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: Jun 01, 2021
To: "Jeannie C. Kelly" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1046

RE: Manuscript Number ONG-21-1046

Home induction of buprenorphine for treatment of opioid use disorder in pregnancy

Dear Dr. Kelly:

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 Jun 22, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Thank you for your work on induction options for pregnant women with OUD. To my knowledge, yours is the first paper that addresses this important issue. Based on my monitoring of forums on this subject, this is a "hot topic" now, so your paper has the potential to add significant knowledge to the group. I will also complement you that your paper is well written.
I have several concerns I this should be addressed:
1. How did you choose the duration of your study? What is the history of home inductions at your institution? Your study covers the dates from June 18, 2018 through 2020. Why June 18, 2018? Was this when you started doing home inductions? If the 17 patients who underwent observed inductions all received care in the second half of 2018 and everyone since has been home-induced, we need to know this fact.
2. Your control group isn't a good control group. That is, criteria for observed inductions included patients who chose that method, patients in active withdrawal at the time of their visit, and patients otherwise admitted for obstetrical indications. If you looked at only those who chose, and eliminated those who were in active withdrawal, or were admitted, a fairer comparison might have been noted.
3. You need to address the glaring differences in your treatment group and your control group. In particular, the racial differences and the gestational age are two important factors that might have affected your results. I don't think you should even include them in the "strengths and weaknesses" section, but in the main body of your discussion. What analysis have you done to evaluate these differences?
a. Were you more willing to offer home inductions to patients earlier in their pregnancies?
b. Was there a potential interaction between race and gestational age? That is, African American women presenting at more advanced gestational age?
c. Were your African American women distributed relatively evenly over the course of the 30 months of your study? (See #1 above)
d. Were your African American women more likely to be observed induced because they were more likely to present in active withdrawal or more likely to be admitted? (See #2 above)
e. Were all patients given the same opportunity to choose? Please reassure the readers that some underlying racial bias is not responsible.
4. Some have suggested that patients who are induced after the age of fetal viability should be induced while on fetal monitors. Was this a consideration for you? I don't favor this option, but it might be an issue that will be questioned by others.
5. I note that your protocol calls for Subutex (buprenorphine only). I assume this is your standard in pregnancy and isn't chosen over (buprenorphine/naloxone) for some reason for home inductions and wouldn't have had any influence on your outcomes.

Reviewer #2:

This is a retrospective cohort study comparing pregnant patients undergoing sublingual buprenorphine induction for OUD at home versus observed induction. The primary outcome was retention in care over three months following treatment initiation. Secondary outcomes were rates of precipitated withdrawal, adherence to buprenorphine, and abstinence from illicit drug use. Home induction of buprenorphine for OUD has been reported to safe and effective outside of pregnancy. This study is novel in that it describes home induction of buprenorphine in the pregnant population.
Abstract:
1. The reported 3-month retention rate for observed induction is not the same that is reported in Table 2.
Introduction
The introduction is of appropriate length. The authors made a convincing case for the need to complete this study. I would recommend including if there is any reported evidence of patient characteristics that make them more likely to be successful with home induction versus observed induction.
Methods
Study methods are well described.
1. It may be helpful to clarify what made patients presenting in active withdrawal appropriate for immediate buprenorphine induction, and why they were admitted. Why couldn't they be managed as outpatients?
2. Please clarify the definition of patient-level change.
3. Patient characteristics that were used as confounding variables for analysis are not described. However, in Table 2 it is reported that gestational age is used. I am not aware this is associated with severity of opioid use disorder. Also, why were outcomes (in table 2) not similarly adjusted for confounding variables? Would there still be a statistically significant difference in outcomes?
4. The addition of obstetric or neonatal outcomes may strengthen the conclusion that home induction of buprenorphine is a safe and effective method of treatment of OUD in the pregnant population.
Results
1. I would be interested to know if there were any patient characteristics that differed between the "outpatients" that elected induction under observation versus the "inpatients."
2. The reported 3-month retention rate for observed induction is not the same that is reported in Table 2.
Discussion
A thorough, clear discussion of the strengths and weaknesses of the study.
1. I would recommend using "substance use disorder" rather than "substance abuse disorder" in the discussion and throughout the paper.
Table 2
1. Denotations are listed as "1, 2, 3, 4" in the table but "1, 1, 2, 3" in notations. Typo in first notation.

