significance.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.

192. In the 2012 paper, Grimes and Schulz comment on the limitations of observational epidemiology. They note that the for cohort studies, the threshold of potential interest stats at RR of 0.5 or 0.33 and 2 or 3 for increased risk. It should be noted that many of your reported RR's are within what they refer to as the zone of potential bias and this should be noted in the discussion section. False Alarms and Pseudo-Epidemics : The Limitations of Observational Epidemiology. Obstetrics & Gynecology 2012, 120 (4), p 920–927. Many of your aOR's reported on lines 191-195 (and I assume later as well) fall within the range of potential bias. This will need to be addressed in your discussion.

198. The AMA style manual, which the Journal uses, asks that "authors provide an explanation of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

In addition, the nonspecific "other" as it is sometimes used for comparison in data analysis may also be a "convenience" grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. Also, White and Black, as racial categories, are now capitalized.

On the discussion, please comment on whether race and ethnicity are considered biologic or social variable and whether you were able to study contributors to any differences found, such as racism.

194-195. This comment and the similar one on line 201 are not "results" but part of the discussion when you discuss the strengths of your paper. Maybe similar issues in later portions of the paper. As your tables will include numbers of patients in each study, and you have a table of risk of bias, please consider summarizing your concerns in the discussion section regarding #'s of included patients, etc. and explaining why this is important.

The way you've presented your qualitative synthesis and meta-analysis is atypical. Could you write this information in complete sentences?

235. I'm puzzled why you think this is a "likely" risk factors with the differing results and small RR, except the one that found it be protective, which is outside the zone of potential bias.

348. We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout to indicate that there is no difference.

391. Curious how "uterine rupture" with the bleeding associated with disruption of the myometrium could be deemed to be due to "atony".

519. iSn't it likely that women in the midst of an immediate post partum hemorrhage just didn't get the cord blood collection done, not that cord blood collection is "protective"?

524. Including breastfeeding seems odd unless you are specifically referring to atonic PPH any time during a delivery hospitalization (or first 24 hours, etc). Certainly would not be a risk factor for immediate post partum hemorrhage. Please clarify.

540-541: Please comment with respect to recent concerns raised about incorporation of race and ethnicity into calculators etc.

558. Noteable that the "higher OR" is still within the zone of potential bias. My take away from this list of pretty unremarkable OR's and RR is that while there are some weak associations, none of them are that important and ALL deliveries should be considered "at risk" and that any unit doing deliveries needs to be ready to deal with an atonic uterus without hesitation.

601. How is “high vaginal trauma” identified and defined.

622. This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMED, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

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. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

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 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.

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

6. 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).

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 limit for Reviews is 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. 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.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

12. Line 622: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

13. 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.

14. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

15. Figures

Figure 1: This figure may be resubmitted as-is.

Figure 2: Please provide at a high resolution.

Figure 3: Please break this figures into 5 individual figures (Figures 3-7), as these will not fit together in print. Please provide at a high resolution.

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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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. Do not omit your responses to the Editorial Office or Editors' comments.

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 14 days from the date of this letter. If we have not heard from you by Oct 29, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

_____

Dear Dr. Chescheir,

Thank you for your careful reading of our manuscript and your thoughtful comments on how it may be clarified and improved. We have taken these suggestions, and we submit our revised manuscript, as well as the detailed responses to each comment below. All manuscript changes are "marked" utilizing Microsoft Word Track Changes. We believe that we have been able to adequately address all comments and concerns and hope that this revised version will be deemed suitable for publication in *Obstetrics & Gynecology*. In making these manuscript revisions, I confirm that I have read the Instructions for Authors and have adhered to all journal standards found therein. Thank you for your time and consideration.

