

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Sep 03, 2021
To: "Marcela C Smid" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1600

RE: Manuscript Number ONG-21-1600

What Obstetrician-Gynecologists should know about substance use disorders in the perinatal period

Dear Dr. Smid:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 24, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Comments to the Author

This is an article submitted for consideration under the clinical expert series. The article's purpose is to describe "What Obstetrician-Gynecologists should know about substance use disorders in the prenatal period." The article reviews the appropriate use of language in the management of substance use disorder, prevalence of substance use disorder in pregnancy, screening of pregnant individuals for substance use disorder, and management considerations of substance use disorder on labor and delivery and in the postpartum period. The article then continues to describe commonly used substance classes. For each substance, general and pregnancy-associated risks are reviewed, along with treatment recommendations. Lastly, the article provides quick reference tables describing appropriate terminology and language for substance use disorder, screening tools, and medications used for opioid use disorder. The summary is concise and relatively updated compared to other review articles.

Introduction

The introduction is of appropriate length. The authors made a convincing case for the need to complete the review article.

Substance use and addiction in pregnancy and postpartum

Regarding child welfare, policies vary significantly state-to-state, and reporting practices can vary by institution. It would be helpful to provide some information on where providers can find out policies associated with their particular area of practice - discussion with social work, or online reference for example.

Screening

Line 142 states "a more thoughtful and judicious use of urine toxicology testing is warranted, if it is to be used at all." This is a controversial topic, and I would recommend at least a few sentences expanding on the pros and cons and urine toxicology screening, as this is commonly encountered in general clinical practice. There should also be some discussion regarding which substances are screened for with urine toxicology, why, and how to determine what is best for a provider's area of practice. For example, should screening be performed for marijuana?

Treatment Recommendations

There are many resources that discuss "SBIRT" training. It may be helpful to mention these.

Opioid Treatment Recommendations

It may be worth mentioning that there are options for outpatient management of opioid use disorder, and there are opportunities for Ob/Gyn providers to become trained in management of medications for opioid use disorder.

Benzodiazepine

Line 417 - this statement is a little misleading, as the combined use of SSRI and benzodiazepine does improve outcome in acute management of anxiety and depression, and therefore could potentially be useful, even in pregnancy.

Reviewer #2: Comprehensive, data-driven and clinically-oriented guidelines and recommendations concerning SUD screening, referral and management in pregnancy are much needed. Therefore, the focus of this Clinical Expert series is relevant and timely. However, the organization, content and focus of the document needs additional editing to increase clarity and accessibility. In particular, the introduction, overview and screening portions of the review are wandering, sometimes unorganized and often difficult to follow. Furthermore, a more robust discussion of best practices around screening and referral, which will typically be the purview of the general OBGYN rather than treatment, is very much warranted. Additionally, I was disappointed at the lack of attention paid to possible preventative efforts (recommendations for prescribing habits for opioids, benzos, etc), areas of need and future research/therapeutic directions. My specific comments by section are detailed below:

1. Abstract: Lines 14 do not seem accurate based on the review's content. There was actually a surprising paucity of information about the maternal mortality crisis related to SUD within the body of the review. It seems a more robust discussion of this issue to ground the topic would be important and should be added.
2. Introduction: The global health crisis around SUD is important to include here. Prevalence, demographic distribution and mortality contribution seem like an important backdrop for the rest of the review.
3. Language: A little historical context around language and naming seems relevant and important, particularly since this has evolved in the past several years. I'd suggest adding some discussion of changing DSM definitions and also highlighting the difference in DSM-recommended terms versus colloquial descriptions of disease. Furthermore, the phrasing of lines 52-53 is awkward and may benefit from revision.
4. Substance use and addiction in pregnancy and postpartum: Again, for me, context around this area is critical. It seems impossible to have a review of what every OBGYN should know about SUD and not discussing the alarming maternal morbidity and mortality rates, yet that seems to be the case here. Additionally, the organization of this section is confusing and chaotic. It moves from racial inequities to postpartum vulnerability to sex and gender differences (including brief mentions of sexual victimization and contraceptive choices) and lastly address child welfare. While these area undoubtedly all important areas to include, the approach needs to be much more logical and systematic. Perhaps discussion of maternal morbidity and mortality trends generally (including timing of most deaths) followed by general addiction trends in pregnancy as well as the postpartum period (including potential contributions). Racial inequities and sex differences could then be addressed followed lastly by child welfare.
5. Screening: This section is a missed opportunity for me. Again, the organization of the section is erratic and the recommendations too broad and non-specific. How should and when should patients be approached for screening? Should it be repeated at every visit or just done once? Should the screening be oral, written or both? Is there any data regarding which screening tool is most sensitive or specific for the pregnant population? This section is perhaps the most critical of the review since this is where OBGYNs may have the most potential for impact. The paragraphs describing urine, meconium and urine testing are also problematic. What does it mean that clinicians are not proficient at urine toxicology interpretation? In line 144, what do the authors mean by "unexpected"? Doesn't this kind of language propagate and reinforces bias? Lines 151-152 suggest that OBGYNs, in addition to screening, should be counseling regarding newborn testing - is that really in the OBGYN purview? The paragraph encompassing lines 153-163 also needs reworking. This comes out of the blue and seems tangential since there is no transition of thoughts. Perhaps the last sentence should introduce the paragraph for a smoother transition? And finally, shouldn't there be an emphasis on referral? What options OBs might consider, when to refer, how to refer, what to do if there are no local options, etc?
6. Substance classes: This portion of the document was the most clear and accessible. However, I would still suggest that it may be beneficial for the reader to have consistent subsections under each substance for accessibility and clarity. Specifically, I would suggest an paragraph of background information, a pregnancy-specific paragraph (important perinatal caveats, data about fetal effects or pregnancy outcomes, need for APT, etc) and then the treatment section that is currently in place already. For OUD specifically, I would personally like to see more information on the role of the community support resources and how that plays into successful treatment. Additionally, a more robust discussion on NAS, including dosing implications of methadone and suboxone, would be additive.
7. Conclusion: It seems like the discussion in lines 472-483 should be mentioned long before the conclusion, since this is integral to the basic understanding of this issue. Perhaps this information along with additional data belongs elsewhere/earlier in the review?