Reviewer #3: ONG 21-1046

In the manuscript under review, Kelly et al present the results of their retrospective analysis evaluating the rate of 3-month retention following treatment initiation using home versus observed buprenorphine induction among pregnant women suffering from opioid use disorder. The authors analyzed 72 cases and found that home induction led to higher rates of treatment retention and lower rates of illicit opioid use.

A few comments on the manuscript are as follows:

ABSTRACT
1. A clear objective is identified

INTRODUCTION
2. No major issues, however no clear hypothesis is identified.

METHODS
3. Line 108 - why was this timeframe chosen? Any major changes to treatment protocols implemented during that time period?

4. Line 123 - how was the sample size calculated? What was the expected rate of change sought by the authors? Was any power calculation done?
5. Since this is not a randomized trial, the choice of primary outcome (rate of retention), is significantly affected by the selection of participants to each of the study groups. In other words, women that are more likely to meet clinical criteria for home induction are also more likely to meet the primary outcome. Therefore, the primary outcome suffers from selection bias based on the original inclusion of participants to each induction group.
6. The authors should add a line stating that the STROBE guidelines were followed in this manuscript.

RESULTS
7. The authors have severely discrepant study groups again indicating that selection bias is most likely present.
8. Do the authors have any data on obstetrical outcomes? Neonatal outcomes? Although treatment retention is a remarkable goal, one can argue that if the intervention evaluated fails to lead to improved obstetrical outcomes, its use in obstetrics is limited and potentially questionable.

DISCUSSION
9. Line 247 one major limitation I would add would be to include the fact that a small sample size may not allow for a true evaluation of treatment and follow-up patterns.
10. Line 272 - what search criteria and what databases were searched to reach the conclusion that this is the first study of this kind.

STATISTICS EDITOR COMMENTS:

Table 1: The two groups had N = 55 and 17, so all %s should be rounded to nearest integer %, not cited to 0.1% precision. Need units for age. Should enumerate any missing data.

Table 2: Need to clarify which adjustors were used for the aRR for 3 month retention in treatment. In any event, there are too few counts of retention vs non-retention in the two groups to allow for multivariable adjustment with either 2 or 4 adjustors. The same issue occurred in the other outcomes tested. On the other hand, there is insufficient power to generalize the NS findings re: RR for return for 1 week visit, buprenorphine metabolites in urine at 1 week follow-up.

Table 3: The slopes may be statistically different, but the groups at baseline were not randomized and were different in multiple baseline characteristics.

EDITOR COMMENT: Thank you for submitting your work to Obstetrics and Gynecology. If you decide to submit a revision, please format it as a research letter and remove the control group of patients who had in-hospital initiation of buprenorphine. The editors are requesting this as multiple reviewers had concerns about the selected control group-specifically differences between patients who would be candidates for in-patient versus out-patient buprenorphine induction. This means that the research letter will simply be a descriptive study of your cohort of patients who underwent out-patient buprenorphine initiation.

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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (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. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

3. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. 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: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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

9. 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 limit for Original Research articles is 300 words. Please provide a word count.

10. 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.

11. 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.

12. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

14. Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

15. 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.

16. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

17. Figure 1: Please separate A and B into separate figures. Both will not fit on a printed page.
Figure 2: okay

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.

18. 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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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.

You will be receiving an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and

instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line 'Please Submit Your Open Access Article Publication Charge(s)'. Please complete payment of the Open Access charges within 48 hours of receipt.

***

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. Do not omit your responses to the Editorial Office or Editors' comments.