Sincerely,

Holly B. Ende MD

Responses to Reviewers:

Reviewer 1 Comments & Responses:

Comment 1: Perhaps further definition of some of the included risk factors should be included within the methods section to ensure it is clear by what is being included. For example, diabetes includes pre-gestational or GDM or both, and placental disorders including accreta spectrum or previa/abruption only (some of this is included in appendix B, but more definition in methods would be helpful). **Response 1**: Thank you for highlighting how we might bring clarity to the reader on specific risk factors assessed. In the Methods section of the manuscript, we attempt to describe first how articles were chosen, second how data on risk factors were collected, and third how those data were statistically analyzed. The full list of risk factors subsequently appears in multiple locations – Table 2, Appendix B (with descriptors such as "gestational" versus "chronic" for diabetes, cutoffs such as BMI≥30 or BMI ≥40 for obesity, etc.), and the newly created Appendix C (which contains the full narrative summary previously found in the Results section). Unfortunately, due to constraints on manuscript length, and requests to decrease word count further, we were unable to also include this information in the Methods section of the manuscript.

Comment 2: Some further explanation of the various definitions used for prolonged labor may also be beneficial to readers.
Response 2: This information is currently included in two locations – in the detailed assessment of risk factors located in Appendix B under "Prolonged Labor" as well as in the narrative description of risk factors located in the newly created Appendix C. Most of the studies evaluating "long labor" as a risk factor for atonic PPH utilized diagnosis codes, and so do not present additional information regarding that definition, other than the stage of labor assessed. Only two studies (Looft et al, Regalia et al) looked at specific time ranges, and these details have been included. Due to constraints on manuscript length, we were unable to also include this information in the Methods section of the manuscript.

Comment 3: Results: Figure 3 with combined Forest Plot images are very blurry and difficult to read, may be an uploading issue.
Response 3: Thank you for pointing out the poor image quality and readability of this figure. Figure 3 has been subdivided into 5 separate figures (Figures 3-7) and images have been uploaded in high quality resolution.

Comment 4: Discussion: You raise an interesting point about IVF as a potential effect modifier vs. risk factor-was there no data from the risk factors you examined looking at ART as risk factor for PPH?
Response 4: Based on our search strategy, only one reference reported on IVF/ICSI as a risk factor for postpartum hemorrhage (Nyflot et al. BMC Pregnancy and Childbirth. 2017 Jan 10;17(1):17). Data from this study were not included in our systematic review as data for the subgroup of patients with atonic postpartum hemorrhage was not reported. This reference has been added to the statements on *in vitro* fertilization included in the Discussion section.

***Comment 5**:* In lines 552 and 553, do you mean higher order perineal lacerations or cervical trauma? The wording here is slightly confusing.
Response 5: Thank you for identifying potential confusion in this statement. The wording has been adjusted per your recommendation.

Reviewer 2 Comments & Responses:

***Comment 1**:* Enda et al performed a meta-analysis and systematic review on risk factors for atonic postpartum hemorrhage. The objectives were to identify risk factors for the most common etiology of PPH, uterine atony to allow refinement of risk stratification tools. Abstract: Authors clearly define their objective. Methods for collection of data are clearly defined in the abstract. Results are clearly stated. Conclusions are appropriate for this manuscript. Introduction: Authors did a great job of providing background and developing the rationale for their study.
Response 1: Thank you for your thoughtful review of our manuscript. We appreciate the time and effort required to review such a lengthy report.

***Comment 2**:* Recommend authors comment on how many patients with PPH have no risk factors.
Response 2: In studies validating current risk assessment tools, anywhere from 3 to 43% of hemorrhages (depending on the study and risk tool used) occurred in those deemed low risk. This information has been added to the Introduction section, paragraph 2.

***Comment 3**:* Materials and Methods: 109-111 Recommend authors describe how they defined uterine atony for inclusion into this meta-analysis.
Response 3: For inclusion in the systematic review, we included all studies that reported on postpartum hemorrhage due to uterine atony, as defined by the authors of each study. Definition of atony varied by study and included clinical diagnosis, uterotonic administration, estimated blood loss, need for transfusion, or ICD code. This information has been added to the Study Selection section (paragraph 1), with reference to Table 1 (where the definition for each individual study can be found).

