

# OBSTETRICS & GYNECOLOGY



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

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

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

**Date:** Apr 17, 2019  
**To:** "Jennifer L. Kerns" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-19-471

RE: Manuscript Number ONG-19-471

Disseminated intravascular coagulation and hemorrhage and after dilation and evacuation abortion for fetal demise

Dear Dr. Kerns:

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 May 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: Overall Comments: This is a fairly large retrospective cohort study in women undergoing 2nd trimester D&E for IUFD and for other indications. They wished to determine if the risk of hemorrhage and DIC was greater in those diagnoses of IUFD vs other indications. They found that the odds of DIC was greater in those women undergoing D&E for IUFD compared to the other indication controls, however, the absolute risk was low. Other reports have not noted this associated, but they did have smaller N's. The paper was reasonably well written, however, rather than being written from the "we" perspective, it would be appreciated if it was written in from the third person prospective, ie every sentence in the Methods section of the abstract starts with "We". Other specific comments below.

#### Specific Comments:

Title: may not need "for fetal demise"

Précis: Good

Abstract: See comment above; overall presents the main results well.

Introduction: Need to cut in half. Should be able to summarize current literature and the objective of the current study in 1 page.

Materials and Methods: Need specific definition for how DIC was diagnosed-were lab studies ie fibrinogen, PT/PTT/INR or CBC performed in all patients?

Results: Was there any gestational age association with DIC/hemorrhage-please specifically describe as this may impact clinical care? How was DIC diagnosed? Would like to see changes in any lab values drawn.

Discussion: Other limitations of the study are the inherent confounding bias and inability to confer causation with a retrospective cohort study. Ultimately, the N's were very low for women having DIC. Can these findings not help with recommendations regarding clinical care of women undergoing D&E for IUFD? Would you not recommend labs and ensure all uterotonics be available?

Tables-OK

Reviewer #2: Title: Appropriately descriptive.

1. Abstract: Clear and concise. Does this really include all D&E's - like in the whole US? I might rephrase - I want to see a word or two about where the cases came from (academic/general practice/geographic range etc) to see if it would apply to my population before I read the entire article.

Intro:

2. Line 62 - I would change the phrasing a little bit - Maybe Post-abortion hemorrhage or just Hemorrhage - more consistent with the language commonly used and prevents creating a new non-standard term. Also use the same terminology throughout the intro paragraph (sometimes abortion-related sometimes post-abortion and in the conclusion it is IUFD-related)

3. Overall good summary of current data on hemorrhage and risk factors.

4. Line 98-100 - I would add to your aim that you are looking specifically at the risk related to D&E "The aim of this study is to determine the risk of post abortion hemorrhage for patients undergoing dilation and evacuation for an IUFD in the second trimester using a large cohort from a public, urban abortion clinic"

Materials & Methods:

5. I would change the terminology from 'we' to 'the clinic' or see if you can eliminate entirely - Example "We reviewed the medical records" to "Medical Records were reviewed"

6. Line 131 - Can you clarify need for additional dilation? (did you have a cut-off point or just needing more beyond the use of overnight dilators?) and your categories for physician training (by life stage - resident, fellow, attending or by years of experience with D&E procedures?)

Inclusion/Exclusion:

7. Line 126 - It would be nice to know if including these excluded individuals would affect the data (for example abnormal placentation diagnosed only post-procedure vs pre-procedure - you would assume that those who are undiagnosed pre-procedure would increase risk of hemorrhage while those diagnosed pre-procedure would be a group that would have recommendations for different precautions to take) - Would it be possible to do an intent-to-treat analysis including these patients to see if there is a difference?

Measures:

8. It would seem if the risk increases with both vaginal delivery and cesarean delivery - does just having prior pregnancy increase risk and if so does this increase more with subsequent pregnancies and is this a stepwise increase? Is there enough info that you have collected to eval/comment on that?

