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: 12/16/2022
To: "Gerald Cochran" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1732

RE: Manuscript Number ONG-22-1732

Nonfatal overdose among pregnant individuals with opioid use disorder

Dear Dr. Cochran:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 01/06/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Thank you for your submission to the Green Journal. We would like to offer you the opportunity to revise this letter to address the Reviewers' comments below. In addition, please also address the following points:

- Please provide more information about the OPTI-Mom trial, including information on enrollment sites and a description of the patients included. It would be helpful to include a baseline comparison between the patients with OUD and those in the original trial. This description and comparison could be included in a supplemental appendix to continue to adhere to the word count limits of the research letter format.

- Can you verify citation for the Overdose Experiences, Self and Witnessed Drug Assessment Tool. The citation does not look to be appropriate, but please confirm. Please add if this tool was previously validated and include information on the methods. If not validated, how does that influence interpretation and generalizability of these findings?

- Please explicitly state how "overdose" was defined? Was a standard definition presented to each patient for comparison? The question in Table 1 implies this was defined as "the most recent time you took too many drugs or medications" -- was this considered an overdose? How may variable interpretations of this statement lead to the results presented in this study?

- Please discuss how this population identified with OUD and enrolled in this study and seeking care may or may not be generalizable to all patients with OUD. Do you hypothesize the rates of overdose are higher or lower in a general OUD population?

- As per the statistical editor comments below, please present any percentages with confidence intervals to show the uncertainty associated with the estimates from a relatively small sample size.

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figure 1: Please upload as a figure file on Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1:
The authors present a brief cross-sectional report. Overall, the manuscript is lacking in some methodology details which make interpretation of the results difficult. Furthermore, it is unclear if the findings from this study are novel or would change public health practice.

Introduction:
Line 24: it is unclear what 'circumstances' refers to when looking at the table and results.

Methods:
Line 28: clarify if ALL individuals enrolled in the parent study were included in this analysis, or only some.

Line 32: although this is a brief report, many details are missing which makes it difficult to understand recruitment. How were patients recruited? Were they already seeking prenatal care?

Line 35: the tool is a single item questionnaire, yet the table presents answers to 5 questions

Results:
Line 42: again, more details needed regarding participants. Were there some participants enrolled in the parent study who were not included in this study? How many patients were approached for recruitment?

Line 52-53: this is the only analysis to look for potential risk factors. The authors could consider also examining the relationship between other collected variables such as depression and anxiety, employment, ect to find potential interventions.

Discussion
Line 62: I'm not sure the data collection is prospective.

Lines 73-76: As the authors point out in the introduction, drug overdose is a leading cause of death in this population. Knowing that, it might be unnecessary to confirm these current findings in a broader population, nor or the findings from this study necessary to advocate for the public health actions proposed.

Table 1:
The n is unclear for the second question, and should be 66 rather than 108. If taking too many drugs is the same as an overdose, only 66 participants should have answered this question.

The n for the last question is 101; there is 1 missing which needs to be included.

Figure 1: easy to read and understand.

Reviewer #2:

This research letter manuscript is a cross sectional analysis of OPTI-Mom trial. They had 102 women that had sought care with OUD while pregnant. The manuscript goal was to provide more accurate data regarding overdose and characteristics of women with OUD.

Line 35: This reference does not mention this Drug Assessment Tool and its validity. Is there a more appropriate citation?

Line 42: Please provide the population that you system provided care to understand the significance of the demographics.

Line 46: How did they meet criteria for "severe" opioid use disorder?

Line 58: That was a population based retrospective study utilizing a database that relied on hospital records and therefore admissions post overdose or on their death certificate. As stated in Table 1 a substantial amount of people to not end up in a hospital setting.

Line 64: Confusing wording.

Citation 8 the terminology "overdose" was described to the patients was this also done in this study as the interpretation could vary with the individual?

