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: Jun 14, 2019
To: "Ashish Premkumar" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-912

RE: Manuscript Number ONG-19-912

Methadone, buprenorphine, or detoxification for management of perinatal opioid use disorder: a cost-effectiveness analysis

Dear Dr. Premkumar:

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 Jul 05, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an interesting manuscript with a purpose to perform "a decision analysis to investigate whether methadone, buprenorphine, or detoxification treatment is the most cost-effective approach in the management of OUD during pregnancy."

1. The authors note that they decided "to specifically analyze a detoxification protocol that employed a buprenorphine taper." In the introduction to their manuscript could the authors please expand their discussion of the use of buprenorphine as a MAT, including the use of a taper protocol over 14 days?

2. Could the authors expand their discussion to include that not only does the current study support the cost-effective use of buprenorphine but that their meta-analysis (ref 13) supported the use of pharmacotherapy over detoxification?

3. This is a well-written, timely manuscript.

Reviewer #2: The study provides a new insight into a very important public health issue. There are limited studies in the literature regarding the cost effective approach to management of opioid use during pregnancy.

The objectives are clearly stated. The analysis is conducted from a health payer perspective and focuses both on both maternal and neonatal outcomes.

All the appropriate alternatives are considered. The authors describe the adverse effects of detoxification. The authors should also discuss no difference in effectiveness between buprenorphine and methadone in the introduction.

All relevant costs are included in the study. All relevant outcomes are measured. All the assumptions are reasonable. The authors appropriately describe the limitations and generalizability of the study.

Reviewer #3: The authors are to be thanked for contributing to the literature on the current opioid crisis.
Their DA methodology is limited by the data available regarding OUD in pregnancy (line 156) and relapses in Obs (p 172).

I would appreciate just a bit of clinical information from the authors' experience with these three methods of treating OUD in pregnancy.

I think this paper will be used to help design future clinial studies to better understand OUD in pregnancy.

STATISTICAL EDITOR'S COMMENTS:

1. Suppl Appendix 1 TreeAge Diagram: Since the tree diagram is replicated (with different probabilities) for the three treatment scenarios, should include one (perhaps the buprenorphine) within the main text, then state that the format is replicated for the other treatments and refer to the on-line figure.

2. lines 209-219: Given how sensitive the cost-analysis outcomes were to the relative cost of detox, methadone and buprenorphine, how much regional variation in the US is there to those costs and relative costs? That is, are there regional or urban vs rural centers where the relative costs vary and therefore dominant management strategy could vary according to regional costs? It would seem that it would not take much variation in local relative costs to change the dominance.

3. lines 276-278, Table 5: In terms of sensitivity analyses, should provide a version of Table 5 with empirical 95% CIs from the 100,000 simulations, in addition to the baseline estimates of events. Also, should explain to reader how the maternal relapse events relate to the initial hypothetical cohorts of N = 20,000. Perhaps another row entry of number of women successfully treated with 1, 2 etc cycles for each treatment arm.

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.

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 studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, 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: Original Research articles, 300 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.

11. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

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

"-Fig 1: The number along the red dotted line is hard to see – is the author able to upload the original file that we could edit?
-Fig 2: The number along the red dotted line is hard to see – is the author able to upload the original file that we could edit?"

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.

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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 Jul 05, 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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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.

[redacted]

Editor
Obstetrics & Gynecology

7/11/19

Dear Editor,

Thank you for the opportunity to revise and resubmit our paper, entitled “Methadone, buprenorphine, or detoxification for management of perinatal opioid use disorder: a cost-effectiveness analysis.” Authors include Ashish Premkumar, Mishka Terplan, William A. Grobman, and Emily S. Miller. The authors report no conflict of interest. All authors have approved this version of the manuscript for submission.

Based on revised data informing the decision analysis, we have updated our probabilities surrounding relapse in the detoxification arm and updated our results and conclusions surrounding the study. We have uploaded a tracked version of the manuscript and tables. In regards to the reviewers comments, we have responded to them below:

Reviewer #1:

1. The authors note that they decided "to specifically analyze a detoxification protocol that employed a buprenorphine taper." In the introduction to their manuscript could the authors please expand their discussion of the use of buprenorphine as a MAT, including the use of a taper protocol over 14 days?
    a. Please see the added sentence on pg. 5, lines 120-121 for further clarification. We do specifically discuss the decision to use a 14 day buprenorphine taper as the detoxification protocol in the Methods section (see p. 6-7, lines 141-145).

2. Could the authors expand their discussion to include that not only does the current study support the cost-effective use of buprenorphine but that their meta-analysis (ref 13) supported the use of pharmacotherapy over detoxification?
    a. A statement has been added on p. 13, lines 301-3 that specifically addresses this issue.

Reviewer #2
1. The authors should also discuss no difference in effectiveness between buprenorphine and methadone in the introduction.

a. We have specifically discussed the issue surrounding effectiveness between buprenorphine and methadone. Please see p. 6, lines 128-9.

Reviewer #3

1. I would appreciate just a bit of clinical information from the authors' experience with these three methods of treating OUD in pregnancy.
    a. Although we appreciate the reviewer's comment, we believe that reflections of personal experience with OUD treatment is outside the scope of this article, which we would prefer to limit to the more objective analytic results.

Statistical Editor:

1. Suppl Appendix 1 TreeAge Diagram: Since the tree diagram is replicated (with different probabilities) for the three treatment scenarios, should include one (perhaps the buprenorphine) within the main text, then state that the format is replicated for the other treatments and refer to the on-line figure.
    a. We have added an additional figure for readers to review. Please see Figure 1, as well as p. 6, lines 139-141 regarding a statement that indicates that the format of Figure 1 is replicated in other treatment arms.
2. Lines 209-219: Given how sensitive the cost-analysis outcomes were to the relative cost of detox, methadone and buprenorphine, how much regional variation in the US is there to those costs and relative costs? That is, are there regional or urban vs rural centers where the relative costs vary and therefore dominant management strategy could vary according to regional costs? It would seem that it would not take much variation in local relative costs to change the dominance.
    a. It is difficult to tell regional variation, as there are limited data in the literature (see p. 10, lines 213-214) regarding detoxification. However, because Medicare/Medicaid offers standard drug pricing for methadone and buprenorphine, these values should be fixed across states. Also, it should be noted that even if the dominance of one strategy were to change, it would require far greater change to lead to that strategy being no longer cost effective (i.e., even reasonable variation should still leave the core conclusion intact). We have added a statement in our Discussion that attends to the concern from the editor. See p. 15, lines 327-9
3. Lines 276-278, Table 5: In terms of sensitivity analyses, should provide a version of Table 5 with empirical 95% CIs from the 100,000 simulations, in addition to the baseline estimates of events. Also, should explain to reader how the maternal relapse events relate to the initial hypothetical cohorts of N = 20,000. Perhaps another row entry of number of women successfully treated with 1, 2 etc cycles for each treatment arm.
    a. We were able to add in 95% CI within Table 5, and have added additional discussion regarding relapse events and successful treatment with buprenorphine alone within the buprenorphine arm itself (p. 12, lines 265-72).

Please find in this upload the manuscript with 5 tables, 3 figures, and 1 appendix figure. We have also uploaded the CHEERS checklist for reporting economic evaluations of health outcomes. Please do not hesitate to reach out to us with any questions or concerns.

Best,

Ashish Premkumar, MD
On behalf of all authors