Conclusions:

9. Line 208-212 - I think saying that risk factors such as prior delivery vaginally or by cesarean, increasing gestational age, etc should be thought about to determine appropriate location of care and other interventions that the provider might want to have available. While your study did not look at the effect of those interventions and cannot therefore say if having any of them will improve outcomes is worth mentioning - but establishing the risks factors first is an important step. I think it is also a reasonable leap of faith to say that the presence of multiple risk factors could potentially increase the risk more and should be considered.

Reviewer #3: This submission studies risks following abortion that are associated with demographic factors, medical histories, medical procedures, hemorrhage and abortion complications in relation to IUFD (intrauterine fetal demise), DIC (Disseminated intravascular coagulation). The initial statistical method used is odds ratio analysis which determines probabilities by Chi square computations. For factors having a p-value of 0.10 or less the authors used adjustments by means of logistic regression.

Overall, I believe this submission is well conceived and the 4+ years of data collection was well conducted and well analyzed.

I would make a few changes in the tables that I believe would help readers:

Table 1. There is no reason to present Age in a different way from all the other variables in the Table. Present two groups for age, <25 and age 25 or more. There is no reason to provide gestational duration in the same manner as age has been presented., especially when the group style of "n" and "percent" is also shown for gestational present, and has been given the same p-value.

Please note that for the variable "vaginal deliveries" the total number 3185 is incorrect for one or more deliveries. The total should be 52 plus 2263 i.e. 2315. The 3185 number

belongs to "non-white" in the ethnicity variable.

In this and the other tables it might be better to indicate that the p value shown may differ from the Pearson Chi squares. It would be even better to have 2 columns, one for Pearson p values, and one from the logistic regression analysis. and the second for for the two computations used for facors that first

Table 2. No comments excep[t that it is useful to see how low the number s in the

Table 3 : The variables of age and gestational age should be presented and analysed in the same manner as the other factors in the study. . This should be done for Tables 4 and 5 as well.

I believe that the division point for BMI should be <25vs 25+. Please reexamine this factor. Overweight (BMI 25-29.99) has the highest IUFD % of all 6 groups qs shown in Table 1.\

#### STATISTICAL EDITOR'S COMMENTS:

1. lines 46-47: See comments re: Table 2, this p-value is incorrect.
2. Table 1: Need units for age, BMI\*.
3. Table 2: Should specify here and in Methods which stats tests were used. For instance, for comparing DIC rates, should use Fisher's test, which has  $p = 0.017$ , apparently Chi-square was used, but many of the comparisons in this Table should use Fisher's test. Also, many rates are so low that there was little power to discern a difference or to generalize the NS findings.
4. Table 3: The risk of hemorrhage was NS with crude OR and there were too few adverse events to adjust for covariates,, in this case , adjustment with 5 covariates was attempted, but is likely an over fitted model.
5. Table 4: The DIC cohort is too few ( $n = 10$ ) to allow adjusted for IUFD counts of  $n = 2, 90$ . Again, the adjustment model is improperly over fitted.
6. Table 5: Same issue with low counts of complications among IUFD ( $n = 12$ ). At maximum, there is enough information to adjust for one covariate, not 5.

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

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts

should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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

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

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

9. 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).

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

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

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

13. 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 on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: [http://edmgr.ovid.com/ong/accounts/table\\_checklist.pdf](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

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

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

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If you choose to revise your manuscript, please submit your revision 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 and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 08, 2019, 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

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In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>) Please contact the publication office if you have any questions.



University of California  
San Francisco

May 8, 2019

**RE: COVER LETTER AND RESPONSE**

To the Editors of *Obstetrics and Gynecology*

We are excited to submit a revision of our manuscript titled, "Disseminated intravascular coagulation and hemorrhage and after dilation and evacuation abortion for fetal demise". We want to thank the reviewers and the editor for their thoughtful review and helpful comments. We have responded to all comments and have made changes to the manuscript. We believe we now have a greatly strengthened manuscript to submit.

Our study found that there is a significantly and clinically relevant increased risk of DIC associated with fetal demise at the time of dilation and evacuation abortion. While the risk is significantly higher than for pregnancy termination, the absolute risk of DIC remains low. Our study was approved by the Committee on Human Research at University of California, San Francisco.