8. Box 1: The phrasing here should be consistent between definitions. There is no need to repeat "addiction is" under the addiction section - the definition should stand along. Same for SUD.

Reviewer #3: This is a clinical expert series on substance abuse disorders in the perinatal period. Authors presented a comprehensive review of treatment strategies for 6 of the most common substances.

Overall, detailed and well written and should be mandatory reading for all practicing OBGYNs.

Suggested edits and comments:

1. Consider discussing in a paragraph or two, evidence-based impact of each specific substance prior to the narrative on treatment strategies. Of the latter, the commentary seems light on treatment outcomes for SUD. Perhaps an overview may suffice.
2. Consider replacing table 4 with a summary of treatment recommendations for each substance discussed. Having a table only for opioids over-emphasizes that SUD more than others. If that is the authors' intent, then a rationale should be presented.
3. Indicate in the abstract and introduction section why these specific substances were the focus of discussions. One would suspect it is related to prevalence and impact but that should be specified.
4. Lines 366-7; what exactly did the literature show? A brief declarative statement will be helpful to readers.
5. Stylistic suggestions; Authors used "individuals" quite liberally in the initial parts of the manuscript and later included "women" and went back and forth (e.g., lines 70-2). Would suggest sticking to one or the other throughout the manuscript.

Lines 151, 164, 226, 263, 354, 368 etc "OBGYNs should be aware/should understand" seems redundant given the manuscript title "What OBGYNs should know..."

Line 9; delete "comfortable"- colloquial; knowledgeable will suffice

Line 485; replace "OB" with OBGYN

EDITOR COMMENTS:

Thank you very much for writing this clinical expert series for the Green Journal. Your cover letter noted that you are over word count and that you were open to suggestions for how to condense the text. I would suggest some refocusing on what a clinician can use in daily practice. For example, while I understand the importance of child welfare laws, would pare this down to what you think is most clinically applicable. Some of the information about appropriate language in the text could be reduced since you have a table summarizing this. The same is true for other duplication between the text and tables/boxes. I also agree with the reviewers that the section on screening and testing needs to be focused on what the authors recommend and why- it is OK to give your expert opinion on this without presenting all the options.

1. The Editors of Obstetrics & Gynecology have increased 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. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).

* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.

- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
- * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. 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.

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. 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.

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. 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.

9. 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.

10. 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.

11. ACOG avoids using "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.

12. 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.

13. 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 references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and 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.

14. 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.

15. 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>.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded as a Microsoft Word document. 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.

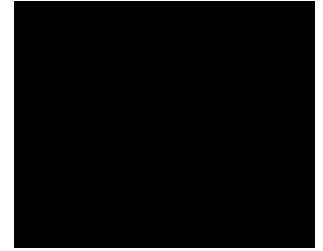
If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

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 Sep 24, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Torri Metz, MD, MS
Associate Editor for Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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September 23rd, 2021

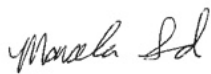
Dear Editors:

Dr. Mishka Terplan and I are pleased to re-submit our manuscript entitled, "What Obstetrician-Gynecologists should know about substance use disorders in the perinatal period" for consideration for publication in *Obstetrics & Gynecology*.

