OBSTETRICS & GYNECOLOGY

Date: Jan 23, 2019
To: "Marcela C Smid" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2312

RE: Manuscript Number ONG-18-2312

Death in the Puerperium - A Decade of Pregnancy-Associated Drug-Induced Deaths

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).

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 Feb 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This paper is a retrospective cohort study comparing pregnancy associated deaths attributed to drug-induced causes in Utah to other pregnancy associated deaths and describe circumstances surrounding the drug-induced deaths to identify opportunities for interventions. Objective in introduction is detailed and stated clearly. authors provide good detail about methods and data base. Small number of drug-induced deaths (35). Authors do meet objectives. Significant limitations, especially limitations of data base, are acknowledged by authors.

1. Line 80-82 - what about specifically for women?

2. Line 86-88 - is this all opioid use, including prescriptions for medical indications used appropriately? Please clarify

3. Line 89-90 - is this current data and what are the reasons?

4. Line 97-98 - please provide this statistic for females

5. Line 98-102 - please provide references to back up these statements

6. Line 138 - is the word "pregnant" needed between "but" and "within"?

7. Line 153 - please clarify if drug use here includes appropriately prescribed medications

8. Line 156 - please quantify significant period of abstinence

9. Line 158-159 - does any use here include apporpriately prescribed medications? Reference here please

10. Line 159-161 - reference here also

11. Line 173-174 - is this the medical examiner's defintion or the athors' definitions? Please clarify

12. Line 218-220 - what were the other causes of pregnancy associated death (% do not add up to 100)?

13. Line 220-221 - figure 1 requires revision as it is hard to determine actual % by year from it. What year were lowest and highest? Any explanations for this large variation by year?

14. Line 227 - is this entire post-partum period (early and late)?

15. Line 242-244 - which substances mostly found in polysubstance abuse?

16. Line 248-250 - why weren't all records available?

17. Line 254-262 - is this due to lack of documentation in the prenatal or delivery chart? Could some of these women have been offered or obtained these services elsewhere?

18. Line 268-270 - how were these deemed not preventable given the findings in lines 245-267? What criteria did the medical examiner use to make these determinations?

19. Line 342-348 - reference here please

20. Table 2 - Age under total (n=35) breakdown into ranges only adds up to 33. Intimate partner violence total is 6 but other 3 categories only adds up to 3. There is nothing under characteristics in 3rd column from the bottom.

Reviewer #2: Overall: This is a paper that examines the contribution of fatal opioid (and other drug) overdoses to maternal mortality in Utah. The authors find that drug-induced deaths are the greatest cause of maternal mortality in the state, and that almost 90% of these deaths occur postpartum. This is a timely and important paper, and re-emphasizes the need for adequate postpartum care, including care beyond the 6 week traditional postpartum period.
I do wonder if these deaths could have been impacted by better prenatal care for their opioid disorders and better psychiatric care - that is what the paper seems to posit, but as most deaths occurred (well) after women stopped seeing their obstetrical providers, I don't know that this is a foregone conclusion. That does not absolve OB providers of the duty to provide psychiatric and substance-abuse related care during and following pregnancy, but I would also be careful throughout the paper to avoid using language that suggests that better care throughout pregnancy will necessarily improve these distal outcomes. After all, only 5/35 deaths (15%) were deemed 'preventable'.

Specific comments are as follows:

Abstract:

1. I occasionally had trouble keeping track of the denominator; maybe keep some of these statistics (such as the number of women with a prior suicide attempt) for the results section.

2. It took me until reading the methods section in the paper to realize the difference between a 'pregnancy-associated' death and a 'pregnancy-related' death - this information was very helpful in determining what this paper was actually about. It would be helpful if you could include this definition here.

Introduction:

3. Instead of using the term 'drug-induced' (and focusing on all drug-induced deaths), would this paper be easier to read if it just focused on opioid-related deaths? Just a thought.

4. What are these other drugs women are dying from? And, here you seem to be including women who commit suicide with drugs in the 'drug-induced death' category - I am not sure this makes sense. It seems you want to focus on accidental overdoses, even if this reduces your total number of deaths.

5. I would use the term 'intimate partner violence' rather than 'domestic abuse'.

Methods:

6. Line 163, you are missing an 'as' between 'defined…death'.

7. line 165, I believe you mean 'drugs'.

Results:

8. Do you know how many pregnancy-related deaths there were in this time period?

9. Why are thromboembolic deaths not considered 'pregnancy-related'? This does not make sense to me.

10. Line 224, can you reword the 'not drug-induced'? It sounds awkward.

11. Lines 225-6, is 57% significantly different than 63%?

12. I know the data are sparse, but was there a trend over time towards increasing risk of deaths from opioids/accidental overdoses? Were more women diagnosed/treated appropriately as time went on?

13. Of the 5 women whose deaths were deemed preventable, what was the possible step OB providers could have taken to prevent the death?

14. Is there any sense of whether these women were using drugs antenatally? Would screening/treatment have identified these women?