***Comment 4**:* Sources appears appropriate and complete. 138-139 How was the data collection form validated? Data abstraction was performed by 2 reviewers on predesigned data abstraction form; differences were settled by a 3rd person arbitrator.
Response 4: All data entered into the data collection form were verified by two separate authors. The form was not otherwise validated.

***Comment 5**:* Recommend authors specify if there were restrictions based on sample size, to make sure that they avoided the overestimation of small studies.
Response 5: There were no restrictions based on sample size. Most studies were large, with only six studies including <1000 subjects. Of those six, three studies were rated as high risk of bias and so were not included in any qualitative or quantitative synthesis. Of the remaining

three studies, where they were included in narrative summaries, a comment on their small size is noted, to aid reader interpretation of the findings. In the meta-analysis, the inverse variance random effects method was utilized, which weights studies based on the size of their standard errors. Since smaller studies had much larger standard errors, they receive appropriately less weight in the quantitative analysis.

***Comment 6**:* Were estimates of effect size determined separately for randomized versus nonrandomized trials? Methods to explore heterogeneity appear appropriate.
Response 6: Twenty-six of the included 27 studies were prospective cohort, retrospective cohort, or case control studies. One study was a secondary analysis of a randomized controlled trial. Effect sizes were not determined differently for these different study designs.

***Comment 7**:* Results: 185-186 Recommend narrative summary of maternal age/history, pregnancy, labor and delivery rated risk factors be moved to an appendix; presenting table 2 with a shorter written summary focusing on the most pertinent result would be recommended in this section.
Response 7: Thank you for pointing out where we can streamline the Results section and move certain information to an appendix. The narrative summary of risk factors has been moved to Appendix C, with a short summary of results presented in its place.

***Comment 8**:* 179-182 This belongs in methods section.
Response 8: This sentence has been moved to the Methods/Study Selection section, paragraph 3.

***Comment 9**:* Discussion: 561-562 Recommend authors make sure readers understand that the risk factors were not found in this particular study with uterine atony as the outcome, but it is possible that they may predict other etiologies of PPH which were not studied in this particular study.
Response 9: Thank you for recommending this important clarification. This information has been added to the Discussion section, paragraph 4.

***Comment 10**:* 638-639 Please explain why articles that were not written in English were excluded.
Response 10: Authors were only fluent in English. This information has been added to the Discussion section, paragraph 9.

***Comment 11**:* 656-658 I would caution the authors in making generalized statements about the risk assessment tools for PPH (from all cause) as their study only looked at risk factors for one etiology of PPH, uterine atony.
Response 11: This sentence has been removed from the Discussion, since as the reviewer points out, current tools assess risk from all causes, not just uterine atony.

***Comment 12**:* Line 659-660 is an acceptable conclusion. Another limitation not highlighted by the authors is that from a clinical standpoint, the risk predictions tools that are currently in use

are meant to capture all causes of PPH, not just those due to uterine atony. Overestimation of the potential risk of PPH, therefore, is acceptable with current risk stratification tools so as to minimize the risk of mis-classifying a patient as low risk. What this study does add, however, is the potential missed risk factors for uterine atony, as the authors point out.
Response 12: Based on this reviewer's comments, we did not revise the paper's conclusions.

***Comment 13**:* Figures and Tables: Appendix A: Please explain why other treatments for uterine atony such as tranexamic acid, intrauterine balloon, curettage, hysterectomy, selective artery embolization were excluded from MeSH search terms.
Response 13: In determining our search strategy, we included the obvious terms that would be used to identify reports on risk for uterine atony (all iterations of postpartum hemorrhage, uterine atony or inertia, and etiology/cause/epidemiology). However, we also evaluated commonly used definitions of atony to identify additional search terms. The MFMU Cesarean Registry defines atony as requiring "both the clinical diagnosis (which was a recorded variable on the maternal complications form), and the administration of an additional uterotonic agent, such as methergine or a prostaglandin" (Rouse et al. AJOG 2005. 193:1056-60). Additionally, the ACOG Practice Bulletin Number 183 notes that "in the setting of postpartum hemorrhage, identification of a soft, poorly contracted (boggy) uterus suggests atony as a causative factor" and suggests "uterine massage" and "second uterotonic agent" as initial steps when atony is suspected (ACOG Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol 2017. 130(4):e168-186). Based on the common inclusion of uterotonics in defining uterine atony, we decided to include these terms in our search strategy. While tranexamic acid, intrauterine balloon tamponade, curettage, hysterectomy, and uterine artery embolization may occasionally be required in cases of uterine atony, they were not included in our search strategy, since they are not frequently used as defining factors.