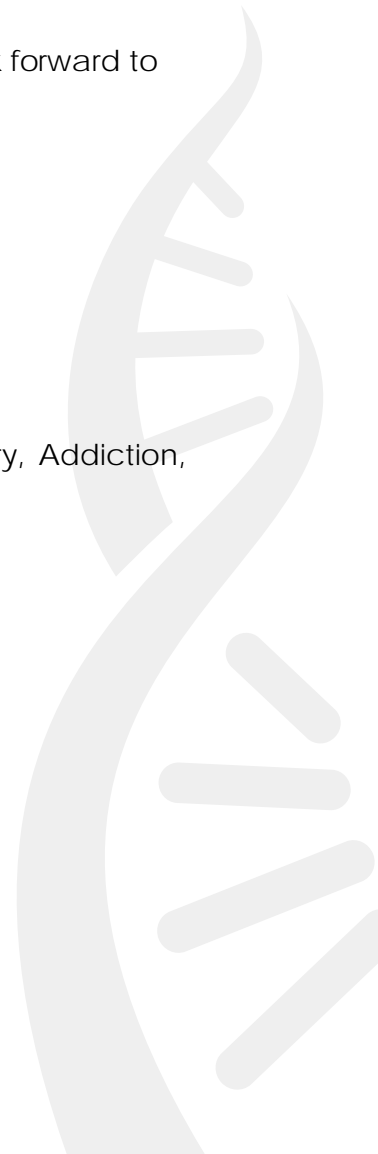
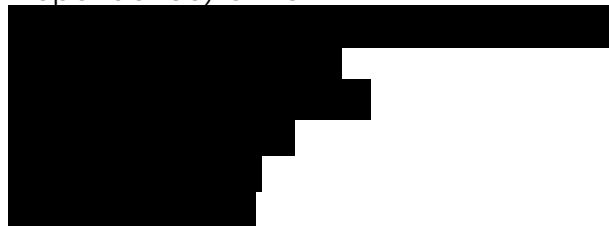
We thank the reviewers for their thoughtful comments. We have responded to each of the comments and include our response and manuscript edits. We have substantially revised the manuscript to focus on those skills that OB-GYNs can incorporate into daily practice and the basics of addiction medicine. After responding to all comments, our manuscript remains slightly over the recommended word limit (6740/6500). We invite further feedback from the editorial board. .

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

Sincerely,



Marcela Smid
Assistant Professor
Division of Maternal Fetal Medicine
Medical director of SUPeRAD (Substance Use and Pregnancy – Recovery, Addiction, Dependence) Clinic



REVIEWER COMMENTS:

Reviewer #1:

This is an article submitted for consideration under the clinical expert series. The article's purpose is to describe "What Obstetrician-Gynecologists should know about substance use disorders in the prenatal period." The article reviews the appropriate use of language in the management of substance use disorder, prevalence of substance use disorder in pregnancy, screening of pregnant individuals for substance use disorder, and management considerations of substance use disorder on labor and delivery and in the postpartum period. The article then continues to describe commonly used substance classes. For each substance, general and pregnancy-associated risks are reviewed, along with treatment recommendations. Lastly, the article provides quick reference tables describing appropriate terminology and language for substance use disorder, screening tools, and medications used for opioid use disorder. The summary is concise is relatively updated compared to other review articles.

Reviewer #1, Comment #1:

Introduction: The introduction is of appropriate length. The authors made a convincing case for the need to complete the review article.

Authors response: We thank Reviewer #1 for this comment.

Reviewer #1, Comment #2: Regarding child welfare, policies vary significantly state-to-state, and reporting practices can vary by institution. It would be helpful to provide some information on where providers can find out policies associated with their particular area of practice - discussion with social work, or online reference for example.

Authors' response: We agree with the reviewer's comments that state laws and local policies vary greatly. We have added the Guttmacher Institute as a resource for up to date state policies on substance use and pregnancy. We also encourage OB-GYNs to collaborate with pediatric and social work teams in order to understand local reporting practices.

Manuscript edits:

Lines 115-118: The Guttmacher Institute provides a broad overview of state-specific statutes including reporting requirements.⁵¹ Importantly, reporting practices vary locally by county and even hospital. OB-GYNs should work with pediatric and social work team to understand local reporting practices and accurately explain them to patients before delivery.

Reviewer #1, Comment #3: Screening: Line 142 states "a more thoughtful and judicious use of urine toxicology testing is warranted, if it is to be used at all." This is a controversial topic, and I would recommend at least a few sentences expanding on the pros and cons and urine toxicology screening, as this is commonly encountered in general clinical practice. There should also be some discussion regarding which substances are screened for with urine toxicology, why, and how to determine what is best for a provider's area of practice. For example, should screening be performed for marijuana?

Authors' response: We have added additional information about the utility of urine toxicology. We do not specifically highlight cannabis as the guiding principle is that urine toxicology should have a clear purpose in guiding clinical care.