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 Jun 22, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

_____

Dear Editors of *Obstetrics & Gynecology*,

We thank you for the opportunity to revise our manuscript for *Obstetrics & Gynecology*. We believe the revisions have resulted in a significantly improved manuscript. STROBE guidelines were followed. Please find our reviewer replies and revisions.

Author declaration of transparency

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.

Signed by:

*The manuscript's guarantor

This research was considered exempt by the Washington University Institutional Review Board.

Sincerely,

Jeannie C. Kelly, MD, MS; corresponding author

Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine

[redacted]

REVIEWER COMMENTS:

Reviewer #1:

Thank you for your work on induction options for pregnant women with OUD. To my knowledge, yours is the first paper that addresses this important issue. Based on my monitoring of forums on this subject, this is a "hot topic" now, so your paper has the potential to add significant knowledge to the group. I will also complement you that your paper is well written.

We thank you for these kind comments.

I have several concerns I this should be addressed:

1. How did you choose the duration of your study? What is the history of home inductions at your institution? Your study covers the dates from June 18, 2018 through 2020. Why June 18, 2018? Was this when you started doing home inductions? If the 17 patients who underwent observed inductions all received care in the second half of 2018 and everyone since has been home-induced, we need to know this fact.

June 18, 2018 was chosen as the start because the date corresponds to the establishment of an OUD-specific prenatal clinic in our division where MFM physicians began seeing and prescribing buprenorphine. Home induction has been routinely offered since the beginning, and for the duration of the study. We included this in line 72-74:

"We conducted a single-center retrospective cohort study of all pregnant patients who underwent outpatient sublingual buprenorphine induction for treatment of OUD at our center from June 18, 2018, when an OUD-specific prenatal clinic opened, through January 1, 2021."

2. Your control group isn't a good control group. That is, criteria for observed inductions included patients who chose that method, patients in active withdrawal at the time of their visit, and patients otherwise admitted for obstetrical indications. If you looked at only those who chose, and eliminated those who were in active withdrawal, or were admitted, a fairer comparison might have been noted.

We agree with this critique. Per the editors' request, we have reformatted our submission as a research letter and only included patients who underwent *outpatient* sublingual buprenorphine induction, and used only descriptive statistics.

3. You need to address the glaring differences in your treatment group and your control group. In particular, the racial differences and the gestational age are two important factors that might have affected your results. I don't think you should even include them in the "strengths and weaknesses" section, but in the main body of your discussion. What analysis have you done to evaluate these differences?

We agree wholeheartedly with this critique. Because so few patients elected for outpatient observed induction, those who underwent observed induction were limited to an overwhelmingly portion of patients who presented in withdrawal, or in labor, without prior access to care. This was clearly demonstrated in the higher gestational age in the observed group, in addition to Black race. We know that Black race is

unfortunately associated with decreased access to both prenatal care and OUD treatment due to systemic, implicit, and explicit bias and racism.

Because of this differential between the groups, we have eliminated all inpatient inductions and statistical comparisons between them. Instead, we have only included outpatient inductions, per the editor request, using descriptive statistics only. We do see this differential persist, and did comment in Table 1 that 7 out of 8 patients who underwent outpatient observed induction presented in withdrawal during their initial visit and thus underwent immediate observed induction. However, we have removed all statements that home induction may be superior to observed induction from our manuscript, as we agree this conclusion cannot be made due to the difference in background characteristics between the groups.

Due to word count restraints from reformatting into a research letter, we were not able to fully explore this in our discussion section.

a. Were you more willing to offer home inductions to patients earlier in their pregnancies?

We offer home induction to all patients who present with OUD, regardless of gestational age.

b. Was there a potential interaction between race and gestational age? That is, African American women presenting at more advanced gestational age?

