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: Jul 18, 2019
To: "Niraj Gowda" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-873

RE: Manuscript Number ONG-19-873

Decision to perform catheter-directed thrombolytic therapy in the management of severe pulmonary embolism in pregnancy.

Dear Dr. Gowda:

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

REVIEWER COMMENTS:

Reviewer #1: The authors present a series of three cases of pulmonary embolism, one of which was categorized as massive and underwent catheter directed thrombolysis. The following items should be addressed:

1. The first teaching point states that CDT is preferred over systemic thrombolytic therapy in patients with massive PE, however two of the cases included in this manuscript had submassive PE's and received neither CDT nor systemic thrombolytic therapy. It is unclear if the authors are suggesting that CDT should be considered in women with any severe PE, including submassive as well as massive, as is approved by the FDA (line 224-225)? If so, the teaching point should be revised, and discussion regarding why it was not considered for the two cases presented with submassive PE. Alternatively, are the authors are intending as in line 66-69, limiting CDT to those with massive PE? If the latter is true, then the two cases with submassive PE do not seem to fit in with the teaching point of this manuscript and probably should be removed since it is not clear what additional benefit they add for the reader.

2. Line 71 - the authors wrote "severe PE" but it appears they meant "massive PE" as they are discussing methods for treatment beyond systemic anticoagulation; this should be replaced. The remainder of the sentence describes a challenge in balancing the risks and benefits of treatment, which are also concerning in non-pregnant individuals; that sentence should be re-worded.

3. Readers of this journal may not be familiar with technical terms specific to cardiology such as "right ventricle/left ventricle ratio" (line 89) or "McConnell's sign" (line 92) - this should be defined.

4. Line 111-112 - is treatment for 1 year consistent with national guidelines? If so, you could leave out the statement about per Cardiology recommendations and instead reference the guideline. Similarly, see line 132 regarding Hematology recommendations.

5. Line 223 - "during all our cases" is confusing, since the authors have only presented one case where CDT was utilized.

Reviewer #2: The authors present a well-written case series on the treatment of submassive and massive pulmonary embolism in pregnancy (PE). This case series is timely as PE remains a significant cause of maternal morbidity and mortality. Given that PE remains relatively rare and unpredictable, a scholarly discussion of the management of severe, submassive or massive PE is also pertinent to the readership of the journal. The case series is concise, clear and has

appropriate teaching points. A few questions or comments are listed below to assist the authors in improving their manuscript:

* Line 204-205: would stick with phrasing that pregnancy is a relative contraindication to systemic tPA (and not use the word "generally", which is colloquial). The authors could consider adding a box with absolute and relative contraindications to systemic thrombolytic therapy (see below).

* The only point I would like to see the authors address is in conclusion (end of discussion section). Even in the absence of high-quality data in pregnancy, we as OBs need to advocate for an approach to pregnant women that is consistent with the standard of care for adult patients. While more data is necessary, the rarity of massive PE likely precludes a clinical trial or publication of data apart from case series, retrospective cohorts or analyses administrative data. In the absence of data, why treat pregnant women with massive PE differently than non-pregnant women (particularly given the consequences of non-treatment, including RV failure, cardiopulmonary arrest, maternal death, fetal hypoxia/death)? As the chest guidelines say, the "nature, severity, temporality, and number of relative contraindications" may alter an individual patient's candidacy for thrombolytic therapy. Preferentially using catheter directed therapy in appropriate candidates for thrombolysis in pregnancy is very reasonable and preferable given available data and the fetal/maternal bleeding risks. However, the authors could also make a statement as to when systemic therapy may be considered/employed (acute cardiopulmonary collapse, failed catheter-directed therapy, etc?) and a statement articulating that standard treatment(s) should not be withheld or limited in the setting of pregnancy (individualized approach must incorporate and balance all fetal/maternal risk factors).