<u>Reviewer 3 Comments & Responses</u>:

***Comment 1**:* This paper is a systematic review and meta-analysis to examine risk factors for atonic hemorrhage. It is an important clinical topic and germane to the readers of Obstetrics & Gynecology. The study is well designed, and the paper is well written. Precis and abstract: good. Introduction: clear statement of background, purpose, and aims. Methods: Used PRISMA, with appropriate study registration. Appropriate search terms. Good attempt to standardize bias.
Response 1: We thank Reviewer 3 for these words of affirmation.

***Comment 2**:* I recommend adding "English language" to inclusion criteria, since in the discussion it was mentioned that English language was an inclusion/exclusion factor.
Response 2: Thank you for pointing out this oversight. This information has been added to the Study Selection section, paragraph 1.

***Comment 3**:* I recommend adding Box 1's information to the methods section, since that information is needed to best understand the prose of the results section. Results: clear, consistently presented. Discussion: clear, backed up by presented data.

Response 3: Additional information from Box 1 has been added to the Methods/Study Selection section, paragraph 3. We were not able to include the entirety of Box 1 in this section due to word count constraints.

Statistical Editor Comments & Responses:

***Comment 1**:* General and Fig 3: Most of the metrics used were aORs, while some were aRRs. So, without further information, the reader cannot be assured that the groups were equivalent, since they may have been adjusted for different baseline characteristics.
Response 1: We appreciate this limitation raised by the statistical reviewer. In general, despite some differences in the specific characteristics adjusted for, each author intended to adjust for potential confounders of postpartum hemorrhage, and so the lists largely overlap. In addition, even where some discrepancies in adjustment for confounders exist, the associations we report are largely consistent across studies. For increased transparency pertaining to adjustment for confounders, we have added a column to Table 1 listing the covariates for which the statistical results were adjusted in each study.

***Comment 2**:* Second, although there were some estimates of aRR, and for an infrequent event, RR and OR approximate the same values numerically, they do not give the reader context. For example, some of the statistically significant ORs were > 2. many were in the 1-2 range, so when the overall population prevalence is eg, 5%, that would mean that the allocation by that variable would be on the order of 3% vs 2% to yield OR ~ 1.5. So, the reader needs more context in terms of the absolute risk and risk differential.
Response 2: While we are unable to completely mitigate this concern, the incidence of atonic PPH reported in each study is included in Table 1, column "Rate of atonic PPH". For cohort studies, the rate is relatively consistent, with most studies reporting values between 1% and 4%.

***Comment 3**:* If the goal is to allow clinically useful prediction of those at risk, there needs to be information as to the number of false positives and false negatives. In other words, what are the trade-offs of any algorithm devised to optimally separate who will have the adverse outcome from those who will not?
Response 3: While this review was conducted to inform future studies attempting to develop risk prediction models, the development of such models is not a goal of this study. Our goal here was to simply characterize the patient factors that might be useful in making such predictions in the future.

***Comment 4**:* As supplemental material, should provide a summary of the counts of adverse outcomes vs total N in the various groups being compared.
Response 4: Unfortunately, many of the studies included in this systematic review reported only unadjusted or adjusted odds ratio, relative risks, or rate ratios, without raw data. Thus, we are unable to provide this raw data (including the number of patients with and without each risk factor who did or did not develop atonic postpartum hemorrhage) to the reader.

Editor's Comments & Responses:

Comment 1: 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. For instance, we don't use subheadings, as you've done for example in the results section.
Response 1: Thank you for pointing us to this comprehensive resource on appropriate formatting of this manuscript. All requested changes have been made (including the removal of all subheadings).