Manuscript edits:

Line 179-193: Urine toxicology tests should only be used when clearly indicated for clinical care and following explicit and documented maternal consent. For example, OB-GYNs can utilize urine toxicology for harm reduction counseling by screening for fentanyl with opioid, non-prescribed benzodiazepine or stimulant use. Of note, opiate immunoassays do not detect synthetic opioids such as fentanyl or oxycodone and generally need to be ordered separately. If urine toxicology is used, OB-GYNs must understand test characteristics. At minimum, OB-GYNs should understand that 1) point of care or "presumptive" immunoassay tests are screening tests,⁸⁰ with high false positive and false negative results; and 2) confirmatory testing (via gas chromatography-mass spectrometry analysis) is recommended in the event of results not consistent with self-report or treatment plan.

Reviewer #1, Comment #4:

Treatment recommendations: There are many resources that discuss "SBIRT" training. It may be helpful to mention these.

Authors' response: We have added in the screening section a more robust discussion of the SBIRT framework.

Manuscript edits:

Lines 162-177: Screening, Brief Intervention and Referral to Treatment (SBIRT) is a useful public health approach to the delivery of early intervention and treatment to people with SUD and those at risk of developing these disorders. Screening assesses substance use and severity and allows for risk stratification. For those at low-risk, OB-GYNs should reinforce abstinence and invite pregnant and postpartum individuals to discuss when or if use patterns change. For those who have moderate risk, brief intervention (1-5 patient-centered sessions lasting < 15 minutes) focuses on increasing awareness regarding substance use and intrinsic motivation for behavioral change. For example, brief intervention is associated with a reduction in alcohol use in pregnancy, and an even greater reduction is observed when a partner chosen by the patient is included in the intervention.⁷¹ For those at high risk who likely have SUD, direct initiation of treatment or referral to specialty addiction services is warranted. Most pregnant individuals with continued use are motivated to engage in treatment to maximize their health and that of their fetus, particularly when that care is non-judgmental and personalized. Therefore, a referral is best accomplished with a clinician-to-clinician warm handoff. Integration of SBIRT does take time and effort. OB-GYNs can utilize billing codes to account for time spent performing structured assessments (<https://www.samhsa.gov/sbirt/coding-reimbursement>).

Reviewer #1, Comment #5: Opioid Treatment Recommendations It may be worth mentioning that there are options for outpatient management of opioid use disorder, and there are opportunities for Ob/Gyn providers to become trained in management of medications for opioid use disorder.

Authors' response: We appreciate the reviewer's comments and have included a brief discussion of outpatient management of OUD by OB/GYNs and resources for additional training. Additionally, there are prescribing "clinical pearls," such as split dosing recommendations, in Box 4.

Manuscript edits:

Lines 364-369: In the outpatient setting, OB-GYNs need a buprenorphine waiver in order to prescribe.¹⁷⁶ Recent policy changes eliminate the special training previously required and allows eligible practitioners to prescribe to up to 30 patients with an X-waiver.¹⁴ For those who intend to prescribe for more than 30 patients or those seeking training, OB-GYN-focused trainings exist (<https://www.asam.org/education/live-online-cme/waiver-qualifying-training/ob-gyn-focus>).

Reviewer #1, Comment #6: Benzodiazepine: Line 417 - this statement is a little misleading, as the combined use of SSRI and benzodiazepine does improve outcome in acute management of anxiety and depression, and therefore could potentially be useful, even in pregnancy.

Authors' response: We thank the author for pointing this potentially misleading statement. We have edited the manuscript to acknowledge that there is evidence to support combination use of SSRI and benzodiazepine in the early phase (first four weeks) of depression/anxiety but that the therapeutic effect does not continue into the acute phase (5-12 weeks) or continuous phase (more than 12 weeks) of treatment.

Manuscript edit:

Lines 454-457: Although benzodiazepines have benefit in the management of acute conditions (such as seizure or alcohol withdrawal), benzodiazepines (alone or in combination with SSRIs) do not improve outcomes in the chronic management of depression or anxiety beyond the first four weeks of treatment.

Reviewer #2: Comprehensive, data-driven and clinically-oriented guidelines and recommendations concerning SUD screening, referral and management in pregnancy are much needed. Therefore, the focus of this Clinical Expert series is relevant and timely. However, the organization, content and focus of the document needs additional editing to increase clarity and accessibility. In particular, the introduction, overview and screening portions of the review are wandering, sometimes unorganized and often difficult to follow. Furthermore, a more robust discussion of best practices around screening and referral, which will typically be the purview of the general OBGYN rather than treatment, is very much warranted. Additionally, I was disappointed at the lack of attention paid to possible preventative efforts (recommendations for prescribing habits for opioids, benzos, etc), areas of need and future research/therapeutic directions. My specific comments by section are detailed below:

Reviewer #2, Comment #1:

Abstract: Lines 14 do not seem accurate based on the review's content. There was actually a surprising paucity of information about the maternal mortality crisis related to SUD within the body of the review. It seems a more robust discussion of this issue to ground the topic would be important and should be added.