We believe the readership of *Obstetrics and Gynecology* will be interested in this research. Thank you for your consideration of our manuscript.

Sincerely,

A handwritten signature in black ink, appearing to read "J. Kerns".

Jennifer Kerns, MD, MS, MPH



## RESPONSE

### Reviewer 1

**1. Overall Comments:** This is a fairly large retrospective cohort study in women undergoing 2nd trimester D&E for IUFD and for other indications. They wished to determine if the risk of hemorrhage and DIC was greater in those diagnoses of IUFD vs other indications. They found that the odds of DIC was greater in those women undergoing D&E for IUFD compared to the other indication controls, however, the absolute risk was low. Other reports have not noted this associated, but they did have smaller N's. The paper was reasonably well written, however, rather than being written from the "we" perspective, it would be appreciated if it was written in from the third person prospective, ie every sentence in the Methods section of the abstract starts with "We". Other specific comments below.

We thank Reviewer 1 for these overall comments. We chose to write in active voice rather than passive voice. We have not made changes to switch to passive voice, but are happy to do so if the editor prefers that we use passive voice.

**2. Title: may not need "for fetal demise"**

We are happy to alter this if the editor deems it appropriate; however, because fetal demise was the primary predictor, we feel that it is relevant to include.

**3. Introduction: Need to cut in half. Should be able to summarize current literature and the objective of the current study in 1 page.**

We very much appreciate this comment. We have reduced the word count by more than 100 (from 576 to 458).

**4. Materials and Methods: Need specific definition for how DIC was diagnosed-were lab studies ie fibrinogen, PT/PTT/INR or CBC performed in all patients?**

Thank you to Reviewer 1 for pointing out that we have not adequately specified how we defined DIC. We defined DIC using clinical criteria – that is, when the clinician indicated in the operative or post-operative notes that DIC was present, we classified cases as DIC. In many, but not all cases, laboratory evaluation was done confirming the coagulopathy. We previously published a paper on the association of obesity with D&E complications, and describe that all cases deemed “complications” in our database underwent a thorough chart review in order to confirm that these were truly complications. During that review, we confirmed the type of complication, including DIC. We are comfortable with this definition, as it is a relevant way to describe cases that are thought to be DIC in the moment, and prompt further intervention. We have added some description to this effect in the Methods section in the second paragraph.

*Lines 143-146*

*We defined DIC as cases where the physician noted DIC on the operative or post-operative notes. Although we did not collect data on laboratory evaluation or confirmation of DIC, it is the practice of all WOC physicians to send labs in cases of suspected DIC.*

**5. Results: Was there any gestational age association with DIC/hemorrhage-please specifically describe as this may impact clinical care? How was DIC diagnosed? Would like to see changes in any lab values drawn.**



We present the results for the association of covariates with hemorrhage and DIC, unadjusted and adjusted, in Tables 3 and 4, respectively. Gestational age was significantly associated with hemorrhage in the adjusted model (OR=1.3, 95% CI: 1.3-1.4) (Table 3). Given the small number of events for DIC, we only adjusted for 1 additional covariate – gestational age (see response below to Editor's comments). There were significantly increased odds of DIC association with each additional week of gestation (OR=1.3, 95% CI: 1.0-1.7,  $p=0.05$ ) (Table 4).

We clarified how DIC was diagnosed in the Methods section, detailed in our response to question 4 above.

**6.Discussion: Other limitations of the study are the inherent confounding bias and inability to confer causation with a retrospective cohort study. Ultimately, the N's were very low for women having DIC. Can these findings not help with recommendations regarding clinical care of women undergoing D&E for IUFD? Would you not recommend labs and ensure all uterotonics be available?**

We thank Reviewer 1 for this comment and we certainly agree that retrospective cohort studies preclude any determination of causation. We seek only to provide evidence of an association. DIC is an uncommon occurrence, and while the Ns are low for the cases of DIC, they do not preclude robust analyses of association, especially given the large N in the denominator.