Comment 2: line 27. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found.
Response 2: The précis was edited to include only 25 words and abbreviations were removed.

Comment 3: line 31. The objective of the abstract should be a simple "To" statement without background information.
Response 3: Background information has been removed from the objective of the abstract, leaving only the "to" statement.

Comment 4: line 41. The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.
Response 4: All uses of the virgule have been removed from the manuscript.

Comment 5: line 46. Do not begin a sentence with a numeral. Either spell out or edit your sentence to avoid the need to start w/ a number
Response 5: The numeral "47" has been spelled out.

Comment 6: line 49. Prior postpartum hemorrhage? Of any sort? Or just from atony?
What is meant by "placental disorders"?
Response 6: Thank you for pointing out where we can add clarity to our abstract. The strongest associations with atonic PPH were found for prior postpartum hemorrhage of any etiology, placenta previa, and placental abruption, among others. The wording has been adjusted to reflect these more precise definitions.

Comment 7: line 54. Rather than conclude with a statement of the goal of the review/meta-analysis, please write a conclusion to what you found.

Response 7: The conclusion of the abstract has been amended to reflect what was found in this systematic review.

Comment 8: line 63. Not all patients with PPH have substantial morbidity—they certainly can, but for some, there is no morbidity. Please edit.
Response 8: Thank you for this suggestion. We have made the requested change.

Comment 9: line 65. I'm not clear what you mean by "early identification". Do you mean, identification of a hemorrhage? How does risk identification affect that? Hopefully, anyone delivering a baby will be able to identify a hemorrhage, risk factors or not. Isn't one of the reasons to identify those at elevated risks to try to mitigate those risks? Not just prepare for the hemorrhage when it occurs.
Response 9: Unfortunately, most of the risk factors we evaluated cannot be mitigated, so we make the argument that identification of patients at risk is important so that providers can prepare for and perhaps change practice to reflect this change in risk. This may include performing type and cross preemptively, having uterotonics at the bedside, etc. We were not able to include this amount of detail in the Introduction due to word count constraints, but hopefully have addressed your concerns here.

Comment 10: line 74. If there was a recent meta-analysis, what gap are you filling with this one? You have not mentioned the machine learning studies of PPH that have been published recently.
Response 10: The recent meta-analysis evaluated only four potential risk factors (age, body mass index, parity, and hypertension). Our meta-analysis, on the other hand, is much more comprehensive, evaluating 47 risk factors. Thank you for pointing us to the recently published articles on machine learning for postpartum hemorrhage risk prediction. We have incorporated this concept into the Discussion section, paragraph 8.

Comment 11: Please shorten your introduction by about 1/3. Introductions should be about 1 page in length.
Response 11: The Introduction has been shortened significantly, to just over one page.

Comment 12: line 176. Please spell out OR, RR, rr, urr and indicate whether these are adjusted or crude.
Response 12: Based on a comment by Reviewer 2, this sentence has been moved to the Methods section. Odds ratio, relative risk, and rate ratio have been spelled out as requested. The values are either adjusted or unadjusted, based on the value reported in each study. This is described in an earlier sentence of the Methods/Study Selection section, paragraph 3.

Comment 13: line 192. P Values vs Effect Size and Confidence Intervals While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P

value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. This is true for the abstract as well as the manuscript, tables and figures. Please provide absolute values for variables, in addition to assessment of statistical significance.
Response 13: We apologize if we misunderstand this comment, but no p-value is reported on line 192 (Section "Maternal History and Demographics," subsection "Age." For reference, this section has been moved to Appendix C).

***Comment 14**:* We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.
Response 14: At the request of Reviewer 2, the narrative summary of risk factors has been moved to Appendix C, with a substantially shorter summary of results now added to the Results section. With this move, only combined odds ratios resulting from the meta-analysis are now reported and discussed in the Results and Discussion sections. No crude or adjusted odds ratios now appear in the body of the manuscript.