Authors' response: We agree with the reviewer and have increased the content about the contribution of overdoses to the maternal mortality crisis.

Manuscript edits:

Lines 91-100: For the complex outlined above, overdose is a leading cause of maternal death in the US. Mounting evidence suggests that for individuals with SUD, the postpartum period is frequently destabilizing. Most deaths occur in setting of unrecognized or untreated SUD, in the late postpartum period (after six weeks postpartum) often after a period of remission, and with opioid and polysubstance use. Contact with the healthcare system is common prior to maternal death, representing a missed opportunities for intervention and prevention.

Reviewer #2, Comment #2:

Introduction: The global health crisis around SUD is important to include here. Prevalence, demographic distribution and mortality contribution seem like an important backdrop for the rest of the review.

Authors' response: We appreciate the reviewer's comments about situating this review within the current overdose crisis. We have included additional language within the introduction to contextualize the urgent need for OB-GYNs to be knowledgeable about identification and treatment of SUD among pregnant and postpartum individuals.

Manuscript edits:

Lines 96-100: The COVID-19 pandemic, specifically social isolation and restricted access to treatment, coupled with the rapid increase of fentanyl in drug supply, has likely worsened drug-related maternal deaths. 2020 saw a 30% increase in overdose deaths, the largest single year increase in over two decades.

Reviewer #2, Comment #3: Language: A little historical context around language and naming seems relevant and important, particularly since this has evolved in the past several years. I'd suggest adding some discussion of changing DSM definitions and also highlighting the difference in DSM-recommended terms versus colloquial descriptions of disease. Furthermore, the phrasing of lines 52-53 is awkward and may benefit from revision.

Authors' response: We appreciate the suggestion to include historical context for terminology shifts as many OB-GYNs may have trained when DSM IV terminology (e.g. substance abuse) was the contemporary nomenclature.

Manuscript edits:

Lines 129-138: One of the most frequent misconceptions of both pregnant individuals and OB-GYNs is that about continued substance use in the setting of SUD is a choice, rather than symptom of the medical condition. By utilizing current medical terminology (**Box 1**) and person-centered language (**Box 2**), OB-GYNs communicate that SUD, like other chronic medical conditions, can be managed and that recovery is possible. We recognize that many OB-GYNs trained when substance abuse and dependence were the appropriate terms under the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). In May 2013, the American Psychiatric Association issued the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which integrated the two DSM-IV criteria into SUD with mild, moderate and severe sub-classifications.

Reviewer #2, Comment #4: Substance use and addiction in pregnancy and postpartum: Again, for me, context around this area is critical. It seems impossible to have a review of what every OBGYN should know about SUD and not discussing the alarming maternal morbidity and mortality rates, yet that seems to be the case here. Additionally, the organization of this section is confusing and chaotic. It moves from racial inequities to postpartum vulnerability to sex and

gender differences (including brief mentions of sexual victimization and contraceptive choices) and lastly address child welfare. While these area undoubtedly all important areas to include, the approach needs to be much more logical and systematic. Perhaps discussion of maternal morbidity and mortality trends generally (including timing of most deaths) followed by general addiction trends in pregnancy as well as the postpartum period (including potential contributions). Racial inequities and sex differences could then be addressed followed lastly by child welfare.

Authors' response: We appreciate the feedback regarding organization and flow of this section. We have re-organized the manuscript to discuss substance use and SUD within the context of pregnancy and the postpartum period. We then move to how these vulnerabilities place individuals at high risk of overdose in the perinatal period. We brief touch about the hormonal shift that impact SUD symptoms (e.g. cravings). We then discuss the role of child welfare in management SUD in this population. We have moved racial disparities of treatment in the paragraph introducing SUD treatment.

Manuscript edits: Because of the number of edits to this section, we will not include all manuscript for this comment. In the section entitled "Substance use in the perinatal period and the crisis of overdose deaths" we have reorganized the flow to first present most common patterns of substance use in pregnancy and postpartum followed by discussion of overdose as a leading cause of maternal deaths. We have moved racial inequities and treatment access to section discussing treatment.

Reviewer #2, Comment #5a: Screening: This section is a missed opportunity for me. Again, the organization of the section is erratic and the recommendations too broad and non-specific.

Authors' response: We have refocused this discussion on concrete recommendations regarding screening. We have also included how the SBIRT approach can help with screening result management.

Manuscript edits:

Lines 140-177: This entire section has been revised and re-focused to provide specific information about screening and the SBIRT approach. See below for specific manuscript changes in response to reviewer comments.

Reviewer #2, Comment #5b : How should and when should patients be approached for screening?

Authors' response: We have increased discussion about how and when screening should be in prenatal care. We have also included suggestions around asking for permission when approaching screening with a patient.