Reviewer #3: I think this is an appropriate and timely article. However, there should be provision of more context in the introduction about the overall mortality rate of massive vs submissive vs acute PE for the general obstetric audience (Xue paper). Furthermore the Martilotti paper clearly cited risks of fetal & maternal mortality, as well as postpartum and antepartum hemorrhage frequency with the more traditional treatment modalities and this info should be completely included in your paper. It seems reasonable to attempt catheter based thrombolysis on pregnant and postpartum patients with massive PE because of the high mortality rate without intervention. Given that the mortality rate for submassive PE is only 3% based on the Xue paper, the known information about fetal and maternal mortality and antepartum & postpartum hemorrhage rates must be disclosed so practioners can make independent risk assessments with your article

Associate Editor's Comments:

1) Please as suggested by Reviewer #1 remove the two non-massive PE case descriptions;
2) The conclusion used in the abstract (and throughout the paper), as well as teaching point #1, are nearly verbatim from a study on the same subject: https://doi.org/10.1016/j.jcin.2015.06.009 or JACC Cardiovasc Interv. 2015 Aug 24;8(10):1393-5
Please reword.

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. 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.

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. 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.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Case Reports should not exceed 8 typed, double-spaced pages (2,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

5. 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.

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

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states 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. Please avoid phrases like "This paper presents" or "This case presents."

9. 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: Case Reports, 125 words. Please provide a word count.

10. 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.

11. 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.

12. 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.

13. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 1: Please upload original high-res versions of these images without any text or arrows (lines are okay) (eps, tiff, jpeg, etc). These items will be added back per journal style."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or

black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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REVIEWER COMMENTS:

Reviewer #1: The authors present a series of three cases of pulmonary embolism, one of which was categorized as massive and underwent catheter directed thrombolysis. The following items should be addressed:

1. The first teaching point states that CDT is preferred over systemic thrombolytic therapy in patients with massive PE, however two of the cases included in this manuscript had submassive PE's and received neither CDT nor systemic thrombolytic therapy. It is unclear if the authors are suggesting that CDT should be considered in women with any severe PE, including submassive as well as massive, as is approved by the FDA (line 224-225)? If so, the teaching point should be revised, and discussion regarding why it was not considered for the two cases presented with submassive PE. Alternatively, are the authors are intending as in line 66-69, limiting CDT to those with massive PE? If the latter is true, then the two cases with submassive PE do not seem to fit in with the teaching point of this manuscript and probably should be removed since it is not clear what additional benefit they add for the reader.

- Thank you for your comment. We are suggesting that CDT should be considered in any pregnant women with massive PE. The other two cases were included to make clear our decision process and differences in management between massive vs. submassive PE.

2. Line 71 - the authors wrote "severe PE" but it appears they meant "massive PE" as they are discussing methods for treatment beyond systemic anticoagulation; this should be replaced. The remainder of the sentence describes a challenge in balancing the risks and benefits of treatment, which are also concerning in non-pregnant individuals; that sentence should be re-worded.

- Thank you for your comment. We have edited that statement to better reflect the differences between pregnant and non-pregnant patients. We meant to use “severe PE” in order to encompass both massive and submassive PE as in the general population. We are suggesting that CDT or other modalities be considered in pregnant women with massive PE.

3. Readers of this journal may not be familiar with technical terms specific to cardiology such as "right ventricle/left ventricle ratio" (line 89) or "McConnell's sign" (line 92) - this should be defined.

- Thank you for your comment. We have added the definitions.

4. Line 111-112 - is treatment for 1 year consistent with national guidelines? If so, you could leave out the statement about per Cardiology recommendations and instead

reference the guideline. Similarly, see line 132 regarding Hematology recommendations.

- Thank you for your comment. The one year is not consistent with national guidelines for either hematology or cardiology, it was the personal preference of the attending cardiologist at the time. The line 132 recommendations are consistent with hematology guidelines and we have adjusted the sentence to reflect this.