***Comment 15**:* line 192. In the 2012 paper, Grimes and Schulz comment on the limitations of observational epidemiology. They note that for cohort studies, the threshold of potential interest stats at RR of 0.5 or 0.33 and 2 or 3 for increased risk. It should be noted that many of your reported RR's are within what they refer to as the zone of potential bias and this should be noted in the discussion section. False Alarms and Pseudo-Epidemics: The Limitations of Observational Epidemiology. Obstetrics & Gynecology 2012, 120 (4), p 920–927. Many of your aOR's reported on lines 191-195 (and I assume later as well) fall within the range of potential bias. This will need to be addressed in your discussion.
Response 15: Thank you for highlighting this important limitation of our study. A description of this limitation and its effect on our results has been added to the Discussion section, paragraph 9.

***Comment 16**:* line 198. The AMA style manual, which the Journal uses, asks that "authors provide an explanation of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).
Response 16: All of the requested information regarding race and ethnicity has been added as an Appendix D. References to this appendix have been added to the Results section as well as to the footnotes of Table 1.

***Comment 17**:* In addition, the nonspecific "other" as it is sometimes used for comparison in data analysis may also be a "convenience" grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. Also, White and Black, as racial categories, are now capitalized.

Response 17: All references to White and Black as racial categories have now been capitalized. Further details regarding the use of the "other" category in categorizations of race or ethnicity have been added in Appendix D.

***Comment 18**:* On the discussion, please comment on whether race and ethnicity are considered biologic or social variable and whether you were able to study contributors to any differences found, such as racism.
Response 18: Thank you for highlighting this oversight in our Discussion. When discussing the implications of associations between Hispanic ethnicity, Asian race, and atonic postpartum hemorrhage (Discussion, paragraph 2), we have added additional explanation of our current lack of understanding as to whether these effects are mediated by biologic or social mechanisms or whether they are the result of systematic racism.

***Comment 19**:* 194-195. This comment and the similar one on line 201 are not "results" but part of the discussion when you discuss the strengths of your paper. Maybe similar issues in later portions of the paper. As your tables will include numbers of patients in each study, and you have a table of risk of bias, please consider summarizing your concerns in the discussion section regarding #'s of included patients, etc. and explaining why this is important.
Response 19: The lengthy narrative summary of risk factors has been moved to Appendix C at the request of Reviewer 2. The Results section now concludes with a short summary of "definite" and "likely" risk factors surmised in this review, with the majority of information presented in Table 2, Appendix B, Appendix C, and Figures 3-7.

***Comment 20**:* The way you've presented your qualitative synthesis and meta-analysis is atypical. Could you write this information in complete sentences?
Response 20: As part of the narrative summary referenced in Response 19, this information has been moved to Appendix C. It has also been edited to improve clarity.

***Comment 21**:* 235. I'm puzzled why you think this is a "likely" risk factors with the differing results and small RR, except the one that found it be protective, which is outside the zone of potential bias.
Response 21: The designation as a likely risk factor comes from the pre-specified definitions of definite, likely, unclear, or not a risk factor established in Box 1. We attempted to highlight the inconsistency of these results by starting the paragraph with "Data on parity were conflicting."

***Comment 22**:* line 348. We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout to indicate that there is no difference.
Response 22: This sentence has been modified to remove the language regarding a non-significant trend.

***Comment 23**:* line 391. Curious how "uterine rupture" with the bleeding associated with disruption of the myometrium could be deemed to be due to "atony".

Response 23: Although the pathophysiologic mechanism of risk factor associations is not described in any of the papers reporting uterine rupture as a risk factor, it is plausible that following repair of the uterine defect, patients suffered from lack of uterine tone, and so were deemed to have PPH due to uterine atony.

Comment 24*:* line 519. Isn't it likely that women in the midst of an immediate postpartum hemorrhage just didn't get the cord blood collection done, not that cord blood collection is "protective"?
Response 24: Thank you for pointing out this important confounder. This is very likely the case, and we have adjusted the wording of this section to remove the term "protective," instead correctly stating that a "negative association" was found in the study.