We agree this interaction is likely, due to systemic disparities in our medical system, and worth exploring, but eliminated all statistical tests for the scope of a research letter.

c. Were your African American women distributed relatively evenly over the course of the 30 months of your study? (See #1 above)

Yes, Black patients were relatively evenly distributed through the study course; no new referral bases were incorporated during the study period for our prenatal OUD clinic.

d. Were your African American women more likely to be observed induced because they were more likely to present in active withdrawal or more likely to be admitted? (See #2 above)

Yes, we a higher percentage of Black patients underwent observed induction because they presented in active withdrawal.

e. Were all patients given the same opportunity to choose? Please reassure the readers that some underlying racial bias is not responsible.

Buprenorphine induction during pregnancy is a universal protocol in our institution, as we aim to give every patient the same opportunity to choose their induction method regardless of race or other background characteristic. We believe this is better reflected in our revisions which include <u>only outpatient inductions</u>, as the majority of observed inductions presented in active withdrawal and thus underwent observed induction – in other words, every patient *except 1* who presented with recent use chose to undergo home induction. We included this in the discussion (line 99-100):

"Notably, almost every patient who presented with recent use chose to undergo home induction; observed inductions consisted almost entirely of patients who presented in withdrawal (Table b)."

4. Some have suggested that patients who are induced after the age of fetal viability should be induced while on fetal monitors. Was this a consideration for you? I don't favor this option, but it might be an issue that will be questioned by others.

We thank you for bringing up this important point, as we agree that this is also a "hot topic" of discussion for buprenorphine induction during pregnancy. We also believe this is important to address, as requiring fetal monitoring during buprenorphine induction essentially eliminates the possibility of home induction. We have included a footnote in our induction protocols to clearly state and support our practice (Figure 2):

"Fetal monitoring in viable pregnancies is reserved for the usual obstetrical indications, and is not required during buprenorphine induction in our clinical practice. Premature buprenorphine induction following opioid use may precipitate withdrawal, and opioid withdrawal in pregnancy has traditionally raised concern for fetal harm. However, these concerns have since been thoroughly debunked by multiple studies on opioid detoxification.[13,16]"

5. I note that your protocol calls for Subutex (buprenorphine only). I assume this is your standard in pregnancy and isn't chosen over (buprenorphine/naloxone) for some reason for home inductions and wouldn't have had any influence on your outcomes.

We routinely use Subutex monotherapy in pregnancy for treatment, because this is the medication covered by our state Medicaid insurance during pregnancy, by which the majority of patients served in our OUD-specific prenatal clinic is covered. Regardless, there should be no difference in induction method and outcome between Subutex and Suboxone, since the naloxone also present in Suboxone is only active if injected, to prevent medication misuse.

Reviewer #2:

This is a retrospective cohort study comparing pregnant patients undergoing sublingual buprenorphine induction for OUD at home versus observed induction. The primary outcome was retention in care over three months following treatment initiation. Secondary outcomes were rates of precipitated withdrawal, adherence to buprenorphine, and abstinence from illicit drug use. Home induction of buprenorphine for OUD has been reported to safe and effective outside of pregnancy. This study is novel in that it describes home induction of buprenorphine in the pregnant population.

Abstract:

1. The reported 3-month retention rate for observed induction is not the same that is reported in Table 2.

We thank you for pointing out this mistake! We have deleted the abstract to reformat as a research letter per editor request.

Introduction

The introduction is of appropriate length. The authors made a convincing case for the need to complete this study. I would recommend including if there is any reported evidence of patient characteristics that make them more likely to be successful with home induction versus observed induction.

We thank you for these comments. Unfortunately, there is limited literature looking at characteristics predictive of success in home versus observed induction.

Methods

Study methods are well described.

1. It may be helpful to clarify what made patients presenting in active withdrawal appropriate for immediate buprenorphine induction, and why they were admitted. Why couldn't they be managed as outpatients?

Inpatient admission is only reserved for the usual obstetric indications; as we are not a Federal Opioid Treatment Center, we are unable to admit for treatment or management of OUD. We have re-formatted our manuscript into a letter that only includes *outpatient* inductions, eliminating the subset of patients who underwent observed induction because they were admitted for a non-OUD indication.