Manuscript edits:

Lines 141-145: ACOG recommends universal screening prior to pregnancy and at the first prenatal visit in partnership with the individual.⁵⁸ While screening may be negative in early pregnancy, substance use patterns may change, particularly postpartum, therefore, OB-GYNs should consider screening at least once postpartum.

Reviewer #2, Comment #5c: Should it be repeated at every visit or just done once?

Authors' response:

We have included recommendation from ACOG that screening should be done prior to pregnancy and at first prenatal visit. We also include that based on previously presented information, OB-GYNs should consider re-screening in the postpartum setting.

Manuscript edits:

Lines 141-145: ACOG recommends universal screening prior to pregnancy and at the first prenatal visit in partnership with the individual.⁵⁸ While screening may be negative in early pregnancy, substance use patterns may change, particularly postpartum, therefore, OB-GYNs should consider screening at least once postpartum.

Reviewer #2, Comment #5d: Should the screening be oral, written or both?

Authors' response: We have included discussion about that screening can be oral, written or electronic.

Manuscript edit:

Lines 151-154: Screening can be verbal, written or electronic depending on patient literacy and clinic resources. In order to promote clinician-patient partnership and to maximize the therapeutic benefit of screening, we suggest that OB-GYNs ask permission first (e.g. "Can I ask you some questions about drinking, smoking and other drugs?").

Reviewer #2, Comment #5e:

Is there any data regarding which screening tool is most sensitive or specific for the pregnant population? This section is perhaps the most critical of the review since this is where OBGYNs may have the most potential for impact.

Authors' response: Information about sensitivity and specificity of screening tools for the pregnant population is available with citations in **Box 3** which included the recommended screening tools in this population.

Manuscript:

Box 3 Comments:

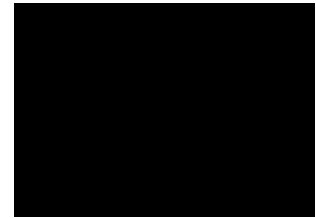
- Two studies directly compare different screening instruments for substance use (other than tobacco or alcohol) in pregnancy.
- Accuracy is low for nearly all measures and none superior.
- OB-GYNs should use a validated instrument that is easily integrated into their existing workflow.

Reviewer #2, Comment #5f: The paragraphs describing urine, meconium and urine testing are also problematic.

Author response: We have focused on urine toxicology as it is the most relevant to OB-GYN practice. We have removed discussion of meconium and cord testing to focus on use of urine toxicology

Manuscript edits:

Lines 179-193: we did not copy the entire paragraph here as specific points are addressed below.



Reviewer #2, Comment #5g: What does it mean that clinicians are not proficient at urine toxicology interpretation?

Authors' response: Several studies, which are cited, indicate that most clinicians do understand urine toxicology test characteristics including sensitivity, specificity, immunoassay cross-reactivity and need for confirmatory testing when screening is positive. We have edited the manuscript to concretely suggest the key urine toxicology interpretation skills that every OB-GYN should have.

Manuscript edits

v

Reviewer #2, Comment #5h:

In line 144, what do the authors mean by "unexpected"? Doesn't this kind of language propagate and reinforces bias?

Authors' response: Unexpected is the preferred term for results that do not fit with a patient's self-report or treatment plan. For example, a urine toxicology may be positive for oxycodone, which would be unexpected in the absence of a known prescription and expected if oxycodone was part of the patient's treatment plan.

Manuscript edits:

Lines 187-191: If urine toxicology is used, OB-GYNs must understand test characteristics.^{77, 78}
⁷⁹ At minimum, OB-GYNs should understand that 1) point of care or "presumptive" immunoassay tests are screening tests,⁸⁰ with high false positive and false negative results;^{81, 82} and 2) confirmatory testing (via gas chromatography-mass spectrometry analysis) is recommended in the event of results not consistent with self-report or treatment plan.

Reviewer #2, Comment #5i:

Lines 151-152 suggest that OBGYNs, in addition to screening, should be counseling regarding newborn testing - is that really in the OBGYN purview?

Authors' response: We agree that while newborn testing is not the purview of OB-GYNs directly. For clarity we have removed the discussion of newborn testing.

Reviewer #2, Comment #5j:

The paragraph encompassing lines 153-163 also needs reworking. This comes out of the blue and seems tangential since there is no transition of thoughts. Perhaps the last sentence should introduce the paragraph for a smoother transition?

Authors' response: We appreciate the feedback regarding transition and have reorganized this section with a smoother transition from screening for substance use to screening for other co-morbidities.

Manuscript edits:

Lines 198-208: Screening for co-morbidities: In addition to substance use screening, OB-GYNs should incorporate universal screening for mental health conditions,^{40, 85} IPV⁸⁶ and infectious diseases (HIV, Hepatitis C, Hepatitis B)⁸⁷ into practice. A significant proportion of pregnant individuals (25-33%) with SUD have co-morbid mental health conditions including depression, anxiety, posttraumatic stress disorder, and trauma,^{536, 537} experience intimate partner violence (IPV),²⁸ and have higher rates of some infectious diseases.⁸⁴ OB-GYNs should understand infectious disease transmission windows (e.g. HIV and Hepatitis C tests may be negative for 4-8 weeks post seroconversion) and consider offering pre-exposure and post

exposure prophylaxis for HIV⁸⁸ and referral to treatment for Hepatitis C postpartum or for studies investigating treatment during pregnancy.⁸⁹ Re-screening should be considered following return to use.

Reviewer #2, Comment #5jk

And finally, shouldn't there be an emphasis on referral? What options OBs might consider, when to refer, how to refer, what to do if there are no local options, etc?

Authors' response:

We agree with the author's feedback and have incorporated a more detailed section about the SBIRT framework for the management of results. For those clinicians working in areas where there are limited options for referral, we have provided information about additional resources available including the National Clinical Consultation Center, the SAMHSA treatment center locator and the state Perinatal Quality Collaboratives.

Manuscript edits:

Lines 172-175: Therefore, a referral is best accomplished with a clinician-to-clinician warm handoff. OB-GYNs should initiate basic addiction care until specialty care can be arranged. We recognize that referrals to specialty care are not always easily accessible, and resources are available (**Box 4**).

Reviewer #2, Comment #6a:

Substance classes: This portion of the document was the most clear and accessible. However, I would still suggest that it may be beneficial for the reader to have consistent subsections under each substance for accessibility and clarify. Specifically, I would suggest an paragraph of background information, a pregnancy-specific paragraph (important perinatal caveats, data about fetal effects or pregnancy outcomes, need for APT, etc) and then the treatment section that is currently in place already.

Authors' response: we appreciate the reviewer's comments. Throughout the treatment section, we have included more pregnancy specific information for each substance and other information. We have kept the sub-headings from the original manuscript. We are happy to work with the editorial board if subheadings are desired.

Reviewer #2, Comment #6b:

For OUD specifically, I would personally like to see more information on the role of the community support resources and how that plays into successful treatment.

Authors' response: We thank the reviewer for the suggestion and added additional information about peer services and community reinforcement programs.

Manuscript edits:

Lines 371-376: OB-GYNs should be aware of community resources including peer recovery support services¹⁷⁷ and community reinforcement programs ("twelve step programs").¹⁷⁸ For individuals with OUD, participation in peer services is associated with greater number of attended OUD medical appointments compared to those not receiving peer services.¹⁷⁹ Recent qualitative data suggests that peer services are acceptable and valued among pregnant and postpartum individuals with OUD.¹⁸⁰ Both peer services¹⁸¹ and community reinforcement programs¹⁸² are available through telehealth and online.

Reviewer #2, Comment #6c:

Additionally, a more robust discussion on NAS, including dosing implications of methadone and suboxone, would be additive.

Authors' response: We have added more information about NAS and the relationship with MOUD dose.

Manuscript edits:

Lines 325-337: OB-GYNs should have a working knowledge of Neonatal Abstinence Syndrome (NAS) which can result from prenatal opioid exposure, including MOUD. NAS is constellation of symptoms characterized by disturbances in the gastrointestinal, autonomic and central nervous systems including irritability, high pitched cry, poor sleep, and uncoordinated sucking leading to poor feeding. NAS is an expected, limited, and treatable condition occurring 30-80% of infants with prenatal opioid exposure.¹⁴⁹ Management includes both non-pharmacological approaches (low stimulation environment, kangaroo or skin-to-skin contact, breastfeeding, and paired care or "rooming-in") and pharmacological interventions including opioids (morphine, buprenorphine or methadone) and adjuvant treatment (phenobarbital, clonidine, ondansetron).¹⁵⁰⁻¹⁵³ Multiple studies demonstrate that when controlled for polysubstance use and other confounding factors, MOUD dose (methadone^{601, 602, 605} or buprenorphine^{154, 155}) is not correlated with NAS. Therefore, OB-GYNs should counsel both patients and treatment providers that arbitrarily restricting MOUD to decrease NAS is discouraged.

Reviewer #2, Comment #7:

Conclusion: It seems like the discussion in lines 472-483 should be mentioned long before the conclusion, since this is integral to the basic understanding of this issue. Perhaps this information along with additional data belongs elsewhere/earlier in the review?

Authors' response: We thank the reviewer for the suggestion. This sentence is meant to summarize the data presented throughout the manuscript. We hope that the current reorganization and flow better reflects this concluding statement.

Reviewer #2, Comment #8:

Box 1: The phrasing here should be consistent between definitions. There is no need to repeat "addiction is" under the addiction section - the definition should stand alone. Same for SUD.

Authors' response: We appreciate the feedback and have made adjustment to remove redundancy.

