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: Feb 14, 2019
To: "Stephanie Martin" drknitter@gmail.com;stephaniemartin@clinicalconceptsinob.com
From: "The Green Journal" [redacted]
Subject: Your Submission ONG-19-113

RE: Manuscript Number ONG-19-113

Pulmonary Hypertension and Pregnancy

Dear Dr. Martin:

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 Mar 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Pulmonary Hypertension is a severe condition that is not rare. This is a thorough review of the physiology, epidemiology, and treatment options.

The report has 6 main sections with subgroups that are well arranged.

An overview at the beginning of the review of the sections, labelled VI a,b,c,d etc, would make it easier for the reader to find a relevant subcategories.

1. 158 If TTE is positive but has low sensitivity in pregnancy what would be the next diagnostic test? Is the specificity of TTTE good?

2. 333 "FDA category X" is superfluous. The categories were abandoned in 2014 by the FDA.

3. 393 All 6 patients ultimately died... Well we all ultimately die, what was the time frame?

4. 414 Patients with PAH generally have lower lung allocations, transplant scores and higher wait list mortality, why is that?

5. "Prostaglandins" when used in obstetric parlance usually infers uterotonic action. A sentence to explain how/why the prostaglandins referred to in the article differ, would be helpful.

6. In a few places it would have been helpful to have the references earlier in the paragraph, for example 209: A recent publication (ref)..... 471 In the ROPAC registry of pulmonary hypertension in pregnancy (ref) -(especially since ROPAC is not defined).

7. The references in the text are not numbered (yet). In the Reference section they are numbered but not in alphabetical order making it difficult for the reviewer to find.

8. The plethora of abbreviations can be disorienting to the uninitiated; a list with definitions at end of paper could be helpful.

9. The following abbreviations lack definitions:
59 ECMO Is defined later
85 PH, is defined several times later.
172 LV, is defined in 181

264 SpO2
320 NYHA
471 ROPAC

Reviewer #2: The authors review the classification, diagnosis, and management of the very important topic of pulmonary hypertension in pregnancy. I only have a few comments:

1. Line 72 - typo, should say "6.5 per 100,000" rather than 100,00. Can you provide reference for these values? Is it also from George 2014?

2. I suggest rearrangement of a few of the sections - consider moving the Pathophysiology section above the Classification and Diagnosis section.

3. Line 299 - please add info in this section on the FDA categories of these medications.You have it later but it might be best to have this information altogether.

Reviewer #3: This is a well-written review of a challenging topic. Comments and suggestions for revision follow.

1. Abstract.
a. Regarding categories of treatment for pulmonary hypertension, algorithms typically list general measures (physical activity, birth control, genetic counseling, infection prevention), supportive therapy (anticoagulation, oxygen, diuretics, digoxin), and specific drug therapy. Would consider these when revising.
b. Minor: In line 57, would include a definition of Group 1 for readers unfamiliar with the WHO classification. Regarding the sentence in lines 61-62, might shorten to "few studies addressing timing and mode of delivery, including anesthetic considerations."

2. Introduction.
a. In this opening section, the authors introduce epidemiology, physiology, and natural history of pulmonary hypertension, with some of the content specific to pregnancy. The flow is not as straightforward as it might be. Suggest trying to limit each paragraph to one of these topics.
b. Suggest including something about the genetic basis of pulmonary hypertension (heritable forms), here or elsewhere in the manuscript.
c. Lines 79-81. This sentence introduces WHO Class (Group) 4, pulmonary arterial hypertension. However, an overview of the classification/groupings has not yet been provided, so this is somewhat confusing. Could address either by inserting a paragraph describing the classification and referring the reader to table 1, or otherwise reorganizing the statements to move this into the next section.
d. Lines 89-92. In these sentences, the authors write about cases of pulmonary hypertension that first present during pregnancy, using 24% of cases of pulmonary hypertension from congenital heart disease as an example. Would clarify if these are women with known congenital cardiac disease who first manifest symptoms during pregnancy or if the women were diagnosed with congenital cardiac disease during pregnancy.