Reviewer #3:
This is a research letter reporting a cross-sectional study of pregnant individuals with OUD enrolled in a multi-site randomized controlled trial of patient navigation compared to usual care to assess patient's lifetime history of overdose. This is important because overdose is a serious risk among patients with OUD in pregnancy, and is a leading cause of death for reproductive aged, pregnant and postpartum individuals in the U.S. The results show that 65% of respondents had a lifetime history of overdose and 41% had at least one overdose within the past year involving opioids (82%) and sedatives (30%). These findings would inform the need for heightened awareness of overdose events in patients with OUD in pregnancy.

SPECIFIC COMMENTS:
1. The authors used the Overdose Experiences, Self and Witnessed - Drug Assessment Tool, a single item questionnaire about self-reported overdose events

2. Enrollment was over a wide gestational age window (7-32 weeks), but there is no analysis by gestation age, which could be informative

3. No sample size consideration is addressed

4. The limitations including limited generalizability are addressed. However, another limitation is that these are based on self-report, which may not be entirely accurate.

STATISTICAL EDITOR COMMENTS:

Table 1: Should include CIs in Abstract. Those with any OD episode comprised 66%, but that has CIs, based on this sample, of ~ 51% to ~ 84%.

Should change wording from lifetime to any prior events, since the lifetime experience is not known yet. The % of events within the past year is 42%, but that estimate (from this sample) has CIs from ~ 30% to ~ 57%.

In summary, each of the relevant %s in table 1 should include CIs.

--
Sincerely,
Mark A. Clapp, MD, MPH
Editorial Fellow

The Editors of Obstetrics & Gynecology

_____

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January 12, 2023

Dear Dr. Clapp and Editors of *Obstetrics and Gynecology*:

I am pleased to resubmit our revised research letter entitled, **"Nonfatal overdoses among pregnant individuals with opioid use disorder"** for consideration for publication in *Obstetrics and Gynecology*.

We affirm that our letter is being submitted only to *Obstetrics & Gynecology*. We have reviewed and followed the instructions for author guidelines. We have also reviewed and edited the submission to omit any identifying information.

We thank the reviewers for their comments and have responded to each. Our responses to their comments can be found at the end of this letter.

Thank you for your consideration of our research letter for publication. We look forward to hearing from you at your earliest convenience.

Sincerely,

Jasmin E Charles MS PA-C
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EDITOR COMMENTS

Editor Comment #1:
- Please provide more information about the OPTI-Mom trial, including information on enrollment sites and a description of the patients included. It would be helpful to include a baseline comparison between the patients with OUD and those in the original trial. This description and comparison could be included in a supplemental appendix to continue to adhere to the word count limits of the research letter format.

Authors' response: We thank the editor for this comment. We have added additional information regarding the parent trial and reference the protocol paper, which provides details regarding the OPTI-Mom trial. We also clarified that the current analysis includes all participants enrolled in the parent trial at baseline.

Letter edits:
Line 52: All 102 enrolled participants were included in this analysis.

Lines 36-40: Details of the study protocol and methods were previously reported[6] and are briefly reviewed here. Participants were recruited from two academic tertiary medical centers. Both centers have perinatal addiction clinics tailored to this population. Participants were identified through medical record review in inpatient and outpatient settings.

6. Cochran G, Smid MC, Krans EE, et al. A pilot multisite study of patient navigation for pregnant women with opioid use disorder. Contemp Clin Trials. Dec 2019;87:105888. doi:10.1016/j.cct.2019.105888

Editor Comment #2:
- Can you verify citation for the Overdose Experiences, Self and Witnessed Drug Assessment Tool. The citation does not look to be appropriate, but please confirm. Please add if this tool was previously validated and include information on the methods. If not validated, how does that influence interpretation and generalizability of these findings?

Authors' response: The Tracy et al. citation is correct as it was the initial study in which this tool was used. We have added additional citations that support the tool's face and criterion validity. Given the word constraints for a research letter, we did not expand upon the methods used to validate this tool. However, we are open to doing so if the editors feel this is an important contribution.