Discussion:

15. I appreciated the data from other contexts/states.

16. This discussion is quite long - I think stick with the major points (better care is needed in pregnancy and beyond pregnancy), and take out/shorten some material that is not as important to the main points of the paper and/or is repetitive (ie, upcoming changes in how deaths are categorized, merge paragraph 3 and the final paragraph, etc).

Reviewer #3: This is retrospective cohort study that addresses one of the preventable causes of maternal mortality which is drug abuse.

Although the topic is important, however, some important rates are missed to understand the impact of drug abuse.

One needs to know the mortality rate in general then to determine the death rate due to drug abuse.

Because study period is long relatively, death rates are better to understand the rise of misuse of drugs and death.

More rates should be included.

STATISTICAL EDITOR'S COMMENTS:

1. Table 2: Should include units for age.

2. Fig 1: The counts within each year are limited, so there is little to be inferred from the variation other than stochastic, random change.

3. Fig 2: Based on the sample sizes, should round the %s to nearest whole number, not .1%. Could also include absolute counts of deaths. May be confusing to reader, since each group (drug related vs non-drug related) is scaled to 100%, yet the non-drug cohort is roughly 3x the size of the drug related, which is not conveyed by the present Fig 2. Might be more useful to show the counts and %s within each time epoch that were drug vs non-drug related.

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, as well as subsequent author queries. 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:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. 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.

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

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 26 typed, double-spaced pages (6,500 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.

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).

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

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. 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. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it

should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

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

"Figure 2: Please add a y-axis with tick marks and a label.
Figure 3: Please add a y-axis with tick marks and a label."

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.

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 http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

HEALTH
UNIVERSITY OF UTAH

[redacted]

February 27th, 2019

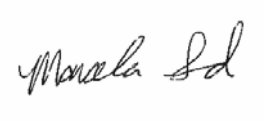
Re: Death in the Puerperium - A Decade of Pregnancy-Associated Drug-Induced Deaths

Dear *Obstetrics and Gynecology* editors:

We thank the reviewer's time and effort in their thoughtful comments. We respectfully submit the attached revised manuscript for consideration to be published in *Obstetrics and Gynecology.* Each of the reviewer's comments are addressed in detail in this letter.

Please do not hesitate to contact me with any questions.
Thank you for your consideration.

Sincerely,



[redacted]

HEALTH
UNIVERSITY OF UTAH

[redacted]

REVIEWER COMMENTS:

Reviewer #1: This paper is a retrospective cohort study comparing pregnancy associated deaths attributed to drug-induced causes in Utah to other pregnancy associated deaths and describe circumstances surrounding the drug-induced deaths to identify opportunities for interventions. Objective in introduction is detailed and stated clearly. authors provide good detail about methods and data base. Small number of drug-induced deaths (35). Authors do meet objectives. Significant limitations, especially limitations of data base, are acknowledged by authors.

Reviewer's comments:

1. Line 80-82 - what about specifically for women?

Authors' response: Drug-induced deaths are the most common cause of death for reproductive age women. We have adjusted the language and reference numbers.
Line numbers: 55-57, 79-81
Revised text: Drug-induced deaths - defined as intentional or unintentional consumption of illicit substances or diverted medications leading to death - are the leading cause of death for reproductive age women in the United States.[1-3]

Reviewer's comments:

2. Line 86-88 - is this all opioid use, including prescriptions for medical indications used appropriately? Please clarify

Authors' response: We have clarified that these rates are for deliveries complicated by maternal opioid use disorder. Opioid use disorder does not include women using opioids for medication indication during pregnancy .
Line numbers: 84-87
Revised text: From 1999 to 2014, the rate of deliveries complicated by maternal opioid use disorder, defined as a problematic pattern of opioid use leading to serious impairment or distress, more than quadrupled (1.5 per 1000 deliveries in 1999 to 6.5 in 2014).[5] These rates *do not* include women using opioids as prescribed for medical indications.

Reviewer's comments:

3. Line 89-90 - is this current data and what are the reasons?

Authors' response: These are the most currently available national data for opioid prescribing in pregnancy.
Line Number: Line 87-91
Revised text: National estimates suggest that 14-40% of pregnant women will receive an opioid prescription at some time during their pregnancy.[6,7] The most common reasons for opioid prescriptions during pregnancy are back pain, abdominal pain, headache or migraine, joint pain or other pain diagnosis [6,7]

Reviewer's comment:

4. Line 97-98 - please provide this statistic for females

Authors' response: We have clarified that by general population, we mean reproductive age women.

[redacted]

Line number: Lines 103-104
Revised text: Among reproductive age women, the majority of drug-induced deaths (84.2%) are accidental,[1] however, less is known about whether drug-induced pregnancy-associated deaths are accidental or intentional.

