OBSTETRICS & GYNECOLOGY

NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Mar 28, 2019
To: "Jason D. Wright" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-401

RE: Manuscript Number ONG-19-401

Use and Misuse of Opioids after Gynecologic Surgical Procedures

Dear Dr. Wright:

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 Apr 18, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective chart review of patients who underwent a major or minor gynecologic surgery. The women in the study cohort were opioid naïve and were evaluated for receipt of an initial opioid prescription as well as persistent opioid use post-operatively.

The Opioid Epidemic is front and center in both the lay media and medical research. Surgery is a common introduction to opioids for the opioid naïve patients. A 2018 study by Overton et al showed that 1 in 16 opioid naïve patients become a long-term opioid user post-operatively [1]. This study is unique in that it brings the focus to both major and minor gynecologic surgeries. Prior publications have demonstrated the over-prescribing of opioids [2], but this study focused on the persistence of use beyond the acute postoperative period as well as the receipt of an initial opioid prescription.

1. The MarketScan database is able to capture the hospital services (inpatient and outpatient) as well as the pharmaceutical claims. Did the authors evaluate if other prescriptions were filled along with the perioperative opioids: gabapentin, celecoxib, ibuprofen, etc.?

2. The authors evaluate comorbidities using ICD9 and 10 codes as well as the Elixhauser Index. They further categorize patients who have underlying psychiatric diagnoses including anxiety and depression, etc. Were patients with known pain disorders classified differently? For example, can patients with
migraines, fibromyalgia, IBS, etc. be evaluated separately?

3. Along those lines, persistent opioid use can be seen in patients with a history of chronic pain who can have a comorbid past history of substance abuse (including opioids) but no current use. Were pain patients able to be identified and analyzed as a separate group?

4. Line 232. Higher doses with more OME prescribed as well as a prescription given prior to surgery were associated with persistent use
   a. Was there a certain opioid that was more associated with persistent use (ex. dilaudid vs oxycodone)?
   b. Did the addition of acetaminophen to the opioid (ex. Percocet vs oxycodone alone) influence the persistence of use past the acute post-operative period?

Reference:
1. Overton HN, Hanna MN, Bruhn WE. Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus. J Am Coll Surg.2018 Oct;227(4):411-418.
2. As-Sanie S, Till SR, Mowers EL, Lim CS, Skinner BD, Fritsch L, Tsodikov A, Dalton VK, Clauw DJ, Brummett CM. Opioid Prescribing Patterns, Patient Use, and Postoperative Pain after Hysterectomy for Benign Indications. Obstet Gynecol. 2017

Dec; 130(6):1261-1268.

Reviewer #2:

1. Line 113 should read "prescribing" not prescription.

2. The correlation between the number of pills prescribed and rates of persistent opioid use is impressive, and greatest when more than 20-30 pills are prescribed. This is a common number of pills for many practices to prescribe routinely. The authors may chose to highlight this finding given its significance to many practices. It also highlights the importance of appropriate opioid prescribing after surgery.

Reviewer #3: This is a cohort study examining the risk factors for persistent prescription of narcotic after gynecologic procedures. The overall rate of persistent opioid use was 6.8%. Authors identified risk factors including, younger age, Medicaid recipients, depression, anxiety and substance abuse disorder. D&C and endometrial ablation were also associated with the outcome.

Main issues:
1- The number of patients with substance use disorder included in the study was 3.3%. Are those still included in the outcome "New persistent opioid use"? Please explain!

2- The outcome is persistent use of opioid; while it can be a marker for abuse, it is not equivalent to abuse, please discuss how this outcome is related to abuse if possible include references from other studies!

Specific issues:
1- Introduction: well written

2- Methods:
a. The study is missing Medicare population which represents a good number of our gynecologic patients, please if possible highlight this in the title and discuss how this would affect the results validity!
b. Did the authors exclude women who are already on narcotics for chronic pain before the procedure?
c.

3- Results:
a. Line 226, please include the ORs for all the specified risk factors (procedures, age, region etc)
b. Line 231, please consider including this reduction in the rate in the start of the results and test for trend if possible!
c. Line 232, were those factors reported significant in the final multivariable regression model?