Letter edits:
Lines 41-45: We utilized the Overdose Experiences, Self and Witnessed – Drug Assessment (OESWD) Tool, a validated tool for assessing overdose history among

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individuals who use drugs.[9-11] Participants completed six questions about prior overdose events at study enrollment (7-32 weeks' gestation).

9. Tracy M, Piper TM, Ompad D, Bucciarelli A, Coffin PO, Vlahov D, et al. Circumstances of witnessed drug overdose in New York City: implications for intervention. Drug Alcohol Depend. 2005;79:181-90. doi: 10.1016/j.drugalcdep.2005.01.010.
10. Fernandez AC, Bush C, Bonar EE, Blow FC, Walton MA, Bohnert ASB. Alcohol and Drug Overdose and the Influence of Pain Conditions in an Addiction Treatment Sample. J Addict Med. 2019;13:61-8. doi: 10.1097/adm.0000000000000451.
11. Brown JL, Cochran G, Bryan MA, Charron E, Winhusen TJ. Associations between elevated depressive symptoms and substance use, prescription opioid misuse, overdose history, pain, and general health among community pharmacy patients prescribed opioids. Subst Abus. 2022;43:1110-5. doi: 10.1080/08897077.2022.2060450.

Editor Comment #3:
- Please explicitly state how "overdose" was defined? Was a standard definition presented to each patient for comparison? The question in Table 1 implies this was defined as "the most recent time you took too many drugs or medications" -- was this considered an overdose? How may variable interpretations of this statement lead to the results presented in this study?

Authors' response: We have updated Table 1 to better explain the definition of overdose used by the Overdose Experiences, Self and Witnessed – Drug Assessment Tool. All six questions about overdose events used this definition.

Table 1:

- Section header: the following questions are about experiences with taking too much drug or medication/s pill. This is sometimes called "poisoning" "nodding out" or an "overdose or "OD." Important: From this point on, future questions will refer to all of these situations as an "overdose." We are interested in learning about your personal "overdose" experiences.

Editor Comment #4:
- Please discuss how this population identified with OUD and enrolled in this study and seeking care may or may not be generalizable to all patients with OUD. Do you hypothesize the rates of overdose are higher or lower in a general OUD population?

Authors' response: Details regarding identification of this population for each site are outlined in the protocol paper. Due to word limit constraints, we did not elaborate

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extensively but have included additional details about identification of participants through medical record review in the letter. We have added a hypothesis statement to the introduction and additional language on interpretation of our results compared to other studies reporting prior and past-year overdose events.

On lines 184-186, we discuss this limitation surrounding the inclusion of only individuals seeking prenatal and addiction care. Furthermore, reference 6 does address inclusion and exclusion criteria providing more specifics.

Regarding rates of overdose in this study compared to the general population, as we discuss in lines 74-80, comparing rates reported in the current study to the general population, we suggest national rates may be underestimates of actual overdose prevalence.

Letter edits:
Lines 28-29: We hypothesized that frequency of overdose events in this population would be higher than previously reported.[3 5]

Lines 36-40: Details of the study protocol and methods were previously reported[6] and are briefly reviewed here. Participants were recruited from two academic tertiary medical centers. Both centers have perinatal addiction clinics tailored to this population. Participants were identified through medical record review in inpatient and outpatient settings.

Lines 68-72: These data suggest that current estimates of prior nonfatal overdose, a significant risk factor for subsequent fatal overdose,[13] may be underestimated in this population.[3 5] However, results must be interpreted with caution as overdose event identification in these prior studies was different than in the current analysis.

Editor Comment #5:
- As per the statistical editor comments below, please present any percentages with confidence intervals to show the uncertainty associated with the estimates from a relatively small sample size.

Authors' response: Thank you for this comment to help clarify the data. We have updated the text and Table 1 to include confidence intervals.

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figure 1: Please upload as a figure file on Editorial Manager.

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Authors' response: We have uploaded figure 1 as a PDF on Editorial Manager.

REVIEWERS' COMMENTS

Reviewer #1 comment 1:
The authors present a brief cross-sectional report. Overall, the manuscript is lacking in some methodology details which make interpretation of the results difficult. Furthermore, it is unclear if the findings from this study are novel or would change public health practice.

Authors' response: Thank you for this feedback and the opportunity to provide additional information about the study. As addressed in Editor comments #1, we have now included additional details regarding study methods as well as references to our previously published protocol paper.

Regarding the findings being novel or change practice, our results are suggestive of underreported overdose. We believe our findings also provide valuable descriptive information regarding the frequency and substances used in overdose experiences among pregnant women. We believe that findings are novel in the field and support the need for further research. We also believe that they support the incorporation of overdose prevention strategies among pregnant individuals with OUD seeking treatment or pregnancy care.

Introduction:
Reviewer #1 comment 2:
Line 24: it is unclear what 'circumstances' refers to when looking at the table and results.

Authors' response: Thank you for your comment; we have edited the letter to remove the word "circumstances" from line 24.

Letter edits:
Lines 25-28: We describe demographics, number of prior overdose events, and substances involved in the most recent nonfatal overdoses among pregnant treatment-seeking individuals with opioid use disorder (OUD).

Methods:
Reviewer #1 comment 3:
Line 28: clarify if ALL individuals enrolled in the parent study were included in this analysis, or only some.

Authors' response: All individuals were included in this analysis, and we have clarified in the letter.

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Letter edits:
Line 52: All 102 enrolled participants are included in this analysis.

Reviewer #1 comment 4:
Line 32: although this is a brief report, many details are missing which makes it difficult to understand recruitment. How were patients recruited? Were they already seeking prenatal care?

Authors' response: In response to the inquiry about recruitment, potential participants were identified through a review of medical records from inpatient and outpatient settings.

Lines 37-40: Participants were recruited from two academic tertiary medical centers. Both centers have perinatal addiction clinics tailored to this population. Participants were identified through medical record review in inpatient and outpatient settings.

Reviewer #1 comment 5:
Line 35: the tool is a single item questionnaire, yet the table presents answers to 5 questions

Authors' response: Thank you for this question. Please see the answer to editor questions #2 and #3 above where we clarified the methods and description of the overdose assessment tool.

Results:
Reviewer #1 comment 6:
Line 42: again, more details needed regarding participants. Were there some participants enrolled in the parent study who were not included in this study? How many patients were approached for recruitment?

Authors' response: We have included additional details about recruitment.

Lines 34-35: In the parent study, 81% eligible individuals approached for participation enrolled.

Lines 39-40: Participants were identified through medical record review in inpatient and outpatient settings.

Reviewer #1 comment 7:
Line 52-53: this is the only analysis to look for potential risk factors. The authors could consider also examining the relationship between other collected variables such as depression and anxiety, employment, etc to find potential interventions.

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Authors' response: We appreciate this important recommendation from the reviewer. We very much agree that additional analyses should be performed to understand the other possible correlates of overdose among these participants, which we now include as a future direction in our limitations section. However, due to the parameters of the current research letter, we are not able to include these additional analyses.

Letter edits:
Lines 83-86: Future studies should include exploration of overdose events in a broader population and relationships between overdose and other factors, including gestational age at study enrollment, perinatal depression and anxiety, and other social stressors.

Discussion
Reviewer #1 comment 8:
Line 62: I'm not sure the data collection is prospective.

Authors' response: Thank you for the feedback; this is a secondary data analysis of a prospective project. The letter has been edited to state as such.

Letter edits:
Lines 31-34: This was an exploratory cross-sectional secondary data analysis of the Optimizing Pregnancy and Treatment Interventions for Moms (OPTI-Mom) 2.0 study (NCT03833245),[6] single-blinded, multi-site, randomized interventional trial assessing patient navigation verses usual care for pregnant individuals with OUD.