5. Line 223 - "during all our cases" is confusing, since the authors have only presented one case where CDT was utilized.

- Thank you for your comment. We have changed the sentence to reflect what happened in Case 1.

Reviewer #2: The authors present a well-written case series on the treatment of submassive and massive pulmonary embolism in pregnancy (PE). This case series is timely as PE remains a significant cause of maternal morbidity and mortality. Given that PE remains relatively rare and unpredictable, a scholarly discussion of the management of severe, submassive or massive PE is also pertinent to the readership of the journal. The case series is concise, clear and has appropriate teaching points. A few questions or comments are listed below to assist the authors in improving their manuscript:

* Line 204-205: would stick with phrasing that pregnancy is a relative contraindication to systemic tPA (and not use the word "generally", which is colloquial). The authors could consider adding a box with absolute and relative contraindications to systemic thrombolytic therapy (see below).

- Thank you for your comment. We have changed the sentence to reflect this difference

* The only point I would like to see the authors address is in conclusion (end of discussion section). Even in the absence of high-quality data in pregnancy, we as OBs need to advocate for an approach to pregnant women that is consistent with the standard of care for adult patients. While more data is necessary, the rarity of massive PE likely precludes a clinical trial or publication of data apart from case series, retrospective cohorts or analyses administrative data. In the absence of data, why treat pregnant women with massive PE differently than non-pregnant women (particularly given the consequences of non-treatment, including RV failure, cardiopulmonary arrest,

maternal death, fetal hypoxia/death)? As the chest guidelines say, the "nature, severity, temporality, and number of relative contraindications" may alter an individual patient's candidacy for thrombolytic therapy. Preferentially using catheter directed therapy in appropriate candidates for thrombolysis in pregnancy is very reasonable and preferable given available data and the fetal/maternal bleeding risks. However, the authors could also make a statement as to when systemic therapy may be considered/employed (acute cardiopulmonary collapse, failed catheter-directed therapy, etc?) and a statement articulating that standard treatment(s) should not be withheld or limited in the setting of pregnancy (individualized approach must incorporate and balance all fetal/maternal risk factors).

Thank you for your comment.

- We believe that pregnant patients with signs and symptoms of massive PE should be considered candidates for catheter directed thrombolysis. However in the setting of acute cardiopulmonary collapse or failed CDT, systemic tPA or surgical embolectomy must be considered.
- We have incorporated the requested suggestions to the conclusions.

Reviewer #3: I think this is an appropriate and timely article.

However, there should be provision of more context in the introduction about the overall mortality rate of massive vs submissive vs acute PE for the general obstetric audience (Xue paper).

Furthermore the Martilotti paper clearly cited risks of fetal & maternal mortality, as well as postpartum and antepartum hemorrhage frequency with the more traditional treatment modalities and this info should be completely included in your paper.

It seems reasonable to attempt catheter based thrombolysis on pregnant and postpartum patients with massive PE because of the high mortality rate without intervention. Given that the mortality rate for submassive PE is only 3% based on the Xue paper, the known information about fetal and maternal mortality and antepartum & postpartum hemorrhage rates must be disclosed so practioners can make independent risk assessments with your article

- Thank you for your comment. We address the post-partum antepartum and fetal/neonatal complications in the discussion section of the paper but have included it in the introduction now and have added a section pertaining to the overall mortality rate of submassive PE in the general population.

Associate Editor's Comments:

1) Please as suggested by Reviewer #1 remove the two non-massive PE case descriptions;

- **Thank you for your comment, we have removed the two sub-massive PE cases.**

2) The conclusion used in the abstract (and throughout the paper), as well as teaching point #1, are nearly verbatim from a study on the same subject: https://doi.org/10.1016/j.jcin.2015.06.009 or JACC Cardiovasc Interv. 2015 Aug 24;8(10):1393-5
Please reword

- **Thank you for your comment, we have reworded the teaching point, conclusion, as well as two other places in the paper that use similar wordings.**