We believe that the findings from this study do indeed help with recommendations regarding clinical care. First and foremost, recognizing that there is a significantly increased risk of DIC among women undergoing D&E for IUFD will help the team to identify DIC as a diagnosis. We agree that having uterotonics available is essential for managing hemorrhage and DIC. However, as we state in the discussion, we do not believe that preoperative labs provide any benefit. Laboratory values will nearly always be normal in women, even those with IUFD, as the onset of the coagulopathy associated with IUFD tends to present rapidly at the time of uterine evacuation. Moreover, while the relative risk is high, the absolute risk remains low. Most D&Es are done in ambulatory settings, and given the low absolute risk, outpatient management is appropriate. We do not believe our findings argue that women who are undergoing D&E for IUFD should be referred to a higher level of care.

## **Reviewer 2**

**1.Abstract: Clear and concise. Does this really include all D&E's - like in the whole US? I might rephrase - I want to see a word or two about where the cases came from (academic/general practice/geographic range etc) to see if it would apply to my population before I read the entire article.**

Thank you to Reviewer 2 for catching this in the abstract. We realize the wording was misleading. We added wording to make it clear that this study included all D&Es done at one academic abortion clinic In San Francisco.

**2.Line 62 - I would change the phrasing a little bit - Maybe Post-abortion hemorrhage or just Hemorrhage - more consistent with the language commonly used and prevents creating a new non-standard term. Also use the same terminology throughout the intro paragraph (sometimes abortion-related sometimes post-abortion and in the conclusion it is IUFD-related)**

Thank you for this suggestion. We agree that it is preferable to keep the language consistent. We have changed the wording throughout the manuscript to be consistent with either hemorrhage or post-abortion hemorrhage.

**3. Overall good summary of current data on hemorrhage and risk factors.**

Many thanks.

**4. Line 98-100 - I would add to your aim that you are looking specifically at the risk related to D&E  
"The aim of this study is to determine the risk of post abortion hemorrhage for patients undergoing dilation and evacuation for an IUFD in the second trimester using a large cohort from a public, urban abortion clinic"**

In an effort to make the introduction more concise, we deleted the sentences that were formerly in lines 98-100. We hope that this change addresses the comment.

**5. I would change the terminology from 'we' to 'the clinic' or see if you can eliminate entirely -  
Example "We reviewed the medical records" to "Medical Records were reviewed"**

Same response as for Reviewer 1, Comment 1.

**6. Line 131 - Can you clarify need for additional dilation? (did you have a cut-off point or just needing more beyond the use of overnight dilators?) and your categories for physician training (by life stage - resident, fellow, attending or by years of experience with D&E procedures?)**

Thank you for this question. Need for additional dilation means the need for mechanical dilation with Pratt dilators on the day of the D&E. We had no cutoff point; this was guided by whether there was enough dilation to allow the appropriate forceps to pass. Physician training levels included resident, family planning fellow, and attending. We chose to analyze by these categories rather than years of experience. We revised that paragraph so it now reads:

*Lines 155-161*

*The primary predictor in our analysis was diagnosis of IUFD. In unadjusted analyses comparing the IUFD and non-IUFD cohorts, we assessed age, race/ethnicity, BMI, parity, prior abortion, prior vaginal delivery, prior cesarean section, gestational age, need for mechanical dilation on the day of the D&E, and physician training level (resident, family planning fellow, or attending).*

**7. Line 126 - It would be nice to know if including these excluded individuals would affect the data (for example abnormal placentation diagnosed only post-procedure vs pre-procedure - you would assume that those who are undiagnosed pre-procedure would increase risk of hemorrhage while those diagnosed pre-procedure would be a group that would have recommendations for different precautions to take) - Would it be possible to do an intent-to-treat analysis including these patients to see if there is a difference?**

Thank you for this comment. We do not have any reason to believe that those with abnormal placentation differed by IUFD status, and since demise versus non-demise was our primary predictor, we do not feel that this would bias our results. Another way to say this is that among those with possibly undiagnosed morbidly adherent placenta, we would not expect any differing proportions of those with or without demise. Moreover, our ability to diagnose morbidly adherent placenta is quite high. Everyone who has a prior cesarean section and is over 15 weeks undergoes a detailed ultrasonographic evaluation. Any suspicion of morbidly adherent placenta prompts further

imaging, and, if indicated, preoperative planning. Given the scope of this study, we cannot do any further analyses based on morbidly adherent placenta, nor do we feel that it would add anything meaningful to this paper.

