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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)*
- Email correspondence between the editorial office and the authors*

*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.
Dear Dr. Prabhu:

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 Nov 12, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors reviewed opioid consumption following cesarean delivery in 949 women delivered at a single institution over a 1-year period. Their objective was to identify risk factors associated with opioid consumption above the cut-off of 45 MME per day, which occurred in roughly half of the cohort. No risk factors were identified among women with scheduled cesarean deliveries. Among those with unscheduled cesarean deliveries, women with mood disorders or reported history of marijuana use were more likely to have higher post-operative opioid consumption. The manuscript is very well written.

Comments and questions follow.

1. General comments.
   a. In 3 places in the manuscript, lines 52-54, 78-80, 121-122, the authors write that ACOG recommends that excess daily opioid use be defined as mean consumption of > 45 MME per day. In 3 other places in the manuscript (6 in total), they write about the ACOG recommendation without quoting the dosage. I am concerned about the way this content is presented. There is just 1 sentence in the 2017 reference that is relevant to the topic: "Oxycodone doses greater than 30 mg/d are not recommended in breastfeeding women (89)." This sentence is not listed as a recommendation in the practice bulletin, and the cited reference (Toxnet/Lactmed) addresses use in the immediate postpartum period in the following way: "In a study of 50 mothers taking oxycodone post-cesarean section, 50 neonates were evaluated for sedation over 48 hours after birth. None was severely sedated and less than 4% had sedation of 3 on a 1 (fully alert) to 5 (difficult to rouse) scale and none more sedated than 3 on the scale. Because these infants were in the first 3 days postpartum, their oxycodone dose was probably limited by the small volumes of colostrum they were ingesting.[6]"

I don't think this should be considered an ACOG recommendation. Further, the authors appear to have overlooked the fact that in the immediate post-operative period (their topic of study), the small volume of colostrum possible for neonates to ingest effectively prevents them from receiving excessive opioids, regardless of whether the mother receives > 45 MME. I am not suggesting that it is a good idea to prescribe high doses of opioids, but the data simply does not support the rationale for neonatal harm, and ACOG doesn’t say as much. It is reasonable for the authors to study whatever post-op MME using whatever cut-offs they select. I suggest that they relegate the explanation of their choice to a paragraph in the discussion in which they convey that it is loosely based on Lactmed recommendations for breastfeeding infants that are not expected to apply to the immediate postpartum period.

b. Considering the above, would report neonatal outcomes relevant to excessive maternal opioid exposure, e.g. breastfeeding information, neonatal hospitalization duration, NICU admission after first 24 hours, or weight change prior to discharge. A study finding that half of all women receive excess opioids warrants something about outcome effects on neonates.
c. Suggest including information about order sets or protocols or individual prescribing patterns that allowed half of the patients studied to receive an opioid dosage defined as excessive.

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3. Introduction. This section is clear and concise. As above, suggest revising wording to convey that, e.g. you sought to study characteristics that were associated with request for higher dosages of opioids.

   a. Use of the > 45 MME cut-off is stipulated in line 121, but another definition of excess daily opioid consumption is presented in lines 146-147, the 75th percentile. The reader isn't told what percentile 45 MME represents, or what MME the 75th percentile represents. These may be useful thresholds, but please also include the entire distributions, either as MME or percentiles (or both). Sometimes the 90th (or 95th) percentile is a better guideline than the 75th. When a large proportion of study participants falls outside of a recommended guideline, the onus falls to authors to show that evidence of harm (or exclude it).
   b. The authors studied opioid consumption up to 96 hours post-op. Did all women remain hospitalized for 96 hours? Please clarify how opioid consumption was quantified or estimated in discharged patients. Suggest limiting the study to only those women who remained hospitalized for each entire 24-hr interval, or if that was done, clarify in the methods.

5. Results.
   a. In table 1 (or in a figure), suggest additional thresholds or additional information about MME consumption in each 24 hr interval. The standard deviations seem quite large. Were the data normally distributed? What was the range? Please provide more data. It won't detract from your message - it can only offer a more complete picture.
   b. Minor. Table 2 is quite long. Suggest making it into a couple of tables. For example, post-partum variables might be considered separately.

6. Discussion. The authors studied practice at their hospital in 2015, but the ACOG cited reference is from 2017. Might include this somewhere in the discussion (the authors were not expected to practice within a standard not yet published). Has the practice changed?

Reviewer #2: Thank you for your work in this important area. We need to have a better understanding of opioid use in obstetrics patients. Your presentation of your research seems methodologically and statistically sound. I note that you looked at a time before the increased focus on opioid prescribing, which really began in early 2017. This is probably a wise choice.

I have a few concerns I hope you might consider addressing:

1. Breastfeeding is a large part of the reason behind the concern about how much opioids are given. While you address why you don't include it in your study in the discussion (Lines 280-6), I think this is a mistake. I don't think it needs to be considered an outcome variable, but breastfeeding status might have influenced your patients in requesting, and your nurses in administering pain medications. Without trying to quantify it, I think you should include it as a potential influencer of opioid use.

2. "Mood disorder" needs to be better defined and you should provide information on how this information was collected.
   a. We can assume this refers to anxiety and depression. Was this taken from the pre-delivery problem list? Is "treated" and "untreated" based on the presence of an antidepressant (SSRI) on the med list? Please clarify.
   b. Do you screen for depression in your inpatients? Some hospitals administer the Edinburgh Postpartum Depression Scale prior to discharge. If so, this might have been tested against the opioid use rate.