Reviewer's comment:
5. Line 98-102 - please provide references to back up these statements
Authors' response: We have provided additional references to support this statement.
Line number: 103-105
Revised text: Additionally, knowledge gaps exist regarding the circumstances surrounding drug use, drug relapse and drug-induced deaths among pregnant and postpartum women.[15-17]

15. Gemmill A, Kiang MV, Alexander MJ. Trends in pregnancy-associated mortality involving opioids in the United States, 2007-2016. *Am J Obstet Gynecol.* 2019;220(1):115-116.
16. Metz TD, Rovner P, Hoffman MC, Allshouse AA, Beckwith KM, Binswanger IA. Maternal Deaths From Suicide and Overdose in Colorado, 2004-2012. *Obstet Gynecol.* 2016;128(6):1233-1240.
17. Bagley SM, Cabral H, Saia K, et al. Frequency and associated risk factors of non-fatal overdose reported by pregnant women with opioid use disorder. *Addict Sci Clin Pract.* 2018;13(1):26.

Reviewer's comment:
6. Line 138 - is the word "pregnant" needed between "but" and "within"?
Authors' response: We appreciate the author's close reading and have edited accordingly.
Line numbers: 146-148
Revised text: 2) selection of pregnancy timing field including 'pregnant at time of death', 'not pregnant, but pregnant within 42 days of death' or 'not pregnant, but pregnant within 43 days to one year before death;'

Reviewer's comment:
7. Line 153 - please clarify if drug use here includes appropriately prescribed medications
Authors' response: According to the Surgeon General's definition we used, drug use includes prescribed medications. We have edited the text to reflect this.
Line numbers: 162-163
Revised text: Drug use includes use of prescribed medications used appropriately.

Reviewer's comment:
8. Line 156 - please quantify significant period of abstinence
Authors' response: Per the Surgeon General's definition that we use throughout this study, significant period of abstinence is not quantified.

Reviewer's comment:
9. Line 158-159 - does any use here include appropriately prescribed medications? Reference here please

[redacted]

Author's response: In defining all of our terms, we used the definitions published by the Surgeon General on Facing Addiction in America. Misuse is defined as the use of any substance in a manner, amount or frequency that can cause harm to the user or to those around them. For some substances or individuals, any use would constitute misuse. We thank the reviewer for commenting about the use of prescribed medications (e.g. opioids, benzodiazepines, stimulants). In this case, misuse would not include medications as prescribed.
Line number: 166-168
Revised text: For specific populations including pregnant women, any drug use is synonymous with misuse with the exception of medications (e.g. opioids, benzodiazepines, stimulants) used as prescribed.

Reviewer's comment:
10. Line 159-161 - reference here also
Author's response: In defining all of our terms, we used the definitions published by the Surgeon General on Facing Addiction in America. To further clarify this, we have moved the appropriate reference to the first sentence in this paragraph. This reference applies to all the definitions referred to in this paragraph (Lines 161-172). If the editors prefer, we will add the reference after each definition (drug use, drug misuse, drug relapse, substance use disorder).
Line number: 159-160
Revised text: To describe women's drug use history, we used definitions published by the US Office of the Surgeon General.[21]

Reviewer's comment
11. Line 173-174 - is this the medical examiner's definition or the authors' definitions? Please clarify
Author's response: The determination of death as "accidental," "intentional" or "could not be determined" is based on the medical examiner's determination
Line number: 182-183
Revised text: Based on Utah medical examiner's assessments, deaths were defined as intentional (i.e. suicide), accidental or could not be determined.

Reviewer's comment
12. Line 218-220 - what were the other causes of pregnancy associated death (% do not add up to 100)?
Authors' response: We have revised the text to highlight the three most common causes of pregnancy-associated death (drug-induced, thromboembolic and motor vehicle accidents). We have also included the remaining causes of pregnancy-associated death during this time period.
Line numbers: 227-232
Revised text: From 2005-2014, the three most common causes of pregnancy-associated deaths (n=136) were drug-induced death (n=35/136, 26%), thromboembolic disease (n=18/136, 13%) and motor vehicle accidents (n=17/136, 12%). The remainder of pregnancy-associated deaths (n=66, 49%) were due to cardiac conditions, hypertension, infection, homicide/suicide, hemorrhage, malignancy and other causes.

[redacted]

Reviewer's comment:
13. Line 220-221 - figure 1 requires revision as it is hard to determine actual % by year from it. What year were lowest and highest? Any explanations for this large variation by year?
Authors' response: We have edited the figure to include the actual percentage by year and have edited the text to include the highest and lowest percentage. We have included that the 2010 spike in drug-induced deaths corresponded to a nationwide increase in heroin overdoses. We feel that it is important to present the drug-induced pregnancy-associated deaths by year in order to highlight that there is tremendous variation from year to year, which is difficult to explain given the current surveillance mechanisms available.
Line numbers: 232-233, 297-302
Revised text:
232-233: The annual proportion of pregnancy-associated deaths that were drug-induced ranged from 17 - 47%, with nadir in 2007 (8%) and peak (47%) in 2010 (Figure 1).
297-302: In 2010, the peak of drug-induced pregnancy-associated deaths in Utah corresponded to an increase in heroin-related deaths nationwide.[4] During our study period, the pregnancy-associated mortality ratio increased 76% and the drug-induced pregnancy-associated mortality ratio increased 200%. While there is variation between years in proportion of deaths that are attributable to drug-induced causes, the overall trend suggests that drug-induced pregnancy-associated deaths are on the rise.

