OBSTETRICS & GYNECOLOGY

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

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

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

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

Date: Jul 18, 2019
To: "Julien Viau-Lapointe" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1092

RE: Manuscript Number ONG-19-1092

Extracorporeal therapies for amniotic fluid embolism.

Dear Dr. Viau-Lapointe:

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: Case report and review of a very complicated amniotic fluid embolus and the use of VA ECMO

1. line 57 "fetal mortality or mortality " do you mean to say "fetal mortality or maternal mortality"?

2. Line 71: ROSC? abbreviation

3. Discussion: 119-126 A more basic explanation of the why and the physiology behind VA vs VV ECMO would be helpful/ I found this paragraph confusing

4. Example VA ECMO is used in instances such as>>> and VV ECMO is used in instances and what we would be treating after an AFE, severe pulmonary hypertension in which case VV is adequate or cardiogenic shock in which case VA is needed

5. I thought you did a good discussion of the complexity of DIC with AFE and how to manage on ECMO

6. When describing the cases and your search describe that these 20 cases span 34 years, oldest case in 1986 and the trend from bypass to ECMO

7. Table 1 and 2 I think adding the year of publication is helpful for the reader to see that there are more case reports of ECMO in the past 5-7 years

8. You have guidelines published for AFE , Are there guidelines for use of ECMO?

Reviewer #2: This is a nice review of an important topic. ECMO has been floating around as a suggested therapy for some cases of AFE and it is nice to see all available reports brought together in one place. A couple of suggestions:

1. Although the reported cumulative survival rate for women receiving ECMO is encouraging, reporting bias is a very important limitation that really has to be discussed. It is not only possible, but likely that cases of ECMO which resulted in survival are more likely to be submitted for publication than cases in which ECMO was associated with maternal death. Thus it is really premature to claim that ECMO improves survival, and very inappropriate to conclude (see last sentence in the article) that such therapy "must be attempted." The authors need to tone this all down significantly and conclude that this therapy has the potential to improve outcomes and ought to be considered in select cases of AFE, but that is it premature to conclude that ECMO actually improves outcomes or that its use in any single case would have resulted in survival.

2. In the abstract I was initially struck by the liver laceration and my first thought was "this was probably not an AFE." In reading the manuscript, it is clear that my initial impression was incorrect. However, I believe the authors have done themselves a disservice by including this incidental, post code issue so prominently in the abstract, while leaving out much more important issues such as the failure to improve oxygenation with PEEP as diagnostic of lung injury. The liver laceration has to be included in the body of the text, but I would not include it in the abstract. Rather, I'd include the statement that the case met the international criteria for research reporting of AFE.

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. 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.

ponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.

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 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.

5. 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.

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 limits for different article types are as follows: Case Reports, 125 words. Please provide a word count.

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

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

10. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

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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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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.

August 5th, 2019

Dear Editors,

First of all, we would like to thank the editorial board and reviewers for their insightful comments. We have made changes to our submission according to the reviewers' comments. Please accept this revised manuscript ("Extracorporeal therapies for amniotic fluid embolism.") for consideration for publication in *Obstetrics & Gynecology*. We confirm that we have read the Instructions for Author of the Journal.

Please find below a point-by-point response to the reviewers' comments.

Sincerely,

Julien Viau-Lapointe
Niall Filewod

Reviewer(s)' Comments to Author:

Reviewer: 1

Case report and review of a very complicated amniotic fluid embolus and the use of VA ECMO

1. line 57 "fetal mortality or mortality " do you mean to say "fetal mortality or maternal mortality"?
We changed the text to "fetal morbidity and mortality"

2. Line 71: ROSC? abbreviation
This abbreviation has been modified including other abbreviations.

3. Discussion: 119-126 A more basic explanation of the why and the physiology behind VA vs VV ECMO would be helpful/ I found this paragraph confusing
4. Example VA ECMO is used in instances such as>>> and VV ECMO is used in instances and what we would be treating after an AFE, severe pulmonary hypertension in which case VV is adequate or cardiogenic shock in which case VA is needed
We thank the reviewer for this comment. Basic physiology underlying VV and VA ECMO has been added including examples which hopefully will explain clearly these concepts to the wide authorship of the journal.

5. I thought you did a good discussion of the complexity of DIC with AFE and how to manage on ECMO
Thank you.

6. When describing the cases and your search describe that these 20 cases span 34 years, oldest case in 1986 and the trend from bypass to ECMO
These details have been added in the manuscript.

7. Table 1 and 2 I think adding the year of publication is helpful for the reader to see that there are more case reports of ECMO in the past 5-7 years
The year of publication have been added in both tables.

8. You have guidelines published for AFE , Are there guidelines for use of ECMO?
There are no widely recognized guidelines for VA ECMO although the Extracorporeal Life Support Organization provides guidance on the use of VA ECMO through a guideline available on their website. We have added these guidelines. To our knowledge, no guidance exists regarding the use of ECMO in the context of AFE.

Reviewer 2

This is a nice review of an important topic. ECMO has been floating around as a suggested therapy for some cases of AFE and it is nice to see all available reports brought together in one place. A couple of suggestions:

1. Although the reported cumulative survival rate for women receiving ECMO is encouraging, reporting bias is a very important limitation that really has to be discussed. It is not only possible, but likely that cases of ECMO which resulted in survival are more likely to be submitted for publication than cases in which ECMO was associated with maternal death. Thus it is really premature to claim that ECMO improves survival, and very inappropriate to conclude (see last sentence in the article) that such therapy "must be attempted." The authors need to tone this all down significantly and conclude that this therapy has the potential to improve outcomes and ought to be considered in select cases of AFE, but that is it premature to conclude that ECMO actually improves outcomes or that its use in any single case would have resulted in survival.
We thank the reviewer for this comment. We agree that our initial message was too strong considering the quality of the data we presented. We have modified our recommendations and hopefully made it clear that ECMO could be attempted if other therapies fail. AFE remains a deadly and morbid disease, and other potential therapies for AFE similarly lack strong evidence to support their use. Unfortunately it seems very unlikely that an intervention trial regarding the use of ECMO in AFE will be completed.

2. In the abstract I was initially struck by the liver laceration and my first thought was "this was probably not an AFE." In reading the manuscript, it is clear that my initial impression was incorrect. However, I believe the authors have done themselves a disservice by including this incidental, post code issue so prominently in the abstract, while leaving out much more important issues such as the failure to improve oxygenation with PEEP as diagnostic of lung injury. The liver laceration has to be included in the body of the text, but I would not include it in the abstract. Rather, I'd include the statement that the case met the international criteria for research reporting of AFE.

We thank the reviewer for this comment. We clarified the abstract, removed the details about the liver laceration and attempted to specify that the bleeding was secondary to resuscitation and ECMO. Unfortunately due to the conciseness of the abstract (125 words) we were not able to specify that the case fulfilled the diagnostic criteria, but the manuscript contains the details.