3. Ketorolac is often administered prophylactically at the time of cesarean section to decrease need for opioids. Is this routinely given at your hospital? Could it also have affected opioid use?

4. You correlate outcomes with pre-pregnancy marijuana use. Can you describe how this information is obtained? Also, a description of the method of collection of data on non-opioid drug use in pregnancy is not provided. How reliable do you consider these data?

5. In the STROBE checklist, you mark missing data management as nonapplicable, but I would disagree. While electronic medical records do allow for more complete data collection, this is a problem that occurs in any study in which you have 1000 patients. I suggest you include a statement in your Methods section.

6. In most electronic medical records, capture of discharge medications should be possible. You might consider correlating your inpatient usage of opioids with discharge prescriptions.
7. Housekeeping: the date of presentation at the SMFM meeting should be included on your title page.

Reviewer #3: This is a retrospective cohort study comparing narcotic analgesia use and predictors between parturients who underwent scheduled and unscheduled cesarean birth in 2015 at MGH. The stated objective was to identify the prevalence of excess opioid consumption, as defined by an ACOG threshold recommendation for breastfeeding mothers in Practice Bulletin 177. Given the current focus on medical narcotic use, this is a relevant investigation to inform future strategies for optimizing post-cesarean pain management. The study provides a thorough evaluation of obstetrical and sociodemographic factors that may influence narcotic use post-cesarean and showed that there is little difference in the primary outcome comparison of scheduled vs unscheduled cesarean.

The use of the term "excess opioid consumption" raises concerns about the key measure of the research, in part because of the arbitrary nature of the threshold of 45 oral MME and the invocation of an ACOG endorsement of this measure that is based on limited breastfeeding data. The relevance of this implied standard is further undermined by the fact that breastmilk transmission of narcotics during inpatient day 1-4 is reduced due to predominance of low volume colostrum production. The conclusion statement that "Future studies should focus on appropriate definitions of excess opioid consumption that incorporate maternal risks to identify appropriate cutoffs..." implies recognition of the limitations of using the LACTMED:OXYCODONE recommendation referenced in the ACOG Practice Bulletin as a relevant threshold measure.

Consider refocusing the conclusions of the research on the absence of significant findings in this population and what that means for the next step in developing opioid-reducing pain management interventions.

Reviewer #4: The authors have analyzed opioid use patterns among gravidas undergoing c-sections.

They used a cohort of just under 1,000 patients, and converted their opioid use to MME, as would be appropriate. The Results are somewhat stunning; nearly 50% of this patient sub-population had excessive opioid use.

Results were stratified by scheduled vs unscheduled sections, finding that it was not possible to predict excess use in the scheduled group.

However, in the unscheduled group "mood disorder" (treated and untreated) was a significant predictor of excess opioid use.

The paper is designed, executed, and well-written. A few minor comments:

1. line 77: some would classify acetaminophen as an NSAID.

2. lines 97-98: the sentence would be stronger if the authors filled in the blank: "We hypothesized that ......after unscheduled deliveries because _________." What led to this idea?

3. line 109: "medical co-morbidities" -- the items in the parentheses are more psychiatric than medical. Would the authors like to be more precise?

4. lines 132-134: this sentence is hinting at an important point. The data analyzed were count data. The correct choice for regression analysis of count data is Poisson. This should be clarified. Whomever made the correct choice could help with this sentence.

5. line 153: if no a priori power analysis was done, did the authors do one after the fact? This may be useful to explore perhaps why differences in the scheduled section group were not different. Was there really no effect, or did you simply not have sufficient power to analyze those differences?

6. line 232: The reviewer realizes you are just mimicking bad behavior from some other quant's person, BUT centile refers to percentile.

7. line 270: Were the marijuana-using by self report patients reported to Mass DCF?

8. line 276: substance abusers manipulate and lie to get what they want. Just a curious question, was it possible to test the heterogeneity between the unscheduled vs. scheduled group? Mood disorder plus MJ use subgroup? The authors comment suggest that comparison between these sub-groups may show a difference in heterogeneity between unscheduled+mood dis+MJ subgroup v. scheduled no Hx of substance use.
9. Question: do the authors believe that treatment of the mood disorder antepartum could help? Realizing that in the analysis there was no difference between those with treated v. untreated by aRR, what is a more effective way to intervene?

Summary: This manuscript is on point for a very important problem in clinical medicine, the opioid conundrum. There are no easy answers, but first trying to understanding the problem is where we are today. This manuscript is a good contribution to finding the way forward.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 59-68: Should include the counts of scheduled vs unscheduled CD within results.

lines 137-145: Were all of the cited covariates included in the final models? Should include notation here or in footnote to Table 3 which covariates were included in the final model.

Table 3: Should include a column of unadjusted RRs to contrast with the aRRs. Could consolidate the estimates of aRR with its CI and omit the column of p-values. Those that are significant could be demarcated with bold or footnotes, the NS findings are identifiable by their CIs.

Since (Table 2) only a minority of women had treated or untreated mood disorders and even smaller minorities identified as having used marijuana, the aRRs (Table 3) would only be useful to perhaps identify some of the women who would use an excess MME after day 1. So, how is this useful for the clinician? The moderate associations were only relevant for the unscheduled cohort and only significantly associated for a minority of the ~ 1/2 of women who were excess MME users. For the scheduled CD, none of the identified variables were significantly associated with excess MME use.

EDITOR COMMENTS:

1. Thank you for your continued work on maximizing pain control for peripartum women, while minimizing their opioid use--likely leading to fewer women who are dependent on these drugs long term. As the reviewers and I have pointed out, there are possibly different conclusions one could draw from this research than you have done. As noted, the 45 MME limit that ACOG endorses is for breastfeeding women, but not specifically for women who have not yet produced mature milk--ie, they are producing colostrum and the baby is consuming quite small volumes of it. As such, during this time as you so rightly point out that women have their peak pain levels, the 45 MME recommendation is likely not relevant. As well, this is supported by the fact that almost 1/2 of your women exceeded this dose during the immediate post partum period. In addition the hazard ratios of the associations you did identify were all < 2.00 (Please note that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7)

An alternative conclusion is that women in the immediate post partum period after unscheduled CS should have pain relief addressed individually and that the 45 MME dose limit recommended by ACOG may not be relevant to this time period. The lack of strong associations with "excessive" dosing suggests the importance of this individualization. While one needs to be cautious about opioid doing during this time frame, women may need more narcotic in this early post partum period than they will later, and the impact on the infant will likely be quite small.

We realize that this is quite a different interpretation of your results. We would like to have you consider this as a possibility and reframe your paper to at least acknowledge that this is a possibility. If you are willing to do so, then we would welcome a revision. Otherwise, we don't feel that your paper is acceptable. It is of course up to you and your co-authors to consider the direction that you wish to take. The message that 1/2 of women are over-narcotized doesn't feel very useful, nor does it seem to adequately describe our personal experience with women in the immediate post-CS period. If you wish to withdraw your paper I would certainly understand, but I hope you won't. In my personal opinion (not as the editor), it seems that giving docs and patients "permission" to use a bit more narcotic early on seems very reasonable and evidence-based.

Please also note that the journal does not consider co-first authors, co-senior authors, or any form of "equal work" statements. This will not be permitted if you intend to submit a revision.
2. 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.

3. Author Agreement Forms:

   Malavika Prabhu, MD - Please provide an ink signature on your Author Agreement Form.

   Please submit Author Agreement Forms for Kaitlyn James, PhD MPH and Brian T Bateman, MD MSc.

   Please note:

   a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

   b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

   c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

   d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

      * Substantial contributions to the conception or design of the work;
      OR
      the acquisition, analysis, or interpretation of data for the work;
      AND
      * Drafting the work or revising it critically for important intellectual content;
      AND
      * Final approval of the version to be published;
      AND
      * Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

   The author agreement form is available online at http://edmogr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

   Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more
information in accordance with 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 signature on the journal's author agreement 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, 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' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College 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. 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 a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

14. 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, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

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 Nov 12, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
November 27, 18

Nancy Chescheir, MD
Editor, Obstetrics & Gynecology

Re: Manuscript ONG-18-1770

Dear Dr. Chescheir,

Thank you for your interest in our study. We have made revisions to our manuscript to address your comments as well as those of the reviewers, and we believe these serve to clarify our work. We appreciate the opportunity to reframe our analysis on high opioid consumption, and hope that you agree with this presentation of our work. A brief summary of the important changes is included here.

In considering the comments regarding the threshold of 45 MME in a 24 hour period, derived from concerns regarding neonatal opioid exposure via breastmilk, we agree that this definition does not reflect the true maternal risks, side effects, and concerns associated with postoperative opioid use, and is not applicable in the immediate post-delivery period, when colostrum is primarily secreted.

As such, we have decided to reframe our primary outcome regarding high opioid consumption to target consumption above the 75th percentile. We recognize this, too, has limitations, as this definition assumes an optimal or appropriate opioid consumption pattern immediately after cesarean delivery. From our work at our institution to minimize opioid consumption while improving postoperative pain, we know that the distribution of opioid consumption, both inpatient and outpatient, has significantly decreased since the data for this study was collected (prior to any interventions being implemented or awareness regarding opioid use being heightened).

We note that there are no measured characteristics associated with high opioid consumption, suggesting that continued efforts to optimize pain control are important, many women are at risk for high consumption without clear risk factors, and additional work is necessary to identify maternal and neonatal risks associated with high, or excess, opioid consumption.

Our responses to each comment is in the text of the manuscript and included below. We reference where the change was made in the track changes version of the manuscript.

We look forward to hearing back from you and would be happy to address any additional questions or concerns. We would also be happy to continue the dialog regarding our work.

Sincerely,

Malavika Prabhu and colleagues

REVIEWER COMMENTS:

Reviewer #1: The authors reviewed opioid consumption following cesarean delivery in 949 women delivered at a single institution over a 1-year period. Their objective was to identify risk factors associated with opioid consumption above the cut-off of 45 MME per day, which occurred in roughly half of the cohort. No risk factors were identified among women with scheduled cesarean deliveries. Among those with unscheduled cesarean deliveries, women with mood disorders or reported history of marijuana use were more likely to have higher post-operative opioid consumption. The manuscript is very well written.

Comments and questions follow.

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other places in the manuscript (6 in total), they write about the ACOG recommendation without quoting the dosage. I am concerned about the way this content is presented. There is just 1 sentence in the 2017 reference that is relevant to the topic: "Oxycodone doses greater than 30 mg/d are not recommended in breastfeeding women (89)." This sentence is not listed as a recommendation in the practice bulletin, and the cited reference (Toxnet/Lactmed) addresses use in the immediate postpartum period in the following way:

"In a study of 50 mothers taking oxycodone post-cesarean section, 50 neonates were evaluated for sedation over 48 hours after birth. None was severely sedated and less than 4% had sedation of 3 on a 1 (fully alert) to 5 (difficult to rouse) scale and none more sedated than 3 on the scale. Because these infants were in the first 3 days postpartum, their oxycodone dose was probably limited by the small volumes of colostrum they were ingesting.[6]"

I don’t think this should be considered an ACOG recommendation. Further, the authors appear to have overlooked the fact that in the immediate post-operative period (their topic of study), the small volume of colostrum possible for neonates to ingest effectively prevents them from receiving excessive opioids, regardless of whether the mother receives > 45 MME. I am not suggesting that it is a good idea to prescribe high doses of opioids, but the data simply does not support the rationale for neonatal harm, and ACOG doesn’t say as much. It is reasonable for the authors to study whatever post-op MME using whatever cut-offs they select. I suggest that they relegate the explanation of their choice to a paragraph in the discussion in which they convey that it is loosely based on Lactmed recommendations for breastfeeding infants that are not expected to apply to the immediate postpartum period.

Based on several comments, we have reframed this aspect of our analysis. We no longer use the definition of excess opioid consumption as being greater than 45 MME in a 24 hour period. We agree this is a poor definition of excess opioid consumption, beyond concerns for neonatal harm. Instead, we define high opioid consumption as greater than the 75th percentile, based on our distributions of mean consumption over the entire postoperative hospitalization.

b. Considering the above, would report neonatal outcomes relevant to excessive maternal opioid exposure, e.g. breastfeeding information, neonatal hospitalization duration, NICU admission after first 24 hours, or weight change prior to discharge. A study finding that half of all women receive excess opioids warrants something about outcome effects on neonates.

The focus of our study was not neonatal outcomes after possible exposure to opioids through colostrum/breast milk but rather describing maternal consumption of opioids for pain management, regardless of feeding choice. Therefore, no specific neonatal outcome data were collected. We have added this into the limitations of our manuscript in lines 638-640.

c. Suggest including information about order sets or protocols or individual prescribing patterns that allowed half of the patients studied to receive an opioid dosage defined as excessive.

At the time of this study, the order set for pain management after cesarean delivery included as needed acetaminophen, NSAIDs, and oxycodone (assuming no contraindications to any class of drug). All patients having a cesarean delivery at our institution are cared for by a single practice (comprised of attending physicians supervising residents), thus there is not practice variation in the ordering of postoperative pain medications. The administration of opioid and non-opioid analgesics is based on the clinical assessment of the patient by her primary nurse. We have included this information in lines 222-233.

2. Abstract. The abstract is well-written and faithfully summarizes the manuscript. Suggest revising the wording so that you are not suggesting that one can predict risk based on retrospective data - these are associations.

We have revised the abstract to discuss possible associations rather than predictors.

3. Introduction. This section is clear and concise.
As above, suggest revising wording to convey that, e.g. you sought to study characteristics that were associated with request for higher dosages of opioids.

**We have similarly revised the introduction to describe our intention to identify characteristics associated with high opioid consumption.**

4. **Methods.**
   a. Use of the > 45 MME cut-off is stipulated in line 121, but another definition of excess daily opioid consumption is presented in lines 146-147, the 75th percentile. The reader isn't told what percentile 45 MME represents, or what MME the 75th percentile represents. These may be useful thresholds, but please also include the entire distributions, either as MME or percentiles (or both). Sometimes the 90th (or 95th) percentile is a better guideline than the 75th. When a large proportion of study participants falls outside of a recommended guideline, the onus falls to authors to show that evidence of harm (or exclude it).

   **We have revised Table 1 to reflect our definition of high opioid consumption as greater than the 75th percentile of opioid consumption for the postoperative hospitalization, and have included both MME means and standard deviations and medians and interquartile ranges. We also include a figure (Figure 1) depicting the distribution of opioid consumption over the entire population.**

   b. The authors studied opioid consumption up to 96 hours post-op. Did all women remain hospitalized for 96 hours? Please clarify how opioid consumption was quantified or estimated in discharged patients. Suggest limiting the study to only those women who remained hospitalized for each entire 24-hr interval, or if that was done, clarify in the methods.

   All women included in this study were not hospitalized for 96 hours postoperatively. However, the mean number of postoperative days hospitalized for women undergoing unscheduled cesarean delivery was approximately 4 days, and those undergoing scheduled cesarean delivery, approximately 3.6 days. Opioid consumption after women were discharged, up to 96 hours postpartum, was not quantified and not included in this study. To account for discharge sooner than 96 hours postpartum, the total MME consumed were standardized to the total number of postoperative hours spent in the hospital (excluding the first 24 postoperative hours). This has been clarified in lines 236-252.

5. **Results.**
   a. In table 1 (or in a figure), suggest additional thresholds or additional information about MME consumption in each 24 hr interval. The standard deviations seem quite large. Were the data normally distributed? What was the range? Please provide more data. It won't detract from your message - it can only offer a more complete picture.

   **We are happy to provided more granular data regarding MME consumption by time period, and have included median and interquartile ranges in Table 1, as well as Figure 1 to denote overall opioid consumption in MME for the entire population. Given the central limit theorem and our sample size, we felt comfortable using means and standard deviations to summarize the data, and as the basis for the definition of our primary outcome. The standard deviations are correct – we have consistently seen large standard deviations in inpatient postoperative opioid consumption at our institution.**

   b. Minor. Table 2 is quite long. Suggest making it into a couple of tables. For example, post-partum variables might be considered separately.

   **We have separated the postpartum variables and created a separate table (Table 3) with this information.**

6. **Discussion.** The authors studied practice at their hospital in 2015, but the ACOG cited reference is from 2017. Might include this somewhere in the discussion (the authors were not expected to practice...
within a standard not yet published). Has the practice changed?

Our institutional approach to postoperative pain management and the importance of opioids to the management has greatly evolved over the last three years, with improvements in our order set, emphasis on scheduled non-opioid multimodal analgesics, early recovery and ambulation, and limited opioids provided on discharge with a targeted pre-discharge counseling session by discharging clinicians. Nursing education on the risks and side effects of opioid administration (primarily sedation, pruritus, constipation, etc, and not neonatal harms) has also occurred, influencing their approach to administration of all analgesics. The ACOG Practice Bulletin was not the impetus for this evolution, but rather a realization that opioid consumption and discharge prescribing was high.

Reviewer #2: Thank you for your work in this important area. We need to have a better understanding of opioid use in obstetrics patients. Your presentation of your research seems methodologically and statistically sound. I note that you looked at a time before the increased focus on opioid prescribing, which really began in early 2017. This is probably a wise choice.

I have a few concerns I hope you might consider addressing:

1. Breastfeeding is a large part of the reason behind the concern about how much opioids are given. While you address why you don't include it in your study in the discussion (Lines 280-6), I think this is a mistake. I don't think it needs to be considered an outcome variable, but breastfeeding status might have influenced your patients in requesting, and your nurses in administering pain medications. Without trying to quantify it, I think you should include it as a potential influencer of opioid use.

We agree that there may be differences in patient requests for opioid administration, or provision of opioids from the nursing staff, based on the mother's breastfeeding choice. We have included this as a potential unmeasured predictor in our study in lines 635-638 in the Discussion. We also believe that the concerns regarding opioid administration should stem more the perspective of the maternal recovery from surgery, rather than solely due to possible neonatal harms.

2. "Mood disorder" needs to be better defined and you should provide information on how this information was collected.
   a. We can assume this refers to anxiety and depression. Was this taken from the pre-delivery problem list? Is "treated" and "untreated" based on the presence of an antidepressant (?SSRI) on the med list? Please clarify.

We have clarified that mood disorder, which is defined as anxiety or depression, was abstracted based on the clinical chart at the time of admission to labor and delivery. Treated or untreated mood disorder was based on the documentation of the use of anxiolytics or antidepressants at the time of admission to labor and delivery. We have clarified this in lines 211-213.

b. Do you screen for depression in your inpatients? Some hospitals administer the Edinburgh Postpartum Depression Scale prior to discharge. If so, this might have been tested against the opioid use rate.

In our obstetric practice, all patients are screened for depression at 28 weeks gestation and at the 6 week postpartum visit. Women are not routinely administered a questionnaire during the inpatient admission to detect depression. We did not assess the chart for new diagnoses of depression at the 6 week postpartum visit.

3. Ketorolac is often administered prophylactically at the time of cesarean section to decrease need for opioids. Is this routinely given at your hospital? Could it also have affected opioid use?
At the time of this study, postpartum pain management consisted of one dose of ketorolac administered prophylactically at the end of the cesarean delivery for the vast majority of patients without contraindications to NSAIDs. Use of non-opioid analgesia, whether preemptive or therapeutic, is associated with decreased opioid consumption. In the immediate postoperative period, when neuraxial morphine contributes greatly to pain management and oral opioid consumption is low, it is not clear how much preemptive ketorolac may contribute to decrease oral opioid consumption. However, we did not specifically study this question as the consumption of NSAIDs (and acetaminophen) co-occurs with the consumption of opioids, and thus we felt it was invalid to include in our model. This is discussed in lines 496-503.

4. You correlate outcomes with pre-pregnancy marijuana use. Can you describe how this information is obtained? Also, a description of the method of collection of data on non-opioid drug use in pregnancy is not provided. How reliable do you consider these data?

We clarify that pre-pregnancy substance use, including marijuana use, was abstracted from the medical record based on self-reported use documented by the clinical provider. Urine toxicology studies for all prenatal patients is not our standard of care. As this data is self-reported, and most patients are made aware that use of substances (excluding tobacco) are reportable to the state Department of Children and Families (DCF), this data has significant limitations and may be underreported. As marijuana is no longer deemed a relevant predictors, we have removed the discussion regarding DCF from the Discussion section.

5. In the STROBE checklist, you mark missing data management as nonapplicable, but I would disagree. While electronic medical records do allow for more complete data collection, this is a problem that occurs in any study in which you have 1000 patients. I suggest you include a statement in your Methods section.

We were fortunate that the specific variables we abstracted for the study were not missing for any patient included in the cohort, as most of the data were derived from routine intrapartum charting, and the remaining variables were easily identified in the prenatal record and admission History and Physical. We note in the methods section that no variables were missing for any patient on line 278-279.

6. In most electronic medical records, capture of discharge medications should be possible. You might consider correlating your inpatient usage of opioids with discharge prescriptions.

Our EMR does allow us to track the number of opioids a patient was prescribed. At the time this study was done, the institution had a “routine” number of opioids on discharge, which was 40 tablets of oxycodone 5mg. There was little attempt made clinically to correlate inpatient consumption of opioids with outpatient prescribing. We do not dwell on outpatient prescribing in this manuscript as the inherent clinical practice of the time would not allow us to answer the question regarding such a correlation with our data. We address this point in lines 630-633.

7. Housekeeping: the date of presentation at the SMFM meeting should be included on your title page.

Thank you. We have corrected this.

Reviewer #3: This is a retrospective cohort study comparing narcotic analgesia use and predictors between parturients who underwent scheduled and unscheduled cesarean birth in 2015 at MGH. The stated objective was to identify the prevalence of excess opioid consumption, as defined by an ACOG threshold recommendation for breastfeeding mothers in Practice Bulletin 177. Given the current focus on medical narcotic use, this is a relevant investigation to inform future strategies for optimizing post-cesarean pain management. The study provides a thorough evaluation of obstetrical and sociodemographic factors that may influence narcotic use post-cesarean and showed that there is little difference in the primary outcome comparison of scheduled v unscheduled cesarean.
The use of the term "excess opioid consumption" raises concerns about the key measure of the research, in part because of the arbitrary nature of the threshold of 45 oral MME and the invocation of an ACOG endorsement of this measure that is based on limited breastfeeding data. The relevance of this implied standard is further undermined by the fact that breastmilk transmission of narcotics during inpatient day 1-4 is reduced due to predominance of low volume colostrum production. The conclusion statement that "Future studies should focus on appropriate definitions of excess opioid consumption that incorporate maternal risks to identify appropriate cutoffs..." implies recognition of the limitations of using the LACTMED:OXYCODONE recommendation referenced in the ACOG Practice Bulletin as a relevant threshold measure.

Consider refocusing the conclusions of the research on the absence of significant findings in this population and what that means for the next step in developing opioid-reducing pain management interventions.

We agree that a threshold of opioid consumption that stems from limited breastfeeding data is not an appropriate definition. We have updated our analysis to reframe high opioid consumption as greater than the 75th percentile. The results of our regression model, for both scheduled and unscheduled cesarean deliveries is now nonsignificant. We appreciate your perspective and have reframed our conclusions to also discuss next steps in opioid-sparing pain control that continues to optimize pain control.

Reviewer #4: The authors have analyzed opioid use patterns among gravidas undergoing c-sections.

They used a cohort of just under 1,000 patients, and converted their opioid use to MME, as would be appropriate. The Results are somewhat stunning; nearly 50% of this patient sub-population had excessive opioid use. Results were stratified by scheduled v. unscheduled sections, finding that it was not possible to predict excess use in the scheduled group. However, in the unscheduled group "mood disorder" (treated and untreated) was a significant predictor of excess opioid use.

The paper is designed, executed, and well-written. A few minor comments:

1. line 77: some would classify acetaminophen as an NSAID.

We agree that acetaminophen is variably classified as an NSAID. We wish to distinguish the use of acetaminophen from the NSAIDs typically used at our institution (ibuprofen, ketorolac), as the mechanisms of action are postulated to be different, and acetaminophen is separately listed in protocols regarding multimodal pain management. We have clarified that our intent when citing the class of drugs NSAIDs is to refer to ibuprofen/ketorolac in line 148-149.

2. lines 97-98: the sentence would be stronger if the authors filled in the blank: "We hypothesized that......after unscheduled deliveries because __________.” What led to this idea?

This hypothesis was based on our clinical experience caring for women with scheduled and unscheduled cesarean deliveries. We have clarified this in line 169-198.

3. line 109: "medical co-morbidities" -- the items in the parentheses are more psychiatric than medical. Would the authors like to be more precise?

Thank you for this comment. We now refer to the parenthetical phrase as “comorbidities” rather than medical comorbidities in line 203.

4. lines 132-134: this sentence is hinting at an important point. The data analyzed were count data. The correct choice for regression analysis of count data is Poisson. This should be clarified. Whomever made the correct choice could help with this sentence.
We agree that Poisson regression the correct choice, and clarify that this is due to count data in line 279-280.

5. line 153: if no a priori power analysis was done, did the authors do one after the fact? This may be useful to explore perhaps why differences in the scheduled section group were not different. Was there really no effect, or did you simply not have sufficient power to analyze those differences?

We did not perform a post-hoc power analysis and acknowledge our findings may be attributable to Type 2 error, particularly for characteristics for which we had limited numbers.

6. line 232: The reviewer realizes you are just mimicking bad behavior from some other quant's person, BUT centile refers to percentile.

We have edited the manuscript to refer to percentile in all relevant instances.

7. line 270: Were the marijuana-using by self report patients reported to Mass DCF?

Yes. All patients with self reported marijuana use are automatically reported to the Massachusetts DCF. The DCF then determines, based on several factors, the implications of this use on the disposition of the baby and the in home surveillance and resources. As marijuana is not a relevant predictor in the current analysis, we no longer discuss this point in the manuscript.

8. line 276: substance abusers manipulate and lie to get what they want. Just a curious question, was it possible to test the heterogeneity between the unscheduled v. scheduled group? Mood disorder plus MJ use subgroup? The authors comment suggest that comparison between these sub-groups may show a difference in heterogeneity between unscheduled+mood dis+MJ subgroup v. scheduled no Hx of substance use.

In the context of reframing our analysis, the association between marijuana and opioid consumption is no longer significant. Thus, we did not investigate subgroup differences further.

9. Question: do the authors believe that treatment of the mood disorder antepartum could help? Realizing that in the analysis there was no difference between those with treated v. untreated by aRR, what is a more effective way to intervene?

In the context of reframing our analysis, mood disorders were no longer associated with postoperative opioid consumption Nonetheless, there is ample literature suggesting significant benefit to pregnancy outcomes with appropriate treatment of mood disorder (whether by medications or other approaches), and this is an area for future investigation.

Summary: This manuscript is on point for a very important problem in clinical medicine, the opioid conundrum. There are no easy answers, but first trying to understanding the problem is where we are today. This manuscript is a good contribution to finding the way forward.

Thank you.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 59-68: Should include the counts of scheduled vs unscheduled CD within results.

We have updated the abstract results to include the number of women in each group in line 72.

lines 137-145: Were all of the cited covariates included in the final models? Should include notation here or in footnote to Table 3 which covariates were included in the final model.
All of the cited covariates in the paragraph are included in the final model. We have included a sentence specifying this in line 292.

Table 3: Should include a column of unadjusted RRs to contrast with the aRRs. Could consolidate the estimates of aRR with its CI and omit the column of p-values. Those that are significant could be demarcated with bold or footnotes, the NS findings are identifiable by their CIs.

We have edited Table 3 to include both adjusted and unadjusted relative risks, and have omitted the p-values.

Since (Table 2) only a minority of women had treated or untreated mood disorders and even smaller minorities identified as having used marijuana, the aRRs (Table 3) would only be useful to perhaps identify some of the women who would use an excess MME after day 1. So, how is this useful for the clinician? The moderate associations were only relevant for the unscheduled cohort and only significantly associated for a minority of the ~ 1/2 of women who were excess MME users. For the scheduled CD, none of the identified variables were significantly associated with excess MME use.

Thank you for this comment. This is an excellent point, and our re-analysis, in which no characteristics are associated with high opioid consumption, essentially speaks to this point – we did not identify clear patient or intrapartum/procedural characteristics that suggest an increased risk of high opioid consumption.

EDITOR COMMENTS:

1. Thank you for your continued work on maximizing pain control for peripartum women, while minimizing their opioid use—likely leading to fewer women who are dependent on these drugs long term. As the reviewers and I have pointed out, there are possibly different conclusions one could draw from this research than you have done. As noted, the 45 MME limit that ACOG endorses is for breastfeeding women, but not specifically for women who have not yet produced mature milk—ie, they are producing colostrum and the baby is consuming quite small volumes of it. As such, during this time as you so rightly point out that women have their peak pain levels, the 45 MME recommendation is likely not relevant. As well, this is supported by the fact that almost 1/2 of your women exceeded this dose during the immediate post partum period. In addition the hazard ratios of the associations you did identify were all < 2.00 (Please note that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7)

An alternative conclusion is that women in the immediate post partum period after unscheduled CS should have pain relief addressed individually and that the 45 MME dose limit recommended by ACOG may not be relevant to this time period. The lack of strong associations with "excessive" dosing suggests the importance of this individualization. While one needs to be cautious about opioid doing during this time frame, women may need more narcotic in this early post partum period than they will later, and the impact on the infant will likely be quite small.

We realize that this is quite a different interpretation of your results. We would like to have you consider this as a possibility and reframe your paper to at least acknowledge that this is a possibility. If you are willing to do so, then we would welcome a revision. Otherwise, we don't feel that your paper is acceptable. It is of course up to you and your co-authors to consider the direction that you wish to take. The message that 1/2 of women are over -narcotized doesn't feel very useful, nor does it seem to adequately describe our personal experience with women in the immediate post-CS period. If you wish to withdraw your paper I would certainly understand, but I hope you won't. IN my personal opinion (not as the editor), it seems that giving docs and patients "permission" to use a bit more narcotic early on seems very reasonable and evidence-based.
Thank you for the opportunity to reframe our work. We agree with your points and therefore chose to define high opioid consumption based on our institutional distribution of opioid consumption for the time period of the study, acknowledging that this has likely shifted over time as approaches to pain control and the role of opioids have evolved since this study was conducted. We very much agree with the goal of individualizing and optimizing women’s pain and recovery after cesarean delivery, rather than focusing on minimizing opioid consumption as the primary goal. We do believe that evidence-based approaches to pain management that include scheduled analgesics (if no contraindications exist) and non-analgesics approaches are appropriate, will address women’s pain after cesarean delivery, and reduce exposure to opioids, which may limit the experience of opioid-associated side effects such as constipation, pruritus, nausea, sedation, that negatively impact a women’s postoperative experience.

Please also note that the journal does not consider co-first authors, co-senior authors, or any form of "equal work" statements. This will not be permitted if you intend to submit a revision.

We have removed this designation. Dr. Blair Wylie is the senior author of this manuscript.

2. 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: please publish our response letter and subsequent email correspondence related to author queries.

3. Author Agreement Forms:

Malavika Prabhu, MD - Please provide an ink signature on your Author Agreement Form.

Please submit Author Agreement Forms for Kaitlyn James, PhD MPH and Brian T Bateman, MD MSc.

We have uploaded these author agreement forms with this revision.

Please note:

a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment to the author agreement form.

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

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The author agreement form is available online at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

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 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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, 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’ (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College 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. 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 a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

14. 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, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

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 Nov 12, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief
Hi Randi,

Here are the additional revisions. Thanks again for the flexibility.

Let me know if there are additional clarifications needed.

Malavika

---

On Nov 26, 2018, at 9:58 AM, Randi Zung <RZung@greenjournal.org> wrote:

Dear Dr. Prabhu:

Dr. Chescheir has reviewed your latest version. She is asking for a few additional edits. Her new comment is highlighted in blue in the attached file (v4):

Abstract-Results: What I’m hoping you’ll add is something like what I’ve suggested below so that the reader has some comparison data to show how different the high consumers’ doses were.

“In the total cohort of 949 women, the mean (Standard deviation, SD) and median (interquartile range, IQR) of daily opioid consumption was 48.6 (22.8) and 44.5 (36.6-66.6) MME, respectively. For those with high opioid consumption, these values were ........ Results for women with scheduled versus unscheduled cesarean deliveries were similar.”