Reviewer's comment:
14. Line 227 - is this entire post-partum period (early and late)?
Authors' response: This statement refers to the entire postpartum period. We have edited the text to reflect this.
Line number: 243-245
Revised text:
Women whose deaths were drug-induced were more likely to have died after delivery (n=31/35, 89%) compared to those whose deaths were from other pregnancy-associated causes (n=62/101, 61%) (p=0.01).

Reviewer's comment:
15. Line 242-244 - which substances mostly found in polysubstance abuse?
Authors' response:
Among women with polysubstance use, opioids, benzodiazepines and anti-depressants were the most frequently identified drugs. We have included a Table 3 to delineate this, although for space purposes this can be removed or placed in an appendix if the editors prefer. Because of small numbers and HIPAA compliance, we cannot include the same breakdown for women with a single drug identified at time of death
Line number: Table 3
Revised text:

<u>Table 3: Drug types identified among women with more than one drug identified at death</u>

[redacted]

Drug type	Polysubstance use (n=29)
	N (%)
Opioids	25 (86)
Benzodiazepines	12 (41)
Anti-depressants	11 (38)
Muscle relaxants	7 (24)
Acetaminophen	4 (14)
Amphetamines	8 (28)
Alcohol	5 (17)
Z drug	4 (14)
Other	10 (34)

Reviewer's comment:

16. Line 248-250 - why weren't all records available?

Authors' response: By Utah state law, we may request records for all women with a pregnancy-associated death, but hospital/provider compliance with the request is voluntary. The Utah Perinatal Mortality Committee makes several attempts to contact providers when we have not received records. Additionally, for some women, no prenatal care was obtained (n=3), or the pregnancy ended prior to a delivery (4). Because compliance is voluntary per state law, the Committee does not have any means to ensure or enforce access to all records.

Reviewer's comment

17. Line 254-262 - is this due to lack of documentation in the prenatal or delivery chart? Could some of these women have been offered or obtained these services elsewhere?

Authors' response:

We agree with the author that services may have been offered or obtained elsewhere. We note this limitation in the discussion section.

Line number: 362-363

Revised text: Comprehensive records were not available for all women. Additionally, women may have sought care from providers we were unable to identify.

Reviewer's comment

18. Line 268-270 - how were these deemed not preventable given the findings in lines 245-267? What criteria did the medical examiner use to make these determinations?

Author's response: We appreciate the reviewer's comment about the factors contributing to pregnancy-associated death. The PMRC, not the medical examiner, makes the assessment of preventability by expert opinion

Line numbers: 153-157

Revised text: The PMRC considers each death for its pregnancy-relatedness, contributing factors and preventability.[20] Preventability was determined by the expert opinion of the PMRC by reviewing all available documents. A death is considered preventable if the committee determines that there was at least some chance of the death being averted by one or more reasonable changes to patient, family, provider, facility, system, and/or community factors.

[redacted]

Reviewer's comment:

19. Line 342-348 - reference here please

Authors' response:

We would be happy to add references, however, in these lines we are describing our results in reference to literature on intimate partner violence and history of abuse in this population.

Line 356-358:

Revised text: n our cohort, abuse and intimate partner violence were lower than other populations of women with substance use disorders,[33] likely representing a lack of systematic screening in prenatal and postpartum care and another opportunity of intervention.

Brogly SB, Saia KE, Werler MM, Regan E, Hernández-Díaz S. Prenatal Treatment and Outcomes of Women With Opioid Use Disorder. *Obstet Gynecol*. 2018;132(4):916-922.

Reviewer's comment:

20. Table 2 - Age under total (n=35) breakdown into ranges only adds up to 33. Intimate partner violence total is 6 but other 3 categories only adds up to 3. There is nothing under characteristics in 3rd column from the bottom.

Author's response:

We thank the reviewer for bringing this error to our attention. We have edited the table accordingly.

	N =35	**N=19**	**N=9**	**N=7**
Age (years)				
15-19	2 (5.7)	1 (5.3)	1 (11.1)	0 (0)
20-34	28 (80.0)	16 (84.2)	7 (77.8)	5 (71.4)
≥35	5 (14.3)	2 (10.5)	1 (11.1)	2 (28.6)
Intimate partner violence	6 (17.1)	2 (11.1)	3 (33.3)	1 (14.3)
Number of infants	N=31	N=17	N=9	N=5
Department of Child and Protective Services involvement	7 (22.5)	2 (11.8)	5 (55.6)	0 (0)
Maternal custody of infant at delivery	17 (54.8)	11 (64.7)	4 (44.4)	2 (40.0)

Reviewer #2: Overall: This is a paper that examines the contribution of fatal opioid (and other drug) overdoses to maternal mortality in Utah. The authors find that drug-induced deaths are the greatest cause of maternal mortality in the state, and that almost 90% of these deaths occur postpartum. This is a timely and important paper, and re-emphasizes the need for adequate postpartum care, including care beyond the 6 week traditional postpartum period.