Comment 25*:* line 524. Including breastfeeding seems odd unless you are specifically referring to atonic PPH any time during a delivery hospitalization (or first 24 hours, etc). Certainly would not be a risk factor for immediate postpartum hemorrhage. Please clarify.
Response 25: Breastfeeding as a risk factor for atonic postpartum hemorrhage was evaluated in only one study (Wetta et al. Am J Obstet Gynecol. 2013;209(1):51-56). This was a secondary analysis of a prospective study, and the authors relied on the data that were abstracted by trained research nurses for the original study. They captured all women who had a postpartum hemorrhage requiring treatment, which included uterotonics, need for transfusion, balloon tamponade, surgery, or interventional radiology procedure. Atony was diagnosed "based on the discretion of the treating obstetrical team." Therefore, this study included both immediate and delayed atonic postpartum hemorrhage. Because there was such a paucity of data, no association was found in the one study that evaluated it, and we classified it as "not a risk factor," we did not think it was necessary to include any further expansion on this topic in the Discussion section.

Comment 26*:* line 540-541: Please comment with respect to recent concerns raised about incorporation of race and ethnicity into calculators etc.
Response 26: Thank you for raising this important point. We have added this topic to the Discussion (paragraph 2) and have included a specific reference.

Comment 27*:* line 558. Notable that the "higher OR" is still within the zone of potential bias. My take away from this list of pretty unremarkable OR's and RR is that while there are some weak associations, none of them are that important and ALL deliveries should be considered "at risk" and that any unit doing deliveries needs to be ready to deal with an atonic uterus without hesitation.
Response 27: We agree that with a few exceptions the majority of associations demonstrated in this systematic review are relatively weak. This could be because no individual risk factors demonstrate significant association or because of the retrospective nature of all included studies and the limitations, confounding, and bias inherent to those designs. Our hope is that with this information in hand, future studies can better refine risk assessments by statistical modeling to estimate the risk conferred by having multiple risk factors. We do, however, acknowledge this limitation and it has been added to the Discussion section.

***Comment 28**:* line 601. How is “high vaginal trauma” identified and defined.
Response 28: Three studies utilize the term “high vaginal laceration” in denoting subtypes of genital tract trauma (Joseph et al, Lutomski et al, and Mehrabadi et al). None of the three manuscripts contain any further descriptions or definitions for this term. Joseph et al includes categories for “perineal laceration”, “cervical laceration”, and “high vaginal laceration”. Lutomski et al includes categories for “episiotomy” and “other genital tract trauma including third- and fourth-degree perineal tears, high vaginal, and cervical lacerations”. Mehrabadi et al describes “third- and fourth-degree perineal tear”, “high vaginal laceration”, and “cervical laceration”. By utilizing context of the comparators, presumably the authors mean to include in this subcategory lacerations which extend beyond the perineum but do not include the cervix. We have adjusted all incidences of “high vaginal trauma” to instead read “high vaginal laceration” to improve clarity.

***Comment 29**:* line 622. This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMED, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.
Response 29: This sentence has been removed. Thank you.

<u>Editorial Office Comments & Responses</u>:

***Comment 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:
Response 1: OPT-IN: Yes, please publish my point-by-point response letter.

***Comment 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.
Response 2: All authors have confirmed that they have no disclosures.

***Comment 3**:* For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should

be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race. Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.
Response 3: All of the requested information regarding race and ethnicity has been added as an Appendix D. References to this appendix were added to the Results section as well as to the footnotes of Table 1.

Comment 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 has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-obstetrics-data-definitions&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041777614%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=MDLQFqUKjodS0Ff5Cdx99EDRkbV2DGzbJDFD2Av%2FzIg%3D&reserved=0 and the gynecology data definitions at https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-gynecology-data-definitions&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041777614%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=qlxFH6LhQUXAvluaw4CpCttzxE2PmpsfLP2%2BmCnWmeY%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
Response 4: The use of reVITALize definitions has been confirmed where appropriate in the manuscript.