3. Classification and Diagnosis.
a. There has been a recent (6th) World Symposium on Pulmonary Hypertension that includes changes to the definition and classification. The authors may want to include this in their CES. An overview is provided in: Galie N, McLaughlin VV< Rubin LJ, et al. Eur Respir J 2019;53:1802148.
b. Lines 94-97. If the diagnosis is based on 25 mm Hg, with normal 11-17 mm Hg and 21-24 mm Hg borderline, what is 18-20 mm Hg?
c. Lines 98-105 is an explanation of the different types of pulmonary hypertension, including a mention of Group 2 in lines 103-105. However, pulmonary hypertension is not classified into groups until the text in lines 105-111. Suggest reorganizing the text to present the classification after the definition.
d. The "Role of Echocardiography" makes up the majority of this section. It would be reasonable to move this to a separate section (Diagnosis).
e. Line 151. This is table 3 rather than figure 3.

4. Pathophysiology.
a. Would consider relabeling this section pathogenesis.
b. In line 164, the authors mention the prostacyclin pathway, endothelin pathway, and nitric oxide pathway. The prostacyclin pathway is discussed in lines 196-207, but there doesn't appear to be any content in this section devoted to the other two pathways, which seems disjointed.
c. Lines 167-195 (Importance of the right ventricle). Might consider moving to the end of the natural history/physiology.

5. Prognosis.
a. Suggest moving text from lines 471-475 to this section.

6. Treatment.

a. Suggest a table/box to summarize the treatment section (to help organize the subheadings).
b. Suggest some clarification that most data regarding treatment is for Group 1 and that treatment of non-Group 1 patients is usually targeted at the underlying disease. Group 1 treatment might be subdivided, e.g. as general measures, supportive therapy, and specific drug therapy.
c. Regarding the statement about category X in line 333, the FDA no longer uses letter categories (the boxed warning statement is correct). Might comment on the importance of the endothelin-receptor signaling pathway for neural-crest development (animal species exposed to these agents have developed cranial neural-crest defects). Endothelin-receptor antagonists may be obtained only through restricted access programs (REMS), each of which has stringent requirements that include contraception and monthly pregnancy testing.
d. Lines 416-431. Suggest including this under general measures.

7. Management.
The medical management subsection seems similar to the treatment section. Might move some of the text for specific agents to that section.

8. Figures and Tables.
For table 1 and figure 1, would consider updating with: 6th WSPH - Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913

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. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source. Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. Please review the following:
a. LINES 184-192: Please add a citation at the end of this paragraph (“Suspicion of RV failure….low cardiac index”)

5. 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.

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

7. 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).

8. 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: Clinical Expert Series, 300 words. Please provide a word count.

9. 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.

10. 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.

11. 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.

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

"For all figures: Please upload the original source files (do not copy and paste into Word)"

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.

13. 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 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 Mar 07, 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

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

February 26, 2019

Dear Editors:

Thank you again for the invitation to submit a manuscript on the topic Pulmonary Hypertension in Pregnancy for the Clinical Expert Series in *Obstetrics and Gynecology*. We are resubmitting our revised manuscript following critique from the reviewers. Below are our bulleted responses to each of the reviewers' critiques.

REVIEWER COMMENTS:

Reviewer #1: Pulmonary Hypertension is a severe condition that is not rare. This is a thorough review of the physiology, epidemiology, and treatment options.

The report has 6 main sections with subgroups that are well arranged.

An overview at the beginning of the review of the sections, labelled VI a,b,c,d etc, would make it easier for the reader to find a relevant subcategories.

- Given space constraints, we opted not to include a table of contents for the review.

1. 158 If TTE is positive but has low sensitivity in pregnancy what would be the next diagnostic test? Is the specificity of TTTE good?

- Sentence added to manuscript to clarify next steps if intermediate or high probability for PH on echo. Specificity of echo for PH not well defined in pregnancy, but negative predictive value very good.

2. 333 "FDA category X" is superfluous. The categories were abandoned in 2014 by the FDA.

- Categories removed.

3. 393 All 6 patients ultimately died... Well we all ultimately die, what was the time frame?

- Added comment: within the first several months

4. 414 Patients with PAH generally have lower lung allocations, transplant scores and higher wait list mortality, why is that?

- Reasons for this are complex and remain unclear. We opted not to expand to address this issue given space constraints.

5. "Prostaglandins" when used in obstetric parlance usually infers uterotonic action. A sentence to explain how/why the prostaglandins referred to in the article differ, would be helpful.

- Manuscript amended to add explanation of the difference in section *Prostacyclin Pathway in PAH*

.

6. In a few places it would have been helpful to have the references earlier in the paragraph, for example 209: A recent publication (ref)..... 471 In the ROPAC registry of pulmonary hypertension in pregnancy (ref) -(especially since ROPAC is not defined).

- Explained ROPAC acronym in its first appearance on page 22. Addressed reference location where able.

7. The references in the text are not numbered (yet). In the Reference section they are numbered but not in alphabetical order making it difficult for the reviewer to find.

- References are listed in order of appearance in article. Article was formatted per OBG submission guidelines.

8. The plethora of abbreviations can be disorienting to the uninitiated; a list with definitions at end of paper could be helpful.

- Given space constraints, list of definitions is not provided separately. Will address definitions more clearly in manuscript where able.

9. The following abbreviations lack definitions:
59 ECMO Is defined later
85 PH, is defined several times later.

172 LV, is defined in 181
264 SpO2
320 NYHA
471 ROPAC

- All definitions corrected so they are provided in manuscript the first time acronym appears

Reviewer #2: The authors review the classification, diagnosis, and management of the very important topic of pulmonary hypertension in pregnancy. I only have a few comments:

1. Line 72 - typo, should say "6.5 per 100,000" rather than 100,00. Can you provide reference for these values? Is it also from George 2014?

- Corrected
- Yes, same reference, so placed at end of both sentences

2. I suggest rearrangement of a few of the sections - consider moving the Pathophysiology section above the Classification and Diagnosis section.

- Deciding how to arrange the sections was a particular challenge. Ultimately, we felt it was important for the reader to be introduced to the classification and diagnosis concepts in order to better be able to understand the concepts presented in the pathophysiology section.

3. Line 299 - please add info in this section on the FDA categories of these medications. You have it later but it might be best to have this information altogether.

- Reviewer 1 requested removal of FDA Categories as they have not been used by FDA since 2014. We complied and have removed references to FDA Categories.

Reviewer #3: This is a well-written review of a challenging topic. Comments and suggestions for revision follow.

1. Abstract.

a. Regarding categories of treatment for pulmonary hypertension, algorithms typically list general measures (physical activity, birth control, genetic counseling, infection prevention), supportive therapy (anticoagulation, oxygen, diuretics, digoxin), and specific drug therapy. Would consider these when revising.

- Addressed by adding clarification

b. Minor: In line 57, would include a definition of Group 1 for readers unfamiliar with

the WHO classification. Regarding the sentence in lines 61-62, might shorten to "few studies addressing timing and mode of delivery, including anesthetic considerations."

- Revisions made as suggested

2. Introduction.

a. In this opening section, the authors introduce epidemiology, physiology, and natural history of pulmonary hypertension, with some of the content specific to pregnancy. The flow is not as straightforward as it might be. Suggest trying to limit each paragraph to one of these topics.

- Reordered paragraphs and edited.

b. Suggest including something about the genetic basis of pulmonary hypertension (heritable forms), here or elsewhere in the manuscript.

- Given strict space limitations on such a large topic, we were unable to be more detailed on each of the many subtypes of PH. We opted to focus more on issues more relevant to the pregnant patient with PH.

c. Lines 79-81. This sentence introduces WHO Class (Group) 4, pulmonary arterial hypertension. However, an overview of the classification/groupings has not yet been provided, so this is somewhat confusing. Could address either by inserting a paragraph describing the classification and referring the reader to table 1, or otherwise reorganizing the statements to move this into the next section.

- Agree this is confusing. Group descriptions have been removed if appearing before discussion and presentation of Table1

d. Lines 89-92. In these sentences, the authors write about cases of pulmonary hypertension that first present during pregnancy, using 24% of cases of pulmonary hypertension from congenital heart disease as an example. Would clarify if these are women with known congenital cardiac disease who first manifest symptoms during pregnancy or if the women were diagnosed with congenital cardiac disease during pregnancy.

- We are unable to address this question. The reference is a report of 47 case reports or series totaling 73 women. They also report that 55% of patient with idiopathic PAH were diagnosed during pregnancy. No additional information is provided on the specific patient characteristics.

3. Classification and Diagnosis.

a. There has been a recent (6th) World Symposium on Pulmonary Hypertension that includes changes to the definition and classification. The authors may want to include this in their CES. An overview is provided in: Galie N, McLaughlin VV< Rubin LJ, et al. Eur Respir J 2019;53:1802148.

- Thank you – this was published following our submission.

- This reference mostly affirms Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur Heart J 2016; 37(1):67-119. However, we found this to be an updated reference to replace McLaughlin 2009.

b. Lines 94-97. If the diagnosis is based on 25 mm Hg, with normal 11-17 mm Hg and 21-24 mm Hg borderline, what is 18-20 mm Hg?

- clarified this in the manuscript

c. Lines 98-105 is an explanation of the different types of pulmonary hypertension, including a mention of Group 2 in lines 103-105. However, pulmonary hypertension is not classified into groups until the text in lines 105-111. Suggest reorganizing the text to present the classification after the definition.

- Reorganized as suggested

d. The "Role of Echocardiography" makes up the majority of this section. It would be reasonable to move this to a separate section (Diagnosis).

- Revised as suggested

e. Line 151. This is table 3 rather than figure 3.

- Revised

4. Pathophysiology.

a. Would consider relabeling this section pathogenesis.

- Revised

b. In line 164, the authors mention the prostacyclin pathway, endothelin pathway, and nitric oxide pathway. The prostacyclin pathway is discussed in lines 196-207, but there doesn't appear to be any content in this section devoted to the other two pathways, which seems disjointed.

- Expanded and clarified this explanation under pathogenesis

c. Lines 167-195 (Importance of the right ventricle). Might consider moving to the end of the natural history/physiology.

- Authors are not clear where the reviewer would suggest this be moved

5. Prognosis.

a. Suggest moving text from lines 471-475 to this section.

- Authors line numbers must be different from document received by reviewers. We are not clear which lines suggested to be moved.

6. Treatment.

a. Suggest a table/box to summarize the treatment section (to help organize the subheadings).

- Original Figure 3 which demonstrated survival curve with CCB use is omitted and replaced with treatment diagram.

b. Suggest some clarification that most data regarding treatment is for Group 1 and that treatment of non-Group 1 patients is usually targeted at the underlying disease. Group 1 treatment might be subdivided, e.g. as general measures, supportive therapy, and specific drug therapy.

- Clarified in manuscript

c. Regarding the statement about category X in line 333, the FDA no longer uses letter categories (the boxed warning statement is correct). Might comment on the importance of the endothelin-receptor signaling pathway for neural-crest development (animal species exposed to these agents have developed cranial neural-crest defects). Endothelin-receptor antagonists may be obtained only through restricted access programs (REMS), each of which has stringent requirements that include contraception and monthly pregnancy testing.

- Categories removed per this and reviewer 1 suggestion. The restricted access program is mentioned in the manuscript. Mechanism of concern for the drugs is not addressed due to space constraints.

d. Lines 416-431. Suggest including this under general measures.

- Authors request additional clarification as our line numbers appear to be different.

7. Management.

The medical management subsection seems similar to the treatment section. Might move some of the text for specific agents to that section.

- Authors modified this section and clarified headings. Intent is to provide Treatment section for PH in general, nonpregnant, followed by a section on pregnancy management. This section will reference meds and concepts from prior treatment section and address issues specific to pregnancy.

8. Figures and Tables.
For table 1 and figure 1, would consider updating with: 6th WSPH - Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913

- Thank you for the reference. We are not clear that this reference applies to Figure 1 and Table 1. However, we have added it in the manuscript, particularly to address comment 3b.

We look forward to feedback from our revised submission.

Sincerely,

Stephanie R Martin DO

Alexandra Edwards, MD