Lines 73-74: The strengths of our study include systematic collection of overdose experiences among pregnant treatment-seeking individuals with severe OUD.

Reviewer #1 comment 9:
Lines 73-76: As the authors point out in the introduction, drug overdose is a leading cause of death in this population. Knowing that, it might be unnecessary to confirm these current findings in a broader population, nor or the findings from this study necessary to advocate for the public health actions proposed.

Authors' response: Thank you for this comment. We agree that further confirmation of the prevalence or general importance of these findings may not be necessary. However, the findings elucidate the more nuanced experiences that may be involved the overdoses of this population. The higher than previously reported lifetime and past year overdose experience in this sample further supports that clinicians should be aware of harm-reduction and other overdose prevention strategies. We have edited the letter to highlight these interventions that clinicians may consider incorporating in their practice.

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Lines 88-91: Overdose reduction interventions; including low barrier access to medications for OUD, naloxone co-prescription, fentanyl test strips, counseling against using alone; should be included in the care of this population.[15]

Table 1:
Reviewer #1 comment 10:
The n is unclear for the second question and should be 66 rather than 108. If taking too many drugs is the same as an overdose, only 66 participants should have answered this question.

Authors' response: Thank you for pointing out the confusion in the N. We have adjusted table 1 by removing the "within a lifetime" total (66) and left the within the past year (42) and 1+ year ago (24) adding up to the n of 66.

Reviewer #1 comment 11:
The n for the last question is 101; there is 1 missing which needs to be included.

Authors' response: Thank you for finding this n error. We have adjusted the n to reflect 102 which is the accurate total for this table.

Reviewer #1 comment 12:
Figure 1: easy to read and understand.

Authors' response: Thank you for your complement.

Reviewer #2:

Reviewer #2 comment 1:
This research letter is a cross sectional analysis of OPTI-Mom trial. They had 102 women that had sought care with OUD while pregnant. The goal of this letter was to provide more accurate data regarding overdose and characteristics of women with OUD.

Authors response: Thank you for the overview.

Reviewer #2 comment 2:
Line 35: This reference does not mention this Drug Assessment Tool and its validity. Is there a more appropriate citation?

Authors' response: Thank you for noting this. Please see Editors comment 2 and 3 for our responses.

Reviewer #2 comment 3:
Line 42: Please provide the population that your system provided care to understand

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the significance of the demographics.

Authors response: Thank you for requesting this clarification. We have updated the letter to provide these details.

Letter edits:
Lines 37-40: Participants were recruited from two academic tertiary medical centers. Both centers have perinatal addiction clinics tailored to this population. Participants were identified through medical record review in inpatient and outpatient settings.

Reviewer #2 comment 4:
Line 46: How did they meet criteria for "severe" opioid use disorder?

Authors response: Opioid use disorder and severity are defined by the Diagnostic and Statistical Manual V (DSM-V) criteria. We now have included the citation in letter.

Letter edits:
Lines 55: All participants met criteria for severe opioid use disorder.[12]

Reviewer #2 comment 5:
Line 58: That was a population based retrospective study utilizing a database that relied on hospital records and therefore admissions post overdose or on their death certificate. As stated in Table 1, a substantial amount of people do not end up in a hospital setting.

Authors response: Thank you, the reviewer is correct that this study was based on hospital data rather than reported. On lines 71-73, we discuss this particular difference in data sources and how this may be a strength of our data given that overdoses reported in our project may have occurred outside of a health system setting alone. We have added additional language noting that these studies utilize different methodologies.

Reviewer #2 comment 6:
Line 64: Confusing wording.

Authors response: We have updated this text to be clearer.

Letter edits:
Lines 76-79 A significant proportion of overdose events in this cohort occurred outside of a healthcare facility. Our data may provide a more accurate estimate of nonfatal overdoses than estimates based on claims data alone.