2. Please clarify the definition of patient-level change.

This was in regards to our analysis of trend in buprenorphine adherence and illicit opioid use over time. Each individual patient's change in the percent of urines positive for buprenorphine or illicit opioids between month 1 and 3 were used calculate trends over time. However, we eliminated this analysis in our revisions to simplify down to the scope of a research letter.

3. Patient characteristics that were used as confounding variables for analysis are not described. However, in Table 2 it is reported that gestational age is used. I am not aware this is associated with severity of opioid use disorder. Also, why were outcomes (in table 2) not similarly adjusted for confounding variables? Would there still be a statistically significant difference in outcomes?

We agree the critique that our two groups are not fair comparisons and thus statistical tests should not be used to make comparisons between them. Thus, we have only included descriptive statistics in our revisions.

4. The addition of obstetric or neonatal outcomes may strengthen the conclusion that home induction of buprenorphine is a safe and effective method of treatment of OUD in the pregnant population.

We have collected obstetric and neonatal outcomes, but wanted to focus solely on *maternal* induction outcomes for the purposes of this manuscript. We do not believe our numbers are powered to demonstrate significant difference in obstetric and neonatal outcomes at this time.

Results

1. I would be interested to know if there were any patient characteristics that differed between the "outpatients" that elected induction under observation versus the "inpatients."

We agree there are likely many differences that confound severity of OUD, access to medical care, and induction outcomes. Thus, we have eliminated inpatients in our revisions per editor request.

2. The reported 3-month retention rate for observed induction is not the same that is reported in Table

We thank you for pointing this out, and this has been corrected.

Discussion

A thorough, clear discussion of the strengths and weaknesses of the study.

1. I would recommend using "substance use disorder" rather than "substance abuse disorder" in the discussion and throughout the paper.

This has been corrected.

Table 2

1. Denotations are listed as "1, 2, 3, 4" in the table but "1, 1, 2, 3" in notations. Typo in first notation.

This has been corrected.

Reviewer #3: ONG 21-1046

In the manuscript under review, Kelly et al present the results of their retrospective analysis evaluating the rate of 3-month retention following treatment initiation using home versus observed buprenorphine induction among pregnant women suffering from opioid use disorder. The authors analyzed 72 cases and found that home induction led to higher rates of treatment retention and lower rates of illicit opioid use.

A few comments on the manuscript are as follows:

ABSTRACT

1. A clear objective is identified

INTRODUCTION

2. No major issues, however no clear hypothesis is identified.

We have included a hypothesis now (line 69-70)

"We hypothesize that outcomes are similar for pregnant patients who undergo home and observed induction, with comparably high rates of success and follow-up."

METHODS

3. Line 108 - why was this timeframe chosen? Any major changes to treatment protocols implemented during that time period?

June 18, 2018 was chosen as the start because the date corresponds to the establishment of an OUD-specific prenatal clinic in our division where MFM physicians began seeing and prescribing buprenorphine. Home induction has been routinely offered since the beginning, and for the duration of the study. We included this in line 72-74:

"We conducted a single-center retrospective cohort study of all pregnant patients who underwent outpatient sublingual buprenorphine induction for treatment of OUD at our center from June 18, 2018, when an OUD-specific prenatal clinic opened, through January 1, 2021."

There were no changes to sublingual treatment protocol made at this time.

4. Line 123 - how was the sample size calculated? What was the expected rate of change sought by the authors? Was any power calculation done?

Due to the limited numbers, sample size was one of convenience over 30 months of our OUD-specific prenatal clinic. We agree that this biases our results so have eliminated statistical comparisons between the groups, and used descriptive statistics only.

5. Since this is not a randomized trial, the choice of primary outcome (rate of retention), is significantly affected by the selection of participants to each of the study groups. In other words, women that are more likely to meet clinical criteria for home induction are also more likely to meet the primary outcome. Therefore, the primary outcome suffers from selection bias based on the original inclusion of participants to each induction group.

We agree wholeheartedly, and have revised our manuscript into a letter with only descriptive statistics.