4- Discussion:
a. Can be shorter
b. Please add the absence of Medicare population as a limitation and discuss how this affects the results!
c. Please provide if possible, some guidance of what duration and the amount would be considered a "good" practice after different gynecologic procedures. This would help the readers to have some sort of standard to refer to!
d. What is the rationale for opioid prescription before the procedure? In table 2 this was happening in up to 37% of patients undergoing endometrial ablation and 32.9% before D&C? What is the explanation of that?

5- Tables, figures and references:
a. Figure 3 and figure 4 include data that is presented in the tables already pleas consider removing figure 3.

STATISTICAL EDITOR COMMENTS:

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

lines 184-185 and Table 1: These are all adjusted RRs, so should cite as aRRs, not as RRs, and provide footnote to Table indicating the adjustment covariates. Given the number of comparisons in this Table, the inference threshold of $p < .05$ likely includes many spurious associations, especially given the large samples. Should use the more restrictive threshold. The strong associations with the "unknown"category for metropolitan statistical area (especially) and for geographic region (less so) makes that part of the analysis limited and may be biased. Likewise, there are many examples in text of citing

RR, when aRR should be used.

Table 3: Same comment re: use of p < .05, citation of aRRs rather than RRs and "unknown" entries. Morphine equivalents should have units.

Fig 4: Should use stricter threshold than 95% CIs, due to large number of comparisons and large sample sizes. Need to be explicit re: the adjustment process. For example, since there was a strong inverse association with age, how much of the difference in new persistent opioid use for type of surgery was attributable directly to surgical type, rather than indirectly via age of that surgical cohort.

Since overall ~ 60% of women received a perioperative opioid Rx and ~ 7% of those subsequently had persistent opioid use, it would be useful to supplement the aRR analysis with proportions of women in various cohorts who went on to persistent use, rather than vs a referent group.

Please do a sensitivity analysis removing the women with history of substance abuse.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- The objective for the abstract should be a simple "to" statement without background.

- should state something like "this is a retrospective cohort study..."

- Some won't know market scan. Could you state something explaining its scope, etc?

- Did you include TAH or other open cases? Given that one of the benefits of MIGS procedures is less pain, surprise that the highest rate wasn't in open cases

- presumably this groups' substance use was non opioid based as by your exclusion criteria they shouldn't be in this group.

- please clarify: is this falling rate per initial opioid prescription or was this likely related to lower initial prescription rates?

- in what time frame?

- are you foretelling one of your outcomes or do you have a reference for young women being at higher risk?

- can you state these as primary and secondary outcomes? If the persistent use is the 2nd outcome, it shouldn't be what you highlight in your discussion or in a precis when you submit one.

- this is what might be helpful in the abstract

- does it include medicare? If not, this would limit your ability to draw conclusions about women of older age

- Important to note Tom's comments re: multiple comparisons

- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like: "xx (outcome in exposed) / yy (outcome in unexposed) (zz%) (Effect size= ; 95% CI=)." An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

- This still concerns me. HOw did you discriminate the patient with pre-existing SUD and the patient with a "new" opioid use disorder after the surgical procedure? Why did you not exclude these patients?

- Is this the overall rate? Might be best to move this to line 198 where you give the average for the total cohort.

- Please limit p values to 3 decimals.

- 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). Not trying to minimize your findings, but this does need to be addressed in discussion, particularly as this is an administrative database.

- similar to the study cited in introduction of about 6%. Your discussion should be ordered with primary outcomes discussed first, then secondary outcomes. Based on what you have told us in introduction, the primary outcome is the pattern of use of opioids after GYN surgery.

- Please limit p values to 3 decimals.

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. 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.

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. Please submit a completed STROBE checklist with the revision.

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.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. 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).

9. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

10. 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.

11. 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.

12. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

13. 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.

14. Abstract-Methods: Please rephrase lines 56-57 (the definition) to be clearer. We recommend, "...>1opioid prescription from 90 to 180 days after surgery with no intervening additional procedures or anesthesia."

15. 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.

16. Figures

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.

Figure 3 may need to be split into two panels.

Figure 4 may need to be split into two panels, or move to online-only SDC.

17. 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.

18. 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 Apr 18, 2019, 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

_____