I do wonder if these deaths could have been impacted by better prenatal care for their opioid disorders and better psychiatric care - that is what the paper seems to posit, but as most deaths occurred (well) after women stopped seeing their obstetrical providers, I don't know that this is a

[redacted]

foregone conclusion. That does not absolve OB providers of the duty to provide psychiatric and substance-abuse related care during and following pregnancy, but I would also be careful throughout the paper to avoid using language that suggests that better care throughout pregnancy will necessarily improve these distal outcomes. After all, only 5/35 deaths (15%) were deemed 'preventable'.

Specific comments are as follows:
Abstract:

Reviewer's comment:

1. I occasionally had trouble keeping track of the denominator; maybe keep some of these statistics (such as the number of women with a prior suicide attempt) for the results section.

Author's response: We appreciate that keeping track of the denominator is tricky. Per the reviewer's suggestion, we have deleted the number of women with a prior suicide attempt and prior overdose event from the abstract
Line number: 65-73
Revised text:
Results: From 2005 - 2014, 136 pregnancy-associated deaths were identified. Drug-induced death was the leading cause of pregnancy-associated death (n=35, 26%) and 89% occurred in the postpartum period. More specifically, those with a drug-induced death were more likely to die in the *late* postpartum period (n=28/35, 80%) compared to women whose deaths were from other pregnancy-associated causes (n=34/101, 34%) ($p<0.001$). The majority of drug-induced deaths were attributed to opioids (n=26/35, 74%), prescription opioids (n=21/35, 60%) and polysubstance use (n=29/35, 83%). From 2005 to 2014, the pregnancy-associated mortality ratio increased 76%, from 23.3 in 2005 to 41.0 in 2014. During this same time period, the drug-induced pregnancy-associated mortality ratio increased 200%, from 3.9 in 2005 to 11.7 in 2014.

Reviewer's comment:

2. It took me until reading the methods section in the paper to realize the difference between a 'pregnancy-associated' death and a 'pregnancy-related' death - this information was very helpful in determining what this paper was actually about. It would be helpful if you could include this definition here.

Authors' response: We have included the definition of pregnancy-associated death in the abstract. Since we are focusing on pregnancy associated death in this manuscript and not pregnancy-related death, we feel that including this definition in the abstract may be more confusing to readers. If the Editors feel strongly, we will include definition of pregnancy-related into the abstract.

Reviewer's comment

3. Instead of using the term 'drug-induced' (and focusing on all drug-induced deaths), would this paper be easier to read if it just focused on opioid-related deaths? Just a thought.

Authors' response

We appreciate the reviewer's comment, however, we think it is important to focus on all drug-induced deaths, not just those that are opioid related.

[redacted]

Reviewer's comment

4. What are these other drugs women are dying from? And, here you seem to be including women who commit suicide with drugs in the 'drug-induced death' category - I am not sure this makes sense. It seems you want to focus on accidental overdoses, even if this reduces your total number of deaths.

Authors' response:

Following the methodology set forth by Metz et al. (2016), we have included all drug-induced deaths that were both accidental and intentional. Our focus is to understand globally how drug use contributes to pregnancy-associated death.

Metz TD, Rovner P, Hoffman MC, Allshouse AA, Beckwith KM, Binswanger IA. Maternal Deaths From Suicide and Overdose in Colorado, 2004-2012. *Obstet Gynecol.* 2016;128(6):1233-1240.

Reviewer's comment:

5. I would use the term 'intimate partner violence' rather than 'domestic abuse'.

Authors' response: We have edited the introduction to reflect this comment.

Line number: 112-115

Revised text: To better understand the circumstances surrounding drug-induced deaths, we aimed to identify the class(es) of drug(s) involved in the death, presence of polysubstance use and mental health conditions, intimate partner violence or history of abuse and involvement with drug treatment, mental health and social services.

Reviewer's comment:

6. Line 163, you are missing an 'as' between 'defined…death'.

Authors' response: We thank the reviewer for pointing out this grammatical error.

Line number: 176-178

Revised text:

Based on the Centers for Disease Control guidelines, drug-induced deaths were defined as deaths from poisoning and medical conditions caused by use of legal or illegal drugs, as well as deaths from poisoning due to medically prescribed drugs and other drugs.

Reviewer's comment:

7. line 165, I believe you mean 'drugs'.

Authors' response: We thank the reviewer for pointing out this grammatical error.

Line number: 172-175

Revised text:

Based on the Centers for Disease Control and Prevention guidelines, drug-induced deaths were defined as deaths from poisoning and medical conditions caused by use of legal or illegal drugs, as well as deaths from poisoning due to medically prescribed drugs and other drugs.[22]

Reviewer's comment:

8. Do you know how many pregnancy-related deaths there were in this time period?

Authors' response: From 2005-2014, there were 69 pregnancy-related deaths, representing 51% of all pregnancy-associated deaths in this time period. We have edited the results section to include this information.

[redacted]

Line number: 225-227
Revised text: During the ten-year span of this study (January 2005 - December 2014), a total of 136 pregnancy-associated deaths, of which 69 were pregnancy-related deaths, were identified in Utah.

Reviewer's comment:
9. Why are thromboembolic deaths not considered 'pregnancy-related'? This does not make sense to me.
Author's response: Thromboembolic deaths are considered pregnancy-related. Pregnancy-associated deaths are those that are considered pregnancy-related as well as those that are pregnancy-associated.
Line number: 131-133
Revised text:
A pregnancy-associated death includes all deaths during pregnancy and within one year of the termination of pregnancy, including those that are pregnancy-related.

Reviewer's comment:
10. Line 224, can you reword the 'not drug-induced'? It sounds awkward.
Authors' response: We have edited the manuscript to reflect the reviewer's comments.
Line number: 237-247
Revised text:
There were no significant differences in age, race/ethnicity, education level, parity, geographical location or number of prenatal visits between women with drug-induced and other pregnancy-associated deaths (Table 1). The distribution of the location of death was significantly different between drug-induced and other pregnancy-associated deaths ($p<0.001$); the majority of women with drug-induced deaths died at home (n=20/35, 57%) while women with other pregnancy-associated deaths died most frequently in the hospital (n=64/101, 63%). Women whose deaths were drug-induced were more likely to have died after delivery (n=31/35, 89%) compared to those whose deaths were from other pregnancy-associated causes (n=62/101, 61%) ($p=0.01$). More specifically, those with a drug-induced death were more likely to die in the *late* postpartum period (n=28/35, 80%) compared to women whose deaths were from other pregnancy-associated causes (n=34/101, 34%) ($p<0.001$) (Figure 2).

Reviewer's comment:
11. Lines 225-6, is 57% significantly different than 63%?
Authors' response: We believe that there is both a statistically significant and clinically difference between women with drug-induced death who died primarily at home (57%), whereas women with other pregnancy-associated causes died primarily in the hospital (63%). This also has important implications for how deaths are tracked. For example, in Gemmil et al, pregnancy-associated mortality ratio was increased however, most of the deaths occurred in the hospital setting. Our results suggest that perinatal epidemiologists need to systematically assess out-of-hospital deaths to adequately capture pregnancy-associated mortality that is drug-induced.

[redacted]

Reviewer's comment:

12. I know the data are sparse, but was there a trend over time towards increasing risk of deaths from opioids/accidental overdoses? Were more women diagnosed/treated appropriately as time went on?

Author's response: In order to address this question, we calculated the pregnancy associated mortality ratio and the drug-induced pregnancy associated mortality ratio. We calculated the percent change between 2005 to 2014.

Line number: 70 -72, 141-145, 255-258, 335-341

Revised text:

Lines 71-73: From 2005 to 2014, the pregnancy-associated mortality ratio increased 76% from 23.3 in 2005 to 41.0 in 2014. During this same time period, the drug-induced pregnancy-associated mortality ratio increased 200% from 3.9 in 2005 to 11.7 in 2014.

Lines 133-135: A pregnancy-associated death includes all deaths during pregnancy and within one year of the termination of pregnancy, including those that are pregnancy-related. Pregnancy-associated mortality ratio is the number of pregnancy-associated death per 100,000 live births. For this study, we calculated the drug-induced pregnancy-associated mortality ratio.

Lines 234-236: From 2005 to 2014, the pregnancy-associated mortality ratio increased 76% from 23.3 in 2005 to 41.0 in 2014. During this same time period, the drug-induced pregnancy-associated mortality ratio increased 200% from 3.9 in 2005 to 11.7 in 2014.

Lines 297-302: In 2010, the peak of drug-induced pregnancy-associated deaths in Utah corresponded to an increase in heroin-related deaths nationwide,[6] however, this does not fully explain the peak between years of drug-induced pregnancy-associated deaths. During this study period, the pregnancy-associated mortality increased by 76% but the drug-induced pregnancy-associated mortality ratio increased 200%. While there is variation between years in proportion of deaths that are attributable to drug-induced causes, the overall trend suggests that drug-induced pregnancy-associated deaths are on the rise.

Reviewer's comments:

13. Of the 5 women whose deaths were deemed preventable, what was the possible step OB providers could have taken to prevent the death?

Author's response:

Of the five women whose deaths were deemed preventable, the steps obstetricians may have taken include systematic screening for drug use, mental health conditions and referral to treatment as described in the discussion section. We are unable to fully describe the recommendations given the small number of women and the specifics of the case preclude fully reporting the Committee's recommendations.

Reviewer's comments:

14. Is there any sense of whether these women were using drugs antenatally? Would screening/treatment have identified these women?

Author's response: Many women in this cohort were using drugs antenatally based on the drug related concerns reported in Table 2. Systematic screen may have identified these women earlier.

[redacted]

Discussion:

15. I appreciated the data from other contexts/states.

16. This discussion is quite long - I think stick with the major points (better care is needed in pregnancy and beyond pregnancy), and take out/shorten some material that is not as important to the main points of the paper and/or is repetitive (ie, upcoming changes in how deaths are categorized, merge paragraph 3 and the final paragraph, etc).

Author's response: We have substantially shortened the discussion section. We do feel that it is important to discuss upcoming changes to how deaths are categorized to contextualize how drug-induced deaths and preventability are being approached nationally.
Line number: 293-376

Reviewer #3: This is retrospective cohort study that addresses one of the preventable causes of maternal mortality which is drug abuse.

Although the topic is important, however, some important rates are missed to understand the impact of drug abuse.
One needs to know the mortality rate in general then to determine the death rate due to drug abuse.
Because study period is long relatively, death rates are better to understand the rise of misuse of drugs and death.
More rates should be included.

Author's response: We appreciate the reviewer's commentary about including rates. Because maternal mortality is expressed in ratios, we have calculated and include the pregnancy-associated death ratio and the drug-induced pregnancy-associated ratios to address this reviewer's concerns.
Line number: 71-73, 133-135, 234-236, 297-302
Revised text:

Lines 71-73: From 2005 to 2014, the pregnancy-associated mortality ratio increased 76% from 23.3 in 2005 to 41.0 in 2014. During this same time period, the drug-induced pregnancy-associated mortality ratio increased 200% from 3.9 in 2005 to 11.7 in 2014.

Lines 133-135: A pregnancy-associated death includes all deaths during pregnancy and within one year of the termination of pregnancy, including those that are pregnancy-related. Pregnancy-associated mortality ratio is the number of pregnancy-associated death per 100,000 live births. For this study, we calculated the drug-induced pregnancy-associated mortality ratio.

Lines 234-236: From 2005 to 2014, the pregnancy-associated mortality ratio increased 76% from 23.3 in 2005 to 41.0 in 2014. During this same time period, the drug-induced pregnancy-associated mortality ratio increased 200% from 3.9 in 2005 to 11.7 in 2014.

[redacted]

Lines 297-302: In 2010, the peak of drug-induced pregnancy-associated deaths in Utah corresponded to an increase in heroin-related deaths nationwide,[6] however, this does not fully explain the peak between years of drug-induced pregnancy-associated deaths. During this study period, the pregnancy-associated mortality increased by 76% but the drug-induced pregnancy-associated mortality ratio increased 200%. While there is variation between years in proportion of deaths that are attributable to drug-induced causes, the overall trend suggests that drug-induced pregnancy-associated deaths are on the rise.

STATISTICAL EDITOR'S COMMENTS:

Statistical reviewer's comment:
1. Table 2: Should include units for age.

Author's response: We thank the editor for noting this oversight. We have edited Table 2 accordingly.

Statistical reviewer's comment:
2. Fig 1: The counts within each year are limited, so there is little to be inferred from the variation other than stochastic, random change.

Author's response: We feel it is important to see change over time. Figure 1 emphasizes the point that drug-induced deaths should be viewed over a period of time and not based on a single point in time.

Statistical reviewer's comment:
3. Fig 2: Based on the sample sizes, should round the %s to nearest whole number, not .1%. Could also include absolute counts of deaths. May be confusing to reader, since each group (drug related vs non-drug related) is scaled to 100%, yet the non-drug cohort is roughly 3x the size of the drug related, which is not conveyed by the present Fig 2. Might be more useful to show the counts and %s within each time epoch that were drug vs non-drug related.
Edited figure 3 attached.

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, as well as subsequent author queries. 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:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

We opt-in to publish response letter.

[redacted]

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. 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.

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

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a

[redacted]

manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. 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.

[redacted]

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

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

"Figure 2: Please add a y-axis with tick marks and a label.
Figure 3: Please add a y-axis with tick marks and a label."

We have labels to y axis for both Figures 2 and 3.

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.

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 http://edmgr.ovid.com/acd/accounts/ifauth.htm.

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[redacted]

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 via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

Daniel Mosier

From: Marcela Smid [redacted]
Sent: Tuesday, March 12, 2019 5:53 PM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-2312R1
Attachments: STROBE_checklist_cohort_MCS.docx; 18-2312R1 ms (3-11-19v2)_MCS.docx

HI Daniel,

Thank you for your email and the opportunity to modify our manuscript. I've addressed the edits and have attached the edited manuscript.
Please let me know if you need anything else.

Marcela

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
   Agree with all changes.
2. LINE 16: Please provide a completed STROBE checklist. The checklist is available at http://ong.editorialmanager.com.
   Please see attached.
3. LINE 18: Dr. Gordon will need to complete our electronic Copyright Transfer Agreement, which was sent to them through Editorial Manager.
   Dr. Gordon has completed the Copyright Transfer Agreement. I've forwarded the email to you.
4. LINE 75: Define please here and at other places in the manuscript where you talk about it
   Late postpartum period is defined as death occurring within 43 days to one year of the end of the pregnancy.
   The abstract has been modified to reflect this. Lines 182-184 in the methods section defines late postpartum period.
5. LINE 77: Line 261 says 27/35, 77%. Which is correct?
   27/35 is correct and the abstract has been corrected.
6. TABLE 3: What is a "Z" drug?
   Z drugs are non-benzodiazepine drugs including zolpidem, zaleplon, eszoplicone and zopiclone. This has been added to Table 3 for clarification.
7. FIGURE 1: As suggested by the Statistical Editor in the revision letter, please remove Figure 1 from the manuscript.
   Figure 1 has been removed and other figures have been renumbered.

From: Daniel Mosier <dmosier@greenjournal.org>
Date: Monday, March 11, 2019 at 1:23 PM
To: Marcela Smid [redacted]
Subject: Manuscript Revisions: ONG-18-2312R1

Dear Dr. Smid,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 16: Please provide a completed STROBE checklist. The checklist is available at http://ong.editorialmanager.com.
3. LINE 18: Dr. Gordon will need to complete our electronic Copyright Transfer Agreement, which was sent to them through Editorial Manager.
4. LINE 75: Define please here and at other places in the manuscript where you talk about it
5. LINE 77: Line 261 says 27/35, 77%. Which is correct?
6. TABLE 3: What is a "Z" drug?
7. FIGURE 1: As suggested by the Statistical Editor in the revision letter, please remove Figure 1 from the manuscript.

When revising, use the attached version of the manuscript. Leave the track changes on, and do not use the "Accept all Changes"

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Wednesday, March 13th**.
Sincerely,
-Daniel Mosier

Daniel Mosier
Editorial Assistant
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Web: http://www.greenjournal.org

Eileen Chang (Temp)

From: Marcela Smid [redacted]
Sent: Monday, March 25, 2019 2:23 PM
To: Eileen Chang (Temp)
Subject: Re: O&G Figure Revision: 18-2312

Hi Eileen,

This looks great!
Thanks!

Marcela

From: "Eileen Chang (Temp)" <echang@greenjournal.org>
Date: Monday, March 25, 2019 at 11:32 AM
To: Marcela Smid [redacted]
Subject: RE: O&G Figure Revision: 18-2312

Hi Marcela,

I have attached all of the figures and legend for your final review and approval. Please let me know if you have any additional concerns.

Best,
Eileen

From: Marcela Smid [redacted]
Sent: Tuesday, March 19, 2019 10:58 AM
To: Eileen Chang (Temp) <echang@greenjournal.org>
Subject: Re: O&G Figure Revision: 18-2312

Hi Eileen,

Here is the edited figure 3 (now figure 2). I've attached the jpg, pdf and the original excel file for convenience.

Please let me know if you need anything else. Thank you!

Marcela

From: "Eileen Chang (Temp)" <echang@greenjournal.org>
Date: Monday, March 18, 2019 at 10:38 AM
To: Marcela Smid [redacted]
Subject: RE: O&G Figure Revision: 18-2312

If you won't be able to send the original file, then it would be great if you could send me the file with the bars re-ordered.

Thank you!

Eileen

From: Eileen Chang (Temp)
Sent: Monday, March 18, 2019 11:25 AM
To: 'Marcela Smid' [redacted]
Subject: RE: O&G Figure Revision: 18-2312

Hi Marcela,

Thank you for your response. In order to reorder the figure 3 graph, I would need the original file so that I can move the bars around. If you could send me the original file I can do all of the edits.

Best,
Eileen

From: Marcela Smid [redacted]
Sent: Wednesday, March 13, 2019 3:37 PM
To: Eileen Chang (Temp) <echang@greenjournal.org>
Subject: Re: O&G Figure Revision: 18-2312

HI Eileen,

Legend: I have edited the legend to mirror Table 3 (sedative/hypnotics include Z-drugs)
Figure 1: The editors have asked us to remove Figure 1.
Figure 2: looks great
Figure 3:

- Other should say 34%
- Benzodiazepine should say 34%
- Would it be possible to reorder the graph in the following order (top to bottom)?
    - Opioids 77%
    - Benzodiazepines 34%
    - Anti-depressants 31%
    - Amphetamines 25%
    - Muscle relaxants 20%
    - Acetaminophen 14%
    - Alcohol 14%
    - Sedative/hypnotics 11%
    - Cocaine 9%
    - Cannabinoid 3%
    - Other 35%

I am also happy to have my team reorder if you would prefer – I realize that this is a tall order.

Thank you.

Marcela

From: "Eileen Chang (Temp)" <echang@greenjournal.org>
Date: Wednesday, March 13, 2019 at 12:56 PM

To: Marcela Smid [redacted]
Subject: O&G Figure Revision: 18-2312

Good afternoon,

Your figures and legend have been edited and they have been attached for your review. Please review the attachments CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would appreciate a reply no later than Friday, 3/15. Thank you for your help.

Best,
Eileen