6. The authors should add a line stating that the STROBE guidelines were followed in this manuscript.

Line 75 has been added: "STROBE guidelines were followed."

RESULTS

7. The authors have severely discrepant study groups again indicating that selection bias is most likely present.
8.

We agree, and have revised our manuscript into a letter with only descriptive statistics.

9. Do the authors have any data on obstetrical outcomes? Neonatal outcomes? Although treatment retention is a remarkable goal, one can argue that if the intervention evaluated fails to lead to improved obstetrical outcomes, its use in obstetrics is limited and potentially questionable.

We do collect obstetric and neonatal outcomes, but we wanted to focus solely on *maternal* induction outcomes for the purposes of this manuscript. We do not believe our numbers are powered to demonstrate significant difference in obstetric and neonatal outcomes at this time. However, the impact of treatment retention for OUD during pregnancy for both obstetric and neonatal outcomes has been previously investigated quite thoroughly to demonstrate benefit for both parent and child.

DISCUSSION

10. Line 247 one major limitation I would add would be to include the fact that a small sample size may not allow for a true evaluation of treatment and follow-up patterns.

We have added this to line 109: "Although limited by a small sample and single institution, our experience suggest that home induction of buprenorphine is a safe, feasible and successful option for patient seeking treatment for OUD in pregnancy."

10. Line 272 - what search criteria and what databases were searched to reach the conclusion that this is the first study of this kind.

We have removed this sentence.

STATISTICS EDITOR COMMENTS:

Table 1: The two groups had N = 55 and 17, so all %s should be rounded to nearest integer %, not cited to 0.1% precision. Need units for age. Should enumerate any missing data.

We have addressed these concerns in Table 1.

Table 2: Need to clarify which adjustors were used for the aRR for 3 month retention in treatment. In any event, there are too few counts of retention vs non-retention in the two groups to allow for multivariable adjustment with either 2 or 4 adjustors. The same issue occurred in the other outcomes tested. On the other hand, there is insufficient power to generalize the NS findings re: RR for return for 1 week visit, buprenorphine metabolites in urine at 1 week follow-up.

We have eliminated the aRR per editor request and included only descriptive statistics.

Table 3: The slopes may be statistically different, but the groups at baseline were not randomized and were different in multiple baseline characteristics.

We have eliminated the slope analysis per editor request and included only descriptive statistics.

EDITOR COMMENT: Thank you for submitting your work to Obstetrics and Gynecology. If you decide to submit a revision, please format it as a research letter and remove the control group of patients who had in-hospital initiation of buprenorphine. The editors are requesting this as multiple reviewers had concerns about the selected control group- specifically differences between patients who would be candidates for in-patient versus out-patient buprenorphine induction. This means that the research letter will simply be a descriptive study of your cohort of patients who underwent out-patient buprenorphine initiation.

We have reformatted the manuscript accordingly.

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.

Opt in, option A

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (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. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

Confirmed

3. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

We have included this in the Table footnote.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys
(CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

This is included.

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Confirmed

6. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

We have reformatted the manuscript as requested into a research letter.

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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Confirmed

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

Confirmed

9. 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 limit for Original Research articles is 300 words. Please provide a word count.

The abstract has been deleted to reformat into a research letter.

10. 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.

Confirmed

11. 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.

Confirmed

12. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

Confirmed

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

Confirmed – statistical tests have been removed

14. Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Confirmed – this statement has been removed.

15. 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.

Confirmed

16. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

Confirmed

In addition, 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 at the Clinical Guidance page
at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

Confirmed

17. Figure 1: Please separate A and B into separate figures. Both will not fit on a printed page.
Figure 2: okay

Confirmed

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.

Confirmed. Figure is in Microsoft word document, but source files are also included in original digital format.

18. 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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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.

You will be receiving an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line 'Please Submit Your Open Access Article Publication Charge(s)'. Please complete payment of the Open Access charges within 48 hours of receipt.

***

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. Do not omit your responses to the Editorial Office or Editors' comments.

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 Jun 22, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals