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: Nov 30, 2018
To: "Georgine Marie Lamvu"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2028

RE: Manuscript Number ONG-18-2028

Opioid Use in Endometriosis Patients A Retrospective Matched Cohort Analysis of a Large US Database

Dear Dr. Lamvu:

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 Dec 21, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an interesting manuscript with a purpose to "to examine the prevalence of opioid use in US patients diagnosed with EM compared to women without EM. In light of evidence that opioid-related risks increase with higher doses,13,14 longer use,15-17 or concomitant use of benzodiazepines,14 the study also assessed the frequency of such prescribing patterns. Finally, the analyses explored the timing of the first opioid prescription in relation to treatment-related events, such as the initial EM diagnosis, outpatient visits, or EM related surgery." This was a retrospective, cohort study using an administrative database, Optum® Clinformatics® Data.

1. How valid is the data in the Optum® Clinformatics® Data Mart database, specifically on diagnosis of endometriosis? How valid is the data on prescriptions for type of opioid and filling the prescription? Do they have a reference which has evaluated the validity of this data?

2. Line 221: Should it be addiction instead of addition?

3. In figure 1, upper box: Should it be May 2000 instead of May 200?

4. In the references please ensure that they follow the Instructions for Authors for the Green Journal, especially for et al and date;volume:page numbers.

Reviewer #2: This manuscript by Lamvu et al. covers an important subject and is a large trial evaluating opioid use in patients diagnosed with endometriosis extracted from a large database that has been. However, there are several issues with this paper that should be addressed:

1. Reference 7 should be completed appropriately in that only one author is included.

2. It would be more appropriate for the authors to change the title to "Prescription Opioid Use..." given that this does not address illicit use of opiates which indeed may be higher in endometriosis patients. It would be worth making a comment in this regard as well in the discussion section.

3. One of the weaknesses of this database is that we cannot state that controls did not have chronic pelvic pain, or that all endometriosis patients presented with pain i.e. some may have presented only with infertility. Comments should be
4. The authors do not explain why the majority of patients are from the south, which certainly does not represent a geographic distribution of the incidence of endometriosis, but may represent a confounding variable with a greater propensity towards opioid drug prescription.

5. Table 2 - The authors should provide statistical analysis for differences in use for each of the medications.

6. The authors should also comment on the fact that they do not control for any impact that concomitant medical therapy for endometriosis may provide.

Reviewer #3: For the review, I think that it was really well done and timely with the opioid use/misuse in the US. They described their matching process and statistically analysis extensively, important in a paper such as this.

A few questions/comments:

1) The inclusion of the matching variables (age, geographic region, insurance type and race) in Table 1 does not add much except showing that the matching worked. Instead, it could be helpful to include these levels in the Methods section.

2) With the retrospective cohort design, the authors have the ability to directly calculate risks, risk ratios, and do time-to-event analyses. While ORs may approximate RRs for rare outcomes, for a more common outcome like measured in the study, the risk may be greatly overestimated.

3) It was difficult to tell if the authors are only looking at the first prescription or refills. Table 3 should clarify if this was the length of the initial fill, or if it was supposed to be more of a continuous use measure-unclear. Additionally, the last category of 90 or more days of use seems very long. The authors should explain how this measure is also calculated.

If it was continuous usage, then the authors did not describe how they allowed for this to occur. For example, how much time did they allow between Rx fills for it to be considered “continuous”? What happened if someone filled their Rx early? This would be helpful as a provider to interpret.

Reviewer #4: Could you please comment further on what alternatives to opioids exist to the practitioner. These patient do often have complaints of persistent discomfort. Would you suggest a consult to a pain specialist, earlier surgical solutions or other means to address this issue. A brief discussion of the latter would be helpful in changing physicians patterns.

STATISTICAL EDITOR COMMENTS:

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

Table 1: As seen in Figure 1, the potential control group was ~ 230x as large as the case group. The matching by age, race, type of health plan and region mitigated those issues, but the differences in comorbidities (all < .001) could also have been matched, thus potentially eliminating those as a potential factor in probability of opioid use. Need units for age.

Table 3: Should round the aORs and their CIs to nearest .01. Should include crude ORs with CIs for contrast. Should supplement the analysis with matching algorithm to corroborate the adjusted regression model.

General: Should consider comparison with another cohort of women with chronic pain.

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.
- higher than what? This is particularly pertinent given the recommendation by several reviewers, which I endorse, that you include a comparison to a referent group with chronic pain.

- it is reasonable to not use abbreviations for words that are seldom used in the paper. As well, please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. Please spell the words out throughout the manuscript. Also, the abbreviation here wouldn't change your word count any way.

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

- Your objective and your methods don't quite match. What you did was compare the use of opioids in women with endometriosis and a control group, you are not just examining the use in women with endometriosis. You might consider one of two approaches here, based on the reviewer comments, You could either write this as a descriptive study of opioid and benzos used in women with endometriosis without a comparison, or include and 2nd comparison group of women with another type of chronic pain. Either way, your objective and methods should be consistent w/ each other.

- 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.

- who were the controls and how were they chosen?

- spell out throughout. Please check instructions re: abbreviations

- when you say "dosing" is that what the prescription said the patient should take? (ie, take 1 table of oxycodone 5mg 3 times a day"-would that convert what ever the MME for 5 mg of oxycodone is or 15 mg oxy? We don't know of course if that's what she took.

- odd if this is a national database, please comment

- Please provide some further information about this administrative database. How is is validated? It seems the geographic distribution of included people is not uniform (based on the 51%+ women from the South). Is there any record of its use for this sort of study by others that might demonstrate its reliability?

- please provide some supporting statement that these types of papers are exempted by your IRB. Also, please name your IRB.

- what about controls?

- please be clear how controls were selected. Based on the # of covered lives in the Optim database, it can't just be any woman without EM diagnosis in the same age range. Did you randomly select from that group? If so, how was that done.

- please respond to comments in abstract about this here as well

- to be concomitant would they have to be filled on the same day or could they be filled so the prescriptions would at least overlap?

- For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

- sample

- what do you mean by "although"?

- Among women with endometriosis

- either "is a common diagnostic test" or "is commonly used to diagnose endometriosis"

- worth mentioning development of an ERAS protocol for these women perioperatively?

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: Please note the following issues with your forms. Updated or corrected forms should be submitted with the revision.

Ahmed M Soliman, PhD - Did not indicate a conflict of interest disclosure.

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

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4. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

5. Obstetrics & Gynecology follows the Good Publication Practice (GPP3) guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices. For publication purposes, the portions of particular importance to industry-sponsored research are below.* Please indicate whether the following statements are true or false, and provide an explanation if necessary:

(a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

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(c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

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7. 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.

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

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* 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).

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16. Figures

Figure 1: Please the update figure with exclusion boxes.

Figures 2–5: These figures may be resubmitted as-is.

17. 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 Dec 21, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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