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.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Nov 16, 2020
To: "Max Jordan Nguemeni tiako" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2764

RE: Manuscript Number ONG-20-2764

Predictors of Initiation of Medication for Opioid Use Disorder and Retention in Treatment Among US Pregnant Women, 2013-2017

Dear Dr. Nguemeni tiako:

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 Dec 07, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Thank you for your work on initiation and retention on MOUD for pregnant women. Your paper is well written and easily understood. It is the proper length, but the number of figures, tables, and charts will probably require modification and some of them being made supplemental.

Large numbers are great, but any large database study suffers from the inevitable lack of detail that can be used to understand the subject better. Patterns of care can be extremely difficult to identify from such data. The biggest and probably most useful piece of information missing is weeks of gestation. Your end-point is 6 months. However, pregnancy's traditional end-point is, of course, delivery. If someone starts MOUD early in the pregnancy, they will complete 6 months before the delivery. However, if they are first seen at 30 weeks, 6 months seems to be of uncertain significance. Shouldn't it be our goal to encourage early engagement and continuous MOUD throughout the pregnancy? Unfortunately, your database doesn't provide gestational age which would allow you to determine if therapy was continuous during the pregnancy.

It appears that this database collects data from drug treatment facilities. So, can we assume that this does not include patient encounters in which buprenorphine was prescribed by the obstetrician. I would want to know who is prescribing the MOUD. Is it better received and more successful if from an Opioid Treatment Program or the obstetrician?

Please clarify the word "primary" from the Abstract (line 39). Does the word refer to primary diagnosis, first visit for treatment, or drug of choice?

Line 73-74. Consider deleting "admitted to the neonatal intensive unit". It isn't necessary to your argument and it is not the current site of treatment for NAS in many hospitals, thanks to the work at Yale and other leaders in NAS treatment.

You very appropriately point out that some states that did not expand Medicaid may have cut off payment for MOUD 6 weeks after delivery. Can you cross-check state of treatment with this variable to determine if this may have been a factor in retention?

Additional speculations you might consider near the end of your discussion:
1. Could initiation and retention serve as useful quality improvement measures for clinics that provide substance use treatment to pregnant women?
2. From your reading of the literature, what factors appear to be most important in maintaining patient engagement?

3. You really need a strong "next steps" statement to help us see the next logical step towards understanding and improving this important concern. How do you intend to bring additional light to this subject?

Reviewer #2:

Tiako and colleagues present an analysis of > 42K treatment episodes for pregnant women with primary OUD treated at federally funded MAT programs between 2013-17. They confirm much of what has been reported to date in existing literature: a predominantly NHW, unemployed population with significant criminal-legal involvement for whom less than half receive MAT and less than 1 in 5 complete treatment. They report variable but positive associations between MAT and retention in treatment.

Major comments about this analysis are as follows:

1) Lack of novelty. While the dataset is relatively large, the findings are largely confirmatory, as the authors themselves note several times. Associations between OUD and the demographic variables analysed are well described, as is the low penetration of MAT initiation in this pregnant population.

2) Lack of precision. Admittedly I would yield to someone with more expertise working with the TEDS-D dataset, but I am concerned about a potential lack of precision with the data. A) Women are only categorized as pregnant if they were "pregnant at admission" (line 132), which could potentially underestimate treatment exposure if women on MAT then get pregnant, as many of my patients do. B) Clinically we see a very high proportion of pregnant women with SUD carrying a diagnosis of a co-morbid stimulant-use disorders + OUDs, with StimUDs being much more refractory to treatment retention and ultimate remission. That said, your reported data have very low co-morbid stimulant-use disorder diagnoses, specifically methamphetamines (line 173). Can you comment on this and compare to national data estimates? C) The 42K count is by episode as I understand it, not by individual woman. Do you know how many total women are represented in this dataset, or conversely, how many women are sampled multiple times? D) Since the exposure of interest is a variably expensive medication regimen, lack of insurance data is a critical missing piece of this analysis, as the authors themselves note (paragraph beginning line 240). E) The inability to distinguish between MAT modalities (Bup vs Methdaone) is a significant (and odd) limitation of the dataset.

3) Will defer comments on the appropriateness of the statistical analysis to the O&G statistical reviewer.

