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:** May 09, 2019
**To:** "Elle Coberger" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-19-611

RE: Manuscript Number ONG-19-611

Transfer of candesartan into human breast milk

Dear Dr. Coberger:

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 30, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Coberger and colleagues present findings from a pharmacologic study designed to evaluate the transfer of the angiotensin II receptor blocker (ARB) candesartan into human breast milk through investigation of 3 women using the medication in the post-partum period. The study addresses an important and understudied area of perinatal medicine. The study appears to have been conducted using appropriate pharmacologic evaluation methods. All 3 women had been breast feeding from 2 1/2 - 13 months. No information is provided regarding the indication for and/or timing (when initiated relative to the sampling) of the candesartan treatment. Overall the paper if well written. A point-by-point critique of the paper follows:

1) No information is provided regarding the indication for and/or timing (when initiated relative to the sampling) of the candesartan treatment in the 3 women studied. This is important information and should be included in the revised paper.

2) In the Introduction of the paper on page 5, line 58, the authors state that ACE inhibitors are not tolerated in breast-feeding women. There is no support provided for this statement. Additional supportive information should be provided or at least a reference should be included.

3) In all 3 cases, women had established breast-feeding for over 2 1/2 months. Are the authors aware of any differences for other medications when drug transfer into breast milk differs when assessed early into lactation (< 1 month) vs later with established lactation (> 1 month)? If there are any differences, how would this information potentially impact the conclusions reached by the authors.

REVIEWER #2:

Interesting challenge but I regret that attempting to generalize upon the available data from only three women, breastfeeding at widely different post-gestational times (none of which were immediate puerperal points), with different body sizes, and greatly different dosages does not provide information that can be broadly applied to all users at all post-natal times. Perhaps extending the study to more users at more relevant times including immediate post-partum usage can be found of greater possible utility.

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. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. Please note in your manuscript that the methods described in your reporthave been described previously (https://journals.sagepub.com/doi/10.1177/0890334412473203).

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

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: Case Reports, 125 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. 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 May 30, 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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Elle Coberger
Dept. of Clinical Pharmacology
Christchurch Hospital
PO Box 4710
Christchurch 8140
New Zealand

The Editors
Obstetrics & Gynecology

28th May, 2019

**RE: Manuscript Number ONG-19-611**

Please find attached a resubmission of the revised manuscript entitled 'Transfer of candesartan into human breast milk'.

Thank you for the review and the opportunity to revise and resubmit this manuscript. Please see below for our responses to the comments provided by the reviewers and the editorial board. For comments where we have revised the manuscript, we have tracked changes and noted the line number where these changes were made.

Elle Coberger
BPharm
Dept. of Clinical Pharmacology

## RESPONSE TO REVIEWERS AND EDITORIAL BORAD COMMENTS

REVIEWER COMMENTS:

REVIEWER #1:

Coberger and colleagues present findings from a pharmacologic study designed to evaluate the transfer of the angiotensin II receptor blocker (ARB) candesartan into human breast milk through investigation of 3 women using the medication in the post-partum period. The study addresses an important and understudied area of perinatal medicine. The study appears to have been conducted using appropriate pharmacologic evaluation methods. All 3 women had been breast feeding from 2 1/2 - 13 months. No information is provided regarding the indication for and/or timing (when initiated relative to the sampling) of the candesartan treatment. Overall the paper if well written. A point-by-point critique of the paper follows:

1) No information is provided regarding the indication for and/or timing (when initiated relative to the sampling) of the candesartan treatment in the 3 women studied. This is important information and should be included in the revised paper.

**Response:**
Further information on indication has been added to explicitly state what candesartan was being used for (lines 124 and 134). We have also added details to the method (line 92) on sample timing, to ensure understanding that the sampling was conducted at steady state.

2) In the Introduction of the paper on page 5, line 58, the authors state that ACE inhibitors are not tolerated in breast-feeding women. There is no support provided for this statement. Additional supportive information should be provided or at least a reference should be included.

**Response:**
Our intention was to communicate that women who are intolerant of ACE inhibitors and who are breastfeeding could consider using an ARB. We have modified the sentence to clarify this.

3) In all 3 cases, women had established breast-feeding for over 2 1/2 months. Are the authors aware of any differences for other medications when drug transfer into breast milk differs when assessed early into lactation (< 1 month) vs later with established lactation (> 1 month)? If there are any differences, how would this information potentially impact the conclusions reached by the authors.

**Response:**
We are aware of reports of drug transfer into breast milk differing when assessed early in lactation (< 1 month) versus later with established lactation (> 1 month). With respect to our study, ARBs are contraindicated during pregnancy and the earliest re-initiation of candesartan in our three cases was one month post-partum. In terms of extrapolating these findings, we are aware that colostrum differs to transitional milk, which differs to mature milk in terms of composition and therefore drug transfer (especially of lipophilic drugs). We also acknowledge the reduced clearance in

younger compared to older infants, which may result in increased drug accumulation. We accept that some readers may not readily appreciate this background and have modified the wording of our conclusion to highlight the concept of increased caution in young infants.

REVIEWER #2:

Interesting challenge but I regret that attempting to generalize upon the available data from only three women, breastfeeding at widely different post-gestational times (none of which were immediate puerperal points), with different body sizes, and greatly different dosages does not provide information that can be broadly applied to all users at all post-natal times. Perhaps extending the study to more users at more relevant times including immediate post-partum usage can be found of greater possible utility.

**Response:**
We would submit that the consistency of the results given the different post-gestational times, body sizes, and doses is reassuring given that human breast milk can vary considerably on an inter-individual basis. Having completed our study in mature milk and at a time when ARB use is more likely to be considered (given that other drugs will have been used during pregnancy when ARBs are contraindicated) we would suggest that our results provide data relevant to real-world practice.

We do acknowledge that this is a small case series and we have modified our conclusion to reflect this. We were only able to recruit three subjects but would argue that it is still of value to this area of research to publish the data available as a case series. This may encourage further studies in countries with larger populations.

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.

**Response:**
OPT-IN: Yes, please 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. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. Please note in your manuscript that the methods described in your reporthave been described previously (https://journals.sagepub.com/doi/10.1177/0890334412473203).

**Response:**
We have inserted the reference to our earlier work. This brings our total number of references to 9. We note the suggested maximum number of references for a case report is 8, and we would respectfully request allowance to include this extra reference.

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.

**Response:**
We note the use of 'term' under reVITALize definitions for 'full-term', and have adjusted this throughout our manuscript.

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.

**Response:**
The manuscript length is 1981 words (14 pages). We deleted lines 105 to 108 in the method to meet the word count requirement, which we do not believe is detrimental to the report. We also made some minor edits in the manuscript to conform to the word count which we have not tracked.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

**Response:**
No financial support was received for the study. We did not receive any direct or indirect assistance in preparing this manuscript. All persons who contributed to the manuscript are acknowledged and have provided their written permission to be acknowledged.

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

**Response:**
The short title is now 39 characters, including spaces.

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

**Response:**
We have adjusted the abstract to ensure it is consistent with the changes made to the manuscript. The word count is 121 words.

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.

**Response:**
We believe we have only used standard abbreviations and acronyms.

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.

**Response:**
We believe we have only used the virgule symbol 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.

**Response:**
We have corrected the use of one trailing zero in Table 1 for the milk AUC $_{0\text{-}24h}$ (µg.h/L) for participant 3. We have changed the other milk AUC $_{0\text{-}24h}$ (µg.h/L) results to 2 significant figures for consistency. We otherwise believe we have conformed to the checklist.

12. 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.