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

***Comment 6**:* 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).
Response 6: We have no acknowledgments of financial support, manuscript preparation assistance, or non-author contributors. This work was submitted in abstract form to the Society for Obstetric Anesthesia and Perinatology 2020 Annual Meeting, which did not occur due to the COVID-19 pandemic. The abstract did appear in the published digital syllabus. This information is included in the title page.

***Comment 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 limit for Reviews is 300 words. Please provide a word count.
Response 7: The abstract has been checked for clarity and consistency with the remainder of the manuscript. The word count of the abstract is <300.

***Comment 8**:* Only standard abbreviations and acronyms are allowed. A selected list is available online at https://nam05.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041777614%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=u0HzKShGNZjmuYdNkOHxs0QVf7%2BMx3JsV5K77jdoCAw%3D&reserved=0. 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.
Response 8: The following standard abbreviations are used in the manuscript: PRISMA, PROSPERO, ICD, OR, RR. Some nonstandard abbreviations are used repeatedly, and so were maintained in the current version. These include postpartum hemorrhage (PPH), cesarean delivery (CD), estimated blood loss (EBL), and rate ratio (rr). A few abbreviations of

organizations are also included: California Maternal Quality Care Collaborative (CMQCC), Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN), and American College of Obstetricians and Gynecologists (ACOG). We confirm that no abbreviations or acronyms are used in the title or precis, and that abbreviations are spelled out the first time they are used in the abstract and again in the manuscript body.

Comment 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.
Response 9: All uses of the virgule symbol have been removed from the manuscript.

Comment 10*:* 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.
Response 10: The one-time use of "providers" in the manuscript has been replaced with "health care professionals."

Comment 11*:* In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts. Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").
Response 11: All results are reported in terms of an effect size (odds ratio, relative risk, rate ratio). P-values are included only in the meta-analysis (Figures 3-7) as footnotes to each risk factor.

Comment 12*:* Line 622: Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
Response 12: This sentence in the Discussion section has been removed.

Comment 13: Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:
https://nam05.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong

%2Faccounts%2Ftable_checklist.pdf&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041777614%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=wkKWMCFttFd1YEMZOZ8uGruPXfDKFYGXXUR4alKkRi4%3D&reserved=0.

Response 13: The Table Checklist has been reviewed, and all Tables conform to the requested formatting.

***Comment 14**:* Please review examples of our current reference style at https://nam05.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041787616%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=jiHrxGaZm9ABKgkk94lU55poCnHcmBPQxFaw5lDHNaQ%3D&reserved=0 (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fclinical&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041787616%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=NKhykIoTDPvdvqd55jRHnTdccUGXxMsYOf1CL%2BlkTnU%3D&reserved=0 (click on "Clinical Guidance" at the top).

Response 14: The reference formatting instructions have been reviewed, and references have been edited to comply with journal standards.

***Comment 15**:* Figure 1: This figure may be resubmitted as-is. Figure 2: Please provide at a high resolution. Figure 3: Please break this figure into 5 individual figures (Figures 3-7), as these will not fit together in print. Please provide at a high resolution.

Response 15: All figures have been resubmitted in high resolution. Figure 3 has been divided into five separate figures (Figures 3-7).

Comment 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 https://nam05.safelinks.protection.outlook.com/?url=http%3A%2F%2Flinks.lww.com%2FLWW-ES%2FA48&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041787616%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=pfjroPQAnbbBCd4%2B4T4pTtzYGPcIixM65Zavgw754q8%3D&reserved=0. The cost for publishing an article as open access can be found at https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwkauthorservices.editage.com%2Fopen-access%2Fhybrid.html&data=04%7C01%7Cholly.ende%40vumc.org%7C1189d421d6a142631bc908d8713ed964%7Cef57503014244ed8b83c12c533d879ab%7C0%7C1%7C637383862041787616%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=XZM0zDX7ZifQeLjJ0nOzoIr5H3EZ0Ah4mKHTaPrXIwI%3D&reserved=0.

Response 16: We decline the option to publish our article as open access.