Minor comments about this manuscript:

1) Multiple careless grammatical errors. Needs thorough proofreading before submission. (eg, lines 173, 180)
2) Multiple punctuation errors (prolific comma use)
3) What is the intended value of the word "serial" in front of cross sectional analysis?
4) Please be cautious about the phrasing in line 257 that "Untreated OUD is associated with ... birth defects." The 2015 paper you reference suggests there "may be" an association between some opioids (ie, codeine) and CHDs, but the data are relatively weak and non-conclusive.
5) The tables are too densely populated for publication in this journal in this reviewer's opinion.

Reviewer #3:

Tiako et al performed a serial retrospective cross-sectional contemporaray analysis between 2013 and 2017) evaluating medication for opioid use disorder (MOUD) administration, retention and completion rate in pregnancy, and identify predictors of MOUD administration and retention over a 4 year period between 2013 and 2017.
Introduction: The authors do a good job of providing historical context and proposing an objective to look at MOUD administration and retention in pregnant patients over a 4 year period through the continuum of care lens proposed by the OUD cascade of care framework. Study aims are very clear (102-106). Innovative approach is clear.

Methods: Study design is retrospective serial cross-sectional analysis, and is appropriate to study MOUD continuum of care in pregnancy, and predictors for MOUD administration and retention. Data source is adequate (TEDS) and includes a high rate of alcohol and drug treatment episodes (83%) in treatment facilities that receive federally funding (123-125). Analysis was restricted to treatment episodes for OUD based on primary substance use reported in which patient was identified as pregnant on admission to treatment facility. Covariates well defined and associated with outcomes of OUD treatment (136-144). Authors did not include health insurance status due to large amount of missing information. Authors clearly define primary outcome as initiation of methadone, buprenorphine or naltrexone. They clearly define secondary outcomes as retention in treatment defined as a length of treatment episode lasting 6 months or longer and completion of

treatment episode as defined by the reason for discharge indicating "Treatment Completion" and "Transfer to a Different Program/Facility." Statistical analysis appear to be appropriate (151-165)
Power analysis/sample size calculation not provided. Authors did not describe any efforts to address potential sources of bias.
Results:
Results are reported in a clear manner.
Very large sample size (n = 42,239).
Bivariate and multivariate analysis, regression including sensitivity analyses reported and appear appropriate.

Discussion:

Nice discussion on MOUD initiation and retention and association with covariates.

Authors have a fair discussion of limitations of their study. Would recommend the authors discuss both direction and magnitude of any potential biases.

Figures and Tables:

Figure 2. Labeling of a) and b) and description do not match.

Literature cited: Seems appropriate and contains most relevant, timely articles.

STATISTICS EDITOR COMMENTS:

General: Not sure whether our readers would be familiar with use of the term "retention". Although it is clear in the title, it should be clearly defined early in text as meaning a length of treatment lasting ≥ 6 months.

lines 164: I think you mean alpha < 0.01, based on Table 2 CIs.

Table 1: Need units for age. Should round all %s to nearest 0.1%

Table 2: Need units for age.

Suggest that Table 2 and Fig 3 could be moved to on-line material.

EDITOR COMMENTS:

1. Please reduce the length of the Discussion to 750 words or less. Much of the review of existing studies on this topic could be pared down or removed.

2. It is difficult to say that these data are completely contemporary given that the dataset only goes through 2017. Please recognize this as a limitation.

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). 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. 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. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

5. 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 observational studies (ie, STROBE), . 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.

6. 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.

7. 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, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

9. 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).

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

11. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

12. 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.

13. 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.

14. 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.

15. 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.

16. 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%").

17. 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.

18. 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.

19. 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).

20. Figures 1-3: Please upload as figure files on Editorial Manager.

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.

21. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

22. 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.

***

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 Dec 07, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Torri Metz, MD
Associate Editor, Obstetrics

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

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.

Nancy C. Chescheir, MD
Editor-in-Chief
Obstetrics and Gynecology
December 7th 2020

Dear Dr. Chescheir,

Please see attached the revision to our manuscript tiled entitled "**Predictors of Initiation of Medication for Opioid Use Disorder and Retention in Treatment Among US Pregnant Women, 2013-2017.**" We greatly appreciate the reviewers' input and have addressed all of their concerns and question regarding our study. Please see below our responses to each comment from reviewers and the assigned editor.