Please make sure the following is present in the body text of your paper (but not the abstract due to word count restrictions):

--Quartile 1 (0-25th percentile): median 26.95, mean +- SD 21.2 +- 14.17
--Quartile 2 (>25th percentile to 50th percentile): median 40.62, mean +- SD 40.6 +- 2.21
--Quartile 3 (>50th percentile to 75th percentile): median 53.41, mean +- SD 54.1 +- 6.61
--Quartile 4 (>75th percentile): median 78.3, mean +- SD 78.8 +- 8.5

Please send your next version back to me when you are finished.

Thanks,
Randi

---

From: Malavika Prabhu
Sent: Monday, November 26, 2018 1:12 AM
To: Randi Zung <RZung@greenjournal.org>
Hi Randi,

Thank you for the opportunity to clarify further. Here are my answers to the queries. Please let me know the next steps.

And thank you again for the extension, I really do appreciate it.

Sincerely,
Malavika Prabhu

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.
   —I read through the edited manuscript - the edits are correct.

2. Line 60: When you write that a study occurred between date 1 and date 2, it literally excludes those boundary dates. For instance, “This study was performed between Feb 2018 and Jan 2019” would mean it was performed from March 2018 to Dec 2018. Do you instead mean that the study was performed from date 1 to date 2? If so, please edit.
   —You are correct, and I have made the edits in the manuscript and abstract to reflect the inclusion of the dates listed

3. Line 71: Could you provide the median for each quartile here?
   For the entire cohort, the median and mean MME consumed for each quartile is listed below. I am not sure if you want this information added to the abstract results, or if you want it stratified by scheduled vs unscheduled cesarean delivery, so I have not added it into the text yet. Please let me know what you prefer, and I will be happy to include this in the abstract text.
   --Quartile 1 (0-25th percentile): median 26.95, mean +- SD 21.2 +- 14.17
   --Quartile 2 (>25th percentile to 50th percentile): median 40.62, mean +- SD 40.6 +- 2.21
   --Quartile 3 (>50th percentile to 75th percentile): median 53.41, mean +- SD 54.1 +- 6.61
   --Quartile 4 (>75th percentile): median 78.3, mean +- SD 78.8 +- 8.5

4. Line 72: In the Results, you indicate that “high” is the 90th percentile at 86.3 MME. What is the difference here?
   —We defined the primary outcome of high opioid use as greater than
the 75th percentile of opioid consumption. As a sensitivity analysis, we redefined high opioid use as consumption more than the 90th percentile. Mean opioid consumption in the latter group was 86.3 MME. In the abstract results, we only refer to the median consumption for the primary outcome, and the data presented is accurate. Please let me know if further clarification is required.

5. Line 77: Isn’t this a tautology? You defined “high” as >75th percentile, so >¼ would be “high”.
—We agree and have edited to be more accurate.

6. Line 209: Please note the following regarding your tables:

1) There appears to be two table 1’s at the end of the manuscript.
—this occurred due to a track changes error. There is also a missing title for “Table 6” that I fixed as it was another track changes error - the tables from the initially submitted paper were to be deleted, but this did not occur. I have fixed all of the tables, as well as the numbering in the text.

2) The journal avoids using different headings mid-table, so one or two tables had to be divided into two.
—I am not sure which tables need to be split beyond how I have already split them. Given the confusion above, can you please let me know which tables you want to split? I can then write titles as need be.

3) Your supplemental files may be numbered in order with your other tables.
—As there are 4 main tables, I renumbered the supplemental tables as numbers 5 and 6.

We need your help renumbering your in-text citations and reordering your tables if needed. Please see the end of the manuscript for edits. The supplemental files still need to be incorporated into the numbering.
—this is done.

7. Page 22: Please provide a title for Table 6. Table 5 was separated into two, since we avoid using different column headings mid-table.
—see above

On Nov 15, 2018, at 2:16 PM, Randi Zung <rzung@greenjournal.org> wrote:

Dear Dr. Prabhu or Dr. Wiley:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. Please track your changes and leave the ones made by the Editorial Office. Please also note your responses to the author queries in your email message back to me.
1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. Line 60: When you write that a study occurred between date 1 and date 2, it literally excludes those boundary dates. For instance, “This study was performed between Feb 2018 and Jan 2019” would mean it was performed from March 2018 to Dec 2018. Do you instead mean that the study was performed from date 1 to date 2? If so, please edit.

3. Line 71: Could you provide the median for each quartile here?

4. Line 72: In the Results, you indicate that “high” is the 90th percentile at 86.3 MME. What is the difference here?

5. Line 77: Isn’t this a tautology? You defined “high” as >75th percentile, so ¾ would be “high”.

6. Line 209: Please note the following regarding your tables:

   1) There appears to be two table 1’s at the end of the manuscript.
   2) The journal avoids using different headings mid-table, so one or two tables had to be divided into two.
   3) Your supplemental files may be numbered in order with your other tables.

We need your help renumbering your in-text citations and reordering your tables if needed. Please see the end of the manuscript for edits. The supplemental files still need to be incorporated into the numbering.

7. Page 22: Please provide a title for Table 6. Table 5 was separated into two, since we avoid using different column headings mid-table.

To facilitate the review process, we would appreciate receiving a response by November 20, if possible. ACOG will be closed November 21-23.

Best,
Randi Zung

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Randi Zung (Ms.)
Editorial Administrator | Obstetrics & Gynecology
The American College of Obstetricians and Gynecologists
409 12th Street, SW
Washington, DC 20024-2188
Hello,

We have reviewed the figure and legend, and have no further edits.

Thank you,

Kaitlyn James and Malavika Prabhu

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