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Reviewer #2 comment 7:
Citation 8 the terminology "overdose" was described to the patients was this also done in this study as the interpretation could vary with the individual?

Authors response: Thank you for your feedback. We have addressed the similar concern from Editor Comment #2 and 3. Please see above for our response.

Reviewer #3:

Reviewer #3 Comment 1:
This is a research letter reporting a cross-sectional study of pregnant individuals with OUD enrolled in a multi-site randomized controlled trial of patient navigation compared to usual care to assess patient's lifetime history of overdose. This is important because overdose is a serious risk among patients with OUD in pregnancy, and is a leading cause of death for reproductive aged, pregnant and postpartum individuals in the U.S. The results show that 65% of respondents had a lifetime history of overdose and 41% had at least one overdose within the past year involving opioids (82%) and sedatives (30%). These findings would inform the need for heightened awareness of overdose events in patients with OUD in pregnancy.

Authors' response: Thank you for your summary, the feedback, and for confirming the message the authors are working to delivery in the letter.

Reviewer #3 Comment 2:
1. The authors used the Overdose Experiences, Self and Witnessed - Drug Assessment Tool, a single item questionnaire about self-reported overdose events

Authors' response: Please see Editor Comment #2 and 3 for our response.

Reviewer #3 Comment 3:
2. Enrollment was over a wide gestational age window (7-32 weeks), but there is no analysis by gestation age, which could be informative

Authors' response: Thank you for this suggestion. In future studies and analyses of data, we will consider specifying gestational ages to see if there is statistical or clinical significance.

Letter edits:
Lines 83-86: Future studies should include exploration of overdose events in a broader population and relationships between overdose and other factors, including gestational age at study enrollment, perinatal depression, and anxiety and other social stressors.

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Reviewer #3 Comment 4:
3. No sample size consideration is addressed

Authors' response: Thank you for enquiring about the sample size. We now reference in the methods section the protocol paper and additional details about the study enrollment. We also now more clearly indicate that the current study was a secondary exploratory analysis of baseline data, and given the descriptive nature of this work, power was not taken into account.

Letter edits:
Lines 46-47: Given the exploratory descriptive nature of this study, power calculations were not performed.

Reviewer #3 Comment 5:
4. The limitations including limited generalizability are addressed. However, another limitation is that these are based on self-report, which may not be entirely accurate.

Authors' response: Thank you for the additional limitation consideration. We have adjusted the letter to address this concern.

Letter edits:
Lines 79-81: However, we recognize that participant self-reported overdose may include less severe events (i.e., not requiring resuscitation or rescue medications) than those determined by clinicians and coded in claims data.

STATISTICAL EDITOR COMMENTS

Statistical editor comment 1:
Table 1: Should include CIs in Abstract. Those with any OD episode comprised 66%, but that has CIs, based on this sample, of ~ 51% to ~ 84%.

Authors' response: Thank you for noting the lack of confidence intervals in the abstract and inconsistencies in some numbers reported. The letter has been adjusted adding confidence intervals to Table 1.

Lines 10-13: Of the 102 participants, all had severe OUD and were between 7-32 weeks gestation. 65% (95% confidence interval (CI): 55-73) had a prior history of overdose and 41% (95% CI: 31-52) had at least one overdose within the past year.

Lines 57-59: Of the entire cohort, 65% (n=66, 95% confidence interval (CI): 55-73) reported a prior overdose, and 41% (n=42, 95% CI: 31-52) had at least one overdose in the past year (Table 1).

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Statistical editor comment 2:
Should change wording from lifetime to any prior events, since the lifetime experience is not known yet. The % of events within the past year is 42%, but that estimate (from this sample) has CIs from ~ 30% to ~ 57%.

In summary, each of the relevant %s in table 1 should include CIs.

Authors response: The letter has been edited and confidence intervals included. We have edited the text and Table 1 to include confidence intervals. We have also replaced lifetime with prior overdose event throughout the letter.