Sincerely,

Max Jordan Nguemeni Tiako, MS
[redacted]

Reviewer #1:

Thank you for your work on initiation and retention on MOUD for pregnant women. Your paper is well written and easily understood. It is the proper length, but the number of figures, tables, and charts will probably require modification and some of them being made supplemental.

Large numbers are great, but any large database study suffers from the inevitable lack of detail that can be used to understand the subject better. Patterns of care can be extremely difficult to identify from such data. The biggest and probably most useful piece of information missing is weeks of gestation. Your end-point is 6 months. However, pregnancy's traditional end-point is, of course, delivery. If someone starts MOUD early in the pregnancy, they will complete 6 months before the delivery. However, if they are first seen at 30 weeks, 6 months seems to be of uncertain significance. Shouldn't it be our goal to encourage early engagement and continuous MOUD throughout the pregnancy? Unfortunately, your database doesn't provide gestational age which would allow you to determine if therapy was continuous during the pregnancy.

Response: Thank you for this comment. The fact that this database does not provide us with gestational age at treatment encounter is indeed a limitation and we have added this as a limitation in the manuscript. ASAM defines retention as 6 months into treatment, and while it is likely that patients who receive MOUD during the first trimester may be more likely to remain in treatment due to concomitant prenatal care. This remains unclear for methadone. In states where postpartum coverage is limited, this might be a barrier that reduces retention rates.

It appears that this database collects data from drug treatment facilities. So, can we assume that this does not include patient encounters in which buprenorphine was prescribed by the obstetrician. I would want to know who is prescribing the MOUD. Is it better received and more successful if from an Opioid Treatment Program or the obstetrician?

Response: Your point is well-taken. It is unlikely that this database would include encounters where buprenorphine is prescribed by an obstetrician. A recent study based on PA Medicaid shows that primary care providers and psychiatrists are the lead prescribers of buprenorphine among pregnant women and have updated the manuscript to note this point. We have a forthcoming paper that shows that fewer than 2% of OB/GYN providers are trained to prescribe buprenorphine, suggesting that there is an opportunity for OBGYNs to potentially fill this gap.

Please clarify the word "primary" from the Abstract (line 39). Does the word refer to primary diagnosis, first visit for treatment, or drug of choice?

Response: Thank you for identifying this opportunity to clarify our work for readers. Primary means opioids are the drug of choice. We have now defined this term in the abstract, as follows, "…for primary OUD among pregnant women (opioids reported as the primary substance used during treatment episode)."

Line 73-74. Consider deleting "admitted to the neonatal intensive unit". It isn't necessary to your argument and it is not the current site of treatment for NAS in many hospitals, thanks to the work at Yale and other leaders in NAS treatment.

Response: Thank you for this comment. We have deleted this.

You very appropriately point out that some states that did not expand Medicaid may have cut off payment for MOUD 6 weeks after delivery. Can you cross-check state of treatment with this variable to determine if this may have been a factor in retention?

Response: Thank you for this comment. We adjusted for geographic region since in some states, the sample size was significantly lower than others. States that did not expand Medicaid are concentrated in the South and Midwest regions, which are both associated with lower odds of retention.

Change:

Additional speculations you might consider near the end of your discussion:
1. Could initiation and retention serve as useful quality improvement measures for clinics that provide substance use treatment to pregnant women?
2. From your reading of the literature, what factors appear to be most important in maintaining patient engagement?
3. You really need a strong "next steps" statement to help us see the next logical step towards understanding and improving this important concern. How do you intend to bring additional light to this subject?

We appreciate these important suggestions to help our work inform policy improvements to come. We now note in the discussion that existing literature shows that MOUD is associated with retention, as are sociodemographic variables such as having insurance coverage. Regarding the role of OB/Gyns, we have a publication in press describing the prevalence and geographic distribution of OBGYNs who can prescribe buprenorphine. We have made edits to the discussion to include next steps to build on this analysis.

Change:
"Integrating addiction treatment and perinatal care could be a way to improve quality of perinatal OUD treatment, [43,44] as currently, fewer than 2% of Ob/Gyns who treat Medicaid patients are trained to prescribe buprenorphine.[45] Measuring MOUD administration rates and retention in treatment especially for vulnerable populations such as pregnant patients may be useful quality metrics for drug treatment centers."

Reviewer #2:

Tiako and colleagues present an analysis of > 42K treatment episodes for pregnant women with primary OUD treated at federally funded MAT programs between 2013-17. They confirm much of what has been reported to date in existing literature: a predominantly NHW, unemployed population with significant criminal-legal involvement for whom less than half receive MAT and less than 1 in 5 complete treatment. They report variable but positive associations between MAT and retention in treatment.

Major comments about this analysis are as follows:

1) Lack of novelty. While the dataset is relatively large, the findings are largely confirmatory, as the authors themselves note several times. Associations between OUD and the demographic variables analyzed are well described, as is the low penetration of MAT initiation in this pregnant population.

Response: Thank you for this perspective and for the opportunity to better communicate how our work builds on the existing literature to bring new insights to this important health management question. Our findings first confirm and lend strength to the findings of prior studies. We proceed to build on this literature with a novel approach through the use of the cascade of care model. That theoretical model drove us to conduct the first study to evaluate both odds of medication administration and retention in treatment for pregnant patients. Our statistical model addresses both simultaneously, using a technique (bivariate probit regression) that is well established in the economics and statistical literature, but has never been applied to this problem before. Furthermore, to our knowledge, no studies of retention of pregnant women in OUD care report reasons behind patients being lost to follow up. [We have made several changes to the manuscript to better highlight these contributions.]

2) Lack of precision. Admittedly I would yield to someone with more expertise working with the TEDS-D dataset, but I am concerned about a potential lack of precision with the data. A) Women are only categorized as pregnant if they were "pregnant at admission" (line 132), which could potentially underestimate treatment exposure if women on MAT then get pregnant, as many of my patients do. B) Clinically we see a very high proportion of pregnant women with SUD carrying a diagnosis of a co-morbid stimulant-use disorders + OUDs, with StimUDs being much more refractory to treatment retention and ultimate remission. That said, your reported data have very low co-morbid stimulant-use disorder diagnoses, specifically methamphetamines (line 173). Can you comment on this and compare to national data estimates? C) The 42K count is by episode as I understand it, not by individual woman. Do you know how many total women are represented in this dataset, or conversely, how many women
are sampled multiple times? D) Since the exposure of interest is a variably expensive medication regimen, lack of insurance data is a critical missing piece of this analysis, as the authors themselves note (paragraph beginning line 240). E) The inability to distinguish between MAT modalities (Bup vs Methdaone) is a significant (and odd) limitation of the dataset.

Thank you for these important caveats..

a) This is a limitation of the dataset which we have included in our limitation section.
b) For this study, we focused on patients with primary OUD, and acknowledge that we were not inclusive of treatment episodes for which the primary substance was stimulants or alcohol. To partially address this concern, our revision more carefully highlights the definition of primary use disorder, and clarifies our confidence that we are not admixing stimulant use disorders.
c) Due to the nature of the data we do not know how many patients are represented in this sample. As shown in table 1, the majority of treatment episodes (over 60%) involve patients who have had prior treatment episodes.
d) Missingness of insurance data is a limitation we noted. However. Among encounters for which insurance is available, the vast majority are covered by Medicaid. We decided to exclude insurance as a variable in our analysis out of concern that given the high rate of missingness we would introduce bias. However, we adjusted for other sociodemographic variables associated with insurance status including education, employment, and age. Prior studies have shown that the majority of patients reported in the TEDS-D are insured by Medicaid.

e) We agree this is an odd quirk of the data. We have acknowledged this limitation. Ultimately, we feel that the advantages of this dataset – its national representativeness and comprehensiveness – outweigh this limitation.

3) Will defer comments on the appropriateness of the statistical analysis to the O&G statistical reviewer.

Minor comments about this manuscript:

1) Multiple careless grammatical errors. Needs thorough proofreading before submission. (eg, lines 173, 180)

2) Multiple punctuation errors (prolific comma use)

Response: We apologize for these and have corrected them in the revised manuscript.

3) What is the intended value of the word "serial" in front of cross-sectional analysis?

Response:

4) Please be cautious about the phrasing in line 257 that "Untreated OUD is associated with ... birth defects." The 2015 paper you reference suggests there "may be" an association between some opioids (ie, codeine) and CHDs, but the data are relatively weak and non-conclusive.

Response: Thank you for this comment. We've removed this reference.

5) The tables are too densely populated for publication in this journal in this reviewer's opinion.

Thank you for this comment. The statistics editor recommended that one of the tables be part of online materials.

Reviewer #3:

Tiako et al performed a serial retrospective cross-sectional contemporary analysis between 2013 and 2017) evaluating medication for opioid use disorder (MOUD) administration, retention and completion rate in pregnancy, and identify predictors of MOUD administration and retention over a 4 year period between 2013 and 2017.
Introduction: The authors do a good job of providing historical context and proposing an objective to look at MOUD administration and retention in pregnant patients over a 4 year period through the continuum of care lens proposed by the OUD cascade of care framework. Study aims are very clear (102-106). Innovative approach is clear.

Methods: Study design is retrospective serial cross-sectional analysis, and is appropriate to study MOUD continuum of care in pregnancy, and predictors for MOUD administration and retention. Data source is adequate (TEDS) and includes a high rate of alcohol and drug treatment episodes (83%) in treatment facilities that receive federally funding (123-125). Analysis was restricted to treatment episodes for OUD based on primary substance use reported in which patient was identified as pregnant on admission to treatment facility. Covariates well defined and associated with outcomes of OUD treatment (136-144). Authors did not include health insurance status due to large amount of missing information. Authors clearly define primary outcome as initiation of methadone, buprenorphine or naltrexone. They clearly define secondary outcomes as retention in treatment defined as a length of treatment episode lasting 6 months or longer and completion of treatment episode as defined by the
reason for discharge indicating "Treatment Completion" and "Transfer to a Different Program/Facility." Statistical analysis appear to be appropriate (151-165)

Power analysis/sample size calculation not provided. Authors did not describe any efforts to address potential sources of bias.

Response:
Thank you for this comment. We edited our limitations to acknowledge the potential biases.
Change: "…our analysis is limited to treatment episodes for which opioids were the primary substance used. Our findings may thus be overestimating MOUD and retention rates, by not including treatment episodes for primary stimulants or alcohol use disorders with comorbid OUD, which may be less likely to include MOUD, and undercounting the number of treatment episodes among pregnant patients."
Results:
Results are reported in a clear manner.
Very large sample size (n = 42,239).
Bivariate and multivariate analysis, regression including sensitivity analyses reported and appear appropriate.

Discussion:

Nice discussion on MOUD initiation and retention and association with covariates.

Authors have a fair discussion of limitations of their study. Would recommend the authors discuss both direction and magnitude of any potential biases.

Thank you for this comment. We've expanded on the potential biases of our study in the limitations section and believe that our analysis may be overestimating MOUD and retention rates.

Figures and Tables:

Figure 2. Labeling of a) and b) and description do not match.

Response: We apologize for this misalignment and have addressed it in the revision.

Literature cited: Seems appropriate and contains most relevant, timely articles.

STATISTICS EDITOR COMMENTS:

General: Not sure whether our readers would be familiar with use of the term "retention". Although it is clear in the title, it should be clearly defined early in text as meaning a length of treatment lasting ≥ 6 months.

Response: Thank you for this comment. We now define retention in the manuscript's introduction: "by retention specifically defined as treatment duration of at least 6 months," as well as in the abstract.

lines 164: I think you mean alpha < 0.01, based on Table 2 CIs.
Response: Thank you**.** We have corrected this in the revised manuscript.

Table 1: Need units for age. Should round all %s to nearest 0.1%
Response: We have made this change.

Table 2: Need units for age.

Response: We have made this change.
Suggest that Table 2 and Fig 3 could be moved to on-line material.
Response: We have moved these to supplemental documents.

EDITOR COMMENTS:

1. Please reduce the length of the Discussion to 750 words or less. Much of the review of existing studies on this topic could be pared down or removed.

Response: Thank you for this comment. We condensed the discussion to under 750 words.

2. It is difficult to say that these data are completely contemporary given that the dataset only goes through 2017. Please recognize this as a limitation.
Response: Thank you for this comment. We acknowledged this in the limitations.

Change: Line 898: "The most recent available data is from 2017, thus we are unable to make inferences on the quality of perinatal OUD treatment between 2018 and 2020."