Reviewer #3: This is a clinical expert series on substance abuse disorders in the perinatal period. Authors presented a comprehensive review of treatment strategies for 6 of the most common substances.

Overall, detailed and well written and should be mandatory reading for all practicing OBGYNs.

Reviewer #3, Comment #1

Consider discussing in a paragraph or two, evidence-based impact of each specific substance prior to the narrative on treatment strategies. Of the latter, the commentary seems light on treatment outcomes for SUD. Perhaps an overview may suffice.

Authors' response: We appreciate this suggestion and have added language to describe that outcomes for treated SUD are universally better compared to untreated SUD. We have not added a paragraph given word count limitations but believe that the current addition is likely sufficient.

Manuscript edits:

Lines 207-210 Once SUD is recognized, treatment should be offered and initiated as soon as possible. Like other chronic medical conditions, SUD outcomes are universally better among treated versus untreated individuals and 30-60% of patients will have symptom recurrence.⁹⁰

Reviewer #3, Comment #2

Consider replacing table 4 with a summary of treatment recommendations for each substance discussed. Having a table only for opioids over-emphasizes that SUD more than others. If that is the authors' intent, then a rationale should be presented.

Authors' response: We have considered the suggestion of the reviewer and decided to keep Box 5 Medications for Opioid Use Disorder as is. Our rationale is that most deaths are associated with opioids therefore OB-GYNs should be familiar specifically with these medications. We have also added specific resources for OB-GYNs looking to obtain additional training for a buprenorphine waiver. We are open to the editorial boards suggestions.

Reviewer #3, Comment #3

Indicate in the abstract and introduction section why these specific substances were the focus of discussions. One would suspect it is related to prevalence and impact but that should be specified.

Authors' response: We have included

Manuscript Edits:

Lines 42-44: We provide a review of maternal, fetal, and child effects of the most common substances including tobacco, alcohol, cannabis, opioids, stimulants, and benzodiazepines and their respective treatment recommendations such that OB-GYNs can incorporate basic addiction management into their daily practice.

Lines 65-67: We then review maternal, fetal, and child effects and treatment recommendations for most common substances including tobacco, alcohol, cannabis, opioids, stimulants, and benzodiazepines.

Reviewer #3, Comment #4

Lines 366-7; what exactly did the literature show? A brief declarative statement will be helpful to readers.

Authors' response:

Additional information has been added to the section on maternal, fetal and child effects of cocaine.

Manuscript edits:

Lines 394-398: The unscientific and racist rhetoric surrounding cocaine use in pregnancy which associated prenatal cocaine exposure with lifelong emotional, mental, and physical disability, is a cautionary tale for the field of substance use in pregnancy.^{46, 190} Subsequent research on

cocaine and birth and developmental outcomes has failed to confirm previously described adverse child neurodevelopmental outcomes.¹⁹¹

Reviewer #3, Comment #5

Stylistic suggestions; Authors used "individuals" quite liberally in the initial parts of the manuscript and later included "women" and went back and forth (e.g., lines 70-2). Would suggest sticking to one or the other throughout the manuscript.

Authors' response: We thank the reviewer for this suggestion. This has been edited through the manuscript.

Reviewer #3, Comment #6

Lines 151, 164, 226, 263, 354, 368 etc "OBGYNs should be aware/should understand" seems redundant given the manuscript title "What OBGYNs should know..."

Authors' response: We thank the reviewer for this suggestion. While this phrasing is redundant, we present information including context and background information. We use this phrasing to highlight what OB-GYNs should incorporate into daily practice.

Reviewer #3, Comment #7

Line 9; delete "comfortable"- colloquial; knowledgeable will suffice

Authors' response: We thank the reviewer for this suggestion. This has been edited.

Reviewer #3, Comment #8 Line 485; replace "OB" with OBGYN

Authors' response: We thank the reviewer for this suggestion. This has been edited.

EDITOR COMMENTS:

Thank you very much for writing this clinical expert series for the Green Journal. Your cover letter noted that you are over word count and that you were open to suggestions for how to condense the text. I would suggest some refocusing on what a clinician can use in daily practice. For example, while I understand the importance of child welfare laws, would pare this down to what you think is most clinically applicable. Some of the information about appropriate language in the text could be reduced since you have a table summarizing this. The same is true for other duplication between the text and tables/boxes. I also agree with the reviewers that the section on screening and testing needs to be focused on what the authors recommend and why- it is OK to give your expert opinion on this without presenting all the options.

Authors' response: We appreciate the editor's suggestion regarding refocusing on the paper on practices that OB-GYNs can incorporate into daily practice. We have made edits through out the paper, including with concrete suggestions for practice change. We edited the child welfare section on the most clinical applicable information. As mentioned in the cover letter, after addressing reviewer's concerns, we continue to be slightly over word count. We would appreciate the editor's feedback on any further edits.