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: Aug 27, 2019
To: "Katrina B Mitchell" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1436

RE: Manuscript Number ONG-19-1436

Breast cancer screening during lactation: Ensuring optimal surveillance of breastfeeding women

Dear Dr. Mitchell:

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 Sep 17, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a current commentary piece that promotes the use of optimized breast cancer screening strategies for lactating women. Delayed child-bearing has resulted in women breast feeding as they reach the age for initiation of screening. The literature was reviewed to identify evidence-based guidelines. The authors determined that breast feeding women should undergo age or risk-based screening. They discussed women at high risk due to BRCA mutations and highlight the emerging data on postpartum women being at elevated risk of biologically aggressive breast cancers. They note the radiographic changes to be anticipated in mammograms, ultrasounds and MRIs. They include several normal screening images demonstrating changes noted in pre-pregnancy films and lactating films. Many of the films are of a single patient at high risk due to BRCA mutations.

Consent to publish radiographic images was obtained from patients.

1. The abstract is specific to the paper.

2. The paper is well written and would be useful to obstetricians and radiologists.

Reviewer #2: This manuscript is submitted as a current commentary addressing a particularly vexing but important area in obstetrics and breast health. The authors have provided opinions about the management of breast cancer screening during lactation based on their review of the literature. This area is particularly challenging because there is insufficient scientifically rigorous evidence to guide many of the clinical decisions that need to made. I applaud the authors for attempting to answer clinical questions surrounding guidance for breast cancer screening in the lactating woman. I have the following comments for the authors:

1. In the precis, the phrase "...optimize the sensitivity of breast cancer screening..."seems confusing as a goal. More clear goals might be "...to avoid delayed diagnosis.." or "...to optimize breast cancer detection with screening...".

2. Line 74. Is there a reference for "more questions are arising regarding breast cancer screening in his population" or is that just the authors' perception.

3. Line 79-80. The authors reference that there are differences in recommendations among national and specialty-specific societies, but don't provide references to those different societies recommendations.

4. Line 97-98. While it is true that USPSTF and ACS recommendations have been criticized, so too have nearly all society

recommendations about screening. I don't think it is all that relevant to the topic of the paper and distracts the viewer. Though I don't disagree with the authors' point, I would still consider deleting this sentence.

5. Line 101. In the era of multi-gene breast cancer panel testing, might want to broaden this beyond just BRCA (e.g., "BRCA and other germline mutations that increase early onset breast cancer".

6. Line 113-116. While this observational data is important, there remains no evidence that screening during lactation (as opposed to after lactation) reduces breast cancer mortality. There are theoretical reasons why screening during pregnancy may improve mortality, and theoretical reasons why routine screening may not improve mortality. Since nearly all of the data to support screening is indirect, one might be a bit more circumspect in making a direct recommendation that there is sufficient evidence to recommend screening routinely. Again, I don't necessarily disagree with the authors' premise that screening during lactation may be appropriate in high risk women, I just don't think it is "clear that this population should at least not forgo routine screening" with a qualifier such as "In the authors' opinion..."

7. Line 118-120. The authors should juxtapose their recommendations that there is no contraindication to MRI with the ACR Appropriateness Criteria statement on Breast Cancer Screening During Lactation, where they state that MRI is "usually not appropriate". Also, the authors should cite the most recent ACR publication J Am Coll Radiol 2018;15:S263-S275. Their MRI statement is on page S264, Variant 1. I actually agree with the authors, but they should point out their distinction from the ACR guidelines including why they differ. A good reference to support use is Myers KS, Green LA, Lebron L, Morris EA. Imaging appearance and clinical impact of preoperative breast MRI in pregnancy-associated breast cancer. AJR Am J Roentgenol 2017;209:W177-83.

8. Line 122-24 Staging studies either deserves more explanation and support, or don't include. My suggestion is that it goes beyond the topic of screening and probably be better left out.

9. Line 153-154. I think referencing a textbook is less than ideal.

Reviewer #3: I believe that throughout the document, the recommendations made are beyond the scope of the article, which has limited references.

In line 90, the recommendations of ACOG are overstated, as ACOG guidelines recommend offering mammography rather than recommending routine mammography at age 40.