- 8. It would seem if the risk increases with both vaginal delivery and cesarean delivery - does just having prior pregnancy increase risk and if so does this increase more with subsequent pregnancies and is this a stepwise increase? Is there enough info that you have collected to eval/comment on that?**

We did examine any association between gravidity and our outcomes, and found no association. As the reviewer points out, there are associations between parity – both for vaginal deliveries and cesarean deliveries. We only evaluated these covariates as dichotomous variables.

- 9. Line 208-212 - I think saying that risk factors such as prior delivery vaginally or by cesarean, increasing gestational age, etc should be thought about to determine appropriate location of care and other interventions that the provider might want to have available. While your study did not look at the effect of those interventions and cannot therefore say if having any of them will improve outcomes is worth mentioning - but establishing the risks factors first is an important step. I think it is also a reasonable leap of faith to say that the presence of multiple risk factors could potentially increase the risk more and should be considered.**

We appreciate Reviewer 2's comment and we have added a sentence to the end of the discussion, as well as a sentence drawing attention to those findings earlier in the discussion:

*Lines 247-250*

*Another study demonstrated that increasing gestational age is associated with DIC<sup>22</sup> which is consistent with findings from this study as well. We did observe an increased risk of hemorrhage among those with prior vaginal deliveries, cesarean sections, and increasing gestation, findings that are consistent with the literature.*

*Lines 265-269*

*While patients with IUFD can be cared for safely in an outpatient setting, providers may consider IUFD alongside other known risk factors when deciding what level of care is best. Given the low incidence of DIC, we do not recommend any specific or additional preoperative or intraoperative management for women undergoing D&E for IUFD.*

### **Reviewer 3:**

- 1. Table 1. There is no reason to present Age in a different way from all the other variables in the Table. Present two groups for age, <25 and age 25 or more. There is no reason to provide gestational duration in the same manner as age has been presented., especially when the group style of "n" and " percent " is also shown for gestational present, and has been given the same p-value. Please note that for the variable "vaginal deliveries" the total number 3185 is incorrect for one or more deliveries. The total should be 52 plus 2263, i.e. 2315. The 3185 number belongs to "non-white" in the ethnicity variable.**

We appreciate Reviewer 2's comment about making Table 1 more easily understandable to the reader. We feel that age should be represented as a continuous variable, and presented as mean (SD), as the cutoff of 25 year holds no clinical meaning. In order to provide some consistency, we have kept gestational duration as a continuous variable also. We agree that it is unnecessary to

present gestational duration as both a continuous and a dichotomous variable, especially when doing so adds no information. And we hope that keeping gestational duration and age consistent, both as continuous variables, adequately addresses Reviewer 2's concern.

Many thanks for catching the error with the total N for "vaginal deliveries". We have corrected that mistake.

**2. In this and the other tables it might be better to indicate that the p value shown may differ from the Pearson Chi squares. It would be even better to have 2 columns, one for Pearson p values, and one from the logistic regression analysis. and the second for the two computations used for factors that first**

We appreciate this comment on including additional information on statistical testing using a logistical regression for Table 1. However, because the purpose of this table is to provide information on overall participant characteristics and compare the distributions of the IUFD and non-IUFD groups, we feel that using just the p-value for the Pearson Chi-squared test is the most appropriate way to compare these two groups.

**3. Table 2. No comments except that it is useful to see how low the numbers in the**

**4. Table 3: The variables of age and gestational age should be presented and analysed in the same manner as the other factors in the study. This should be done for Tables 4 and 5 as well.**

Thanks to Reviewer 2 for this. We agree and are treating them both as continuous variables.

**5. I believe that the division point for BMI should be <25 vs 25+. Please reexamine this factor. Overweight (BMI 25-29.99) has the highest IUFD % of all 6 groups as shown in Table 1.**

We appreciate this comment, but we feel that BMI of 30 is an appropriate cutoff. Our analysis plan was to examine BMI at a cutoff of 30, as obesity is defined starting at 30. Obesity as a risk factor for obstetric and abortion complications has been studied at a cutoff of 30. We are not accustomed to choosing a cutoff based on the distribution in the study sample unless the groups are so unbalanced that they are meaningless to study as such. With a cutoff of 30, there are enough subjects in each group to evaluate if obesity is associated with hemorrhage and DIC.

#### STATISTICAL EDITOR'S COMMENTS:

**1. lines 46-47: See comments re: Table 2, this p-value is incorrect.**

When we look at the p value listed in the abstract ( $p=0.28$ ), it looks like it agrees with the p value as listed in Table 2. If we are mistaken, we are happy to investigate and correct this.

<i>Variable</i>	<i>Total N (%)</i>	<i>IUFD n (%)</i>	<i>Non-IUFD n (%)</i>	<i>p value</i>
<i>Total</i>	4,520	92	4,428	
<i>All complications</i>	442 (10)	12 (13)	430 (10)	0.29
<i>Major complications</i>	78 (2)	3 (3)	75 (2)	0.25
<i>Any hemorrhage</i>	314 (7)	9 (10)	305 (7)	0.28

**2. Table 1: Need units for age, BMI\*.**

We have made this correction.

**3. Table 2: Should specify here and in Methods which stats tests were used. For instance, for comparing DIC rates, should use Fisher's test, which has  $p = 0.017$ , apparently Chi-square was used, but many of the comparisons in this Table should use Fisher's test. Also, many rates are so low that there was little power to discern a difference or to generalize the NS findings.**

Thank you for this correction. We have re-done the analyses using Fisher's exact tests when cell sizes are 5 or less. We also added language in the methods section to specify this (shown below). While the rates of these very rare events are quite low, we feel that providing these results accompanied by the statistical testing can still be informative for clinicians and researchers.

*Lines 169-170*

*When appropriate, we compared proportions using chi-square tests with p-values and 95% confidence intervals, and Fisher's exact test for cell sizes of five or less.*

**4. Table 3: The risk of hemorrhage was NS with crude OR and there were too few adverse events to adjust for covariates, in this case, adjustment with 5 covariates was attempted, but is likely an over fitted model.**

Our primary outcome for the analysis in this table was hemorrhage, and there were 314 cases of hemorrhage within this cohort. With this number of events, using the conservative "rule of 10" (rule that suggests at least 10 events per variable within regressions), we feel that we have sufficient events to include 5 covariates within this model.

**5. Table 4: The DIC cohort is too few ( $n = 10$ ) to allow adjusted for IUFD counts of  $n = 2, 90$ . Again, the adjustment model is improperly over fitted.**

Thank you for this correction. We have repeated the analysis with only 2 covariates (age plus the covariates of interest individually) to address this. We feel that 2 covariates are reasonable, given an analysis by Vittinghoff and McCulloch of the "rule of 10" applied to logistic regression (<https://academic.oup.com/aje/article/165/6/710/63906>). We changed both the methods and results sections to reflect this. We also changed the abstract to reflect this.

*Lines 170-174*

*We then compared the primary outcomes of hemorrhage, DIC and overall complications using logistic regression, adjusting for covariates that were associated with the outcome in unadjusted analyses at a p-value of  $\leq 0.1$ , only adjusting for as many as permissible based on the number of events for each outcome.*

*Lines 207-209*

*In the adjusted analysis of DIC, IUFD was significantly associated with 23 times higher odds of DIC and each gestational week was significantly associated with 1.3 times higher odds of DIC (Table 4).*

**6. Table 5: Same issue with low counts of complications among IUFD ( $n = 12$ ). At maximum, there is enough information to adjust for one covariate, not 5.**

Similar to Table 3, our primary outcome for the analysis in this table was any complications, and there were 442 events. Based on this number of events, we feel that the risk of overfitting is low.