I would be comfortable with the document if in all relevant areas, the authors stated that routine screening may be offered to age appropriate lactating patients with a discussion of the potential limitations of such screening, versus an alternative strategy of delaying screening until cessation of breast feeding.

A document suggesting such guidance should only be provided from committee of experts---otherwise the authors should use educational language (above) or clearly indicate that this is their opinion only.

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: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 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. 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).

6. 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: Current Commentary articles, 250 words. Please provide a word count.

7. 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.

8. 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.

9. 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.

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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 Sep 17, 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 30, 2019

Nancy C. Chescheir, MD
Editor-in-Chief, *Obstetrics & Gynecology*

RE: Manuscript Number ONG-19-1436
Breast cancer screening during lactation: Ensuring optimal surveillance of breastfeeding women

Dear Dr. Chescheir:

We thank the journal for your review of the above referenced submission. We appreciate the constructive feedback from the reviewers, and offer the following replies to the comments/questions:

Reviewer #1: This is a current commentary piece that promotes the use of optimized breast cancer screening strategies for lactating women. Delayed child-bearing has resulted in women breast feeding as they reach the age for initiation of screening. The literature was reviewed to identify evidence-based guidelines. The authors determined that breast feeding women should undergo age or risk-based screening. They discussed women at high risk due to BRCA mutations and highlight the emerging data on postpartum women being at elevated risk of biologically aggressive breast cancers. They note the radiographic changes to be anticipated in mammograms, ultrasounds and MRIs. They include several normal screening images demonstrating changes noted in pre-pregnancy films and lactating films. Many of the films are of a single patient at high risk due to BRCA mutations.

Consent to publish radiographic images was obtained from patients.
1. The abstract is specific to the paper.
2. The paper is well written and would be useful to obstetricians and radiologists.

Response: Thank you for the positive feedback.

Reviewer #2: This manuscript is submitted as a current commentary addressing a particularly vexing but important area in obstetrics and breast health. The authors have provided opinions about the management of breast cancer screening during lactation based on their review of the literature. This area is particularly challenging because there is insufficient scientifically rigorous evidence to guide many of the clinical decisions that need to made. I applaud the authors for attempting to answer clinical questions surrounding guidance for breast cancer screening in the lactating woman. I have the following comments for the authors:

1. In the precis, the phrase "...optimize the sensitivity of breast cancer screening..."seems confusing as a goal. More clear goals might be "...to avoid delayed diagnosis.." or "...to optimize breast cancer detection with screening...".

Response: Thank you for the feedback. Based on your comments as well as those of Reviewer #3, we have modified the precis (lines 26-28).

2. Line 74. Is there a reference for "more questions are arising regarding breast cancer screening in his population" or is that just the authors' perception.

Response: We are not aware of a reference for this statement. In our practice as breast radiologists and surgeons, we receive frequent questions regarding when and how to perform breast cancer screening in breastfeeding women.

3. Line 79-80. The authors reference that there are differences in recommendations among national and specialty-specific societies, but don't provide references to those different societies recommendations.

Response: We have added these references (line 81).

4. Line 97-98. While it is true that USPSTF and ACS recommendations have been criticized, so too have nearly all society recommendations about screening. I don't think it is all that relevant to the topic of the paper and distracts the viewer. Though I don't disagree with the authors' point, I would still consider deleting this sentence.

Response: Thank you for your insight. We have omitted this sentence (lines 99-101).

5. Line 101. In the era of multi-gene breast cancer panel testing, might want to broaden this beyond just BRCA (e.g., "BRCA and other germline mutations that increase early onset breast cancer".

Response: We have modified this sentence accordingly (lines 104-105).

6. Line 113-116. While this observational data is important, there remains no evidence that screening during lactation (as opposed to after lactation) reduces breast cancer mortality. There are theoretical reasons why screening during pregnancy may improve mortality, and theoretical reasons why routine screening may not improve mortality. Since nearly all of the data to support screening is indirect, one might be a bit more circumspect in making a direct recommendation that there is sufficient evidence to recommend screening routinely. Again, I don't necessarily disagree with the authors' premise that screening during lactation may be appropriate in high risk women, I just don't think it is "clear that this population should at least not forgo routine screening" with a qualifier such as "In the authors' opinion..."

Response: We appreciate the feedback and have clarified that this is our opinion (line 119).

7. Line 118-120. The authors should juxtapose their recommendations that there is no contraindication to MRI with the ACR Appropriateness Criteria statement on Breast Cancer Screening During Lactation, where they state that MRI is "usually not appropriate". Also, the authors should cite the most recent ACR publication J Am Coll Radiol 2018;15:S263-S275. Their MRI statement is on page S264, Variant 1. I actually agree with the authors, but they should point out their distinction from the ACR guidelines including why they differ. A good reference to support use is Myers KS, Green LA, Lebron

L, Morris EA. Imaging appearance and clinical impact of preoperative breast MRI in pregnancy-associated breast cancer. AJR Am J Roentgenol 2017;209:W177-83.

Response: Our understanding is that the ACR Appropriateness Criteria for Breast Imaging of Pregnant and Lactating Women (reference 3) categorizes MRI as "usually not appropriate" because it is not the recommended first-line imaging modality for average-risk women. The discussion on page S268 includes the following statement: "…although not the initial imaging tool of choice, screening breast MRI is not contraindicated during lactation and may be considered in lactating women with a high lifetime risk of breast cancer." We include the ACR's recommendations about screening MRI in this population in a later paragraph (lines 163-169).

Thank you for the suggested reference by Myers et al. We have elected to maintain our citation of the ACR Manual on Contrast Media manual for the statement that MRI is safe in lactation in order to cite the highest level of evidence possible. In these expert consensus recommendations, the ACR states, "Because of the very small percentage of gadolinium-based contrast medium that is excreted into the breast milk and absorbed by the infant's gut, we believe that the available data suggest that it is safe for the mother and infant to continue breast-feeding after receiving such an agent" (page 100). Of note, the sentences in the study by Myers et al. about the lactational safety of MRI include references to three papers (reference numbers 24-26 in their article) which are also cited in the ACR Manual (reference numbers 4-6 on page 100 of the manual). We have added two sentences to our manuscript to expand on the considerations that should be given to breastfeeding after receipt of gadolinium contrast (lines 124-127).

8. Line 122-24 Staging studies either deserves more explanation and support, or don't include. My suggestion is that it goes beyond the topic of screening and probably be better left out.

Response: We have omitted these sentences to ensure focus on screening (lines 128-131).

9. Line 153-154. I think referencing a textbook is less than ideal.

Response: We have changed this reference to the seminal article on milk fistula (line 161).

Reviewer #3: I believe that throughout the document, the recommendations made are beyond the scope of the article, which has limited references.

In line 90, the recommendations of ACOG are overstated, as ACOG guidelines recommend offering mammography rather than recommending routine mammography at age 40.

Response: We have corrected the statement about the ACOG recommendations (lines 92-94).

I would be comfortable with the document if in all relevant areas, the authors stated that routine screening may be offered to age appropriate lactating patients with a discussion of the potential limitations of such screening, versus an alternative strategy of delaying screening until cessation of breast feeding.

A document suggesting such guidance should only be provided from committee of experts---otherwise the authors should use educational language (above) or clearly indicate that this is their opinion only.

Response: Thank you for the constructive feedback. Throughout the document, we have made modifications in favor of more educational language (examples: lines 26-28, 52-55, 60, 167-168). In two instances, we added designations for our opinions (line 119 and line 171).

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 authors have no conflicts of interest to disclose. This manuscript is not under consideration elsewhere and will not be submitted elsewhere unless a final negative decision is made by the editors of *Obstetrics & Gynecology*. The authors confirm that we have read the Instructions for Authors.

All authors have discussed the reviewers' comments and have approved this letter as well as the revised manuscript. With respect to the journal's efforts to increase transparency, we elect to: "OPT-IN: Yes, please publish our point-by-point response letter".

Thank you kindly for your consideration of our revised manuscript. We look forward to any further comments or concerns.

Sincerely,

Katrina B. Mitchell, MD
[redacted]