OBSTETRICS & GYNECOLOGY

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

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

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

**Date:** Aug 20, 2019
**To:** "Jessica Young" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-19-1311

RE: Manuscript Number ONG-19-1311

Persistent opioid use after hysterectomy: United States 2005-2015

Dear Dr. Young:

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 Sep 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a retrospective cohort study. Authors reviewed database records of women who underwent a hysterectomy using a large commercial insurance database in US, using prescription claims to estimate opioid use postop. Aim was to assess for risk of long-term opiod use and to look at what factors results in opiod prescriptions getting filled. Time period was 2005 to 2015. Sample size was large.

General comment:
1. Most MIS hysterectomies if ERAS is followed properly do not need any narcotics. Same can be said about very aggressive ERAS after open cases, but it is more likely that patients took narcotics while in the hospital and did not need them at home. As this paper predates ERAS era, would it be possible to put your work into perspective in the modern era of ERAS?

Methods:
2. Thank you for detailed description of the database you used and for putting it into perspective. Why was it chosen over other insurance databases?

3. Why was the period of 2004-2015 chosen as a convenience sample?

4. One of the major strengths of the database is that it is not just inpatient, but also outpatient hysterectomies (which is majority of them in current era).

5 Lines 134-136
Women with prevalent opioid use were excluded. One of the definitions was filling opioid prescriptions within 180-30 days preop. Some surgeons give their patients medications to fill for post-op use at pre-op visits, and some of theses preop visits happen before 30 days to allow patients to plan their lives and work ahead of time. What was 30-day assumption based on? Is this standard of care in opioid research?

It seems a bit high that 31% of women were excluded because of prevalent opioid use. That seems much higher than what I am seeing in practice as a high volume benign gyn surgeon. What can explain this?

6. Your definitions of prevalent opioid use includes one use in 30-180 days prior to surgery. If patient filled >2 fills in 30 days they were also excluded. What is this based on? Is that a standard in opioid research? Lines 158-161 do explain how prolonged opioid use is used in other publications, which was very helpful.

Results

7. Route
Lines 164-173 were very helpful to highlight trend in route.

8. Descriptive findings were very interesting. Thank you for including.
Line 182, 192-194: it is very interesting that factors like age made a difference in terms of filling the prescription but route of surgery did not. While that was the case, out of those who did fill opioid prescriptions, more patients in abdominal group were more likely to use more narcotics for longer. This is interesting to explore in more depth in discussion.

Most MIS hysterectomies if ERAS is followed properly do not need any narcotics. Same can be said about very aggressive ERAS after open cases, but it is more likely that patients took narcotics while in the hospital and did not need them at home. Also this paper predates ERAS era.

9. Lines 211-220
Time periods mostly pre-dates ERAS era. Now we do not use narcotics after hysterectomies and rely on non-narcotic meds and multimodal pain therapies. How would this practice change affect these findings? Even though surgery shifted to MIS route, unless you aggressively implement ERAS policies, surgeons will keep prescribing narcotics post-op. I think this is important to note, and that might be why reference 13 did not see decrease in narcotic prescription with increase in MIS routes. May be your findings are telling us that we should stop worrying about addiction and focus on patient satisfaction and cost savings?

10. Line 216: I am wondering if this needs to be expanded on. Age is very interesting. Is there something about those age groups that makes them less likely to receive narcotics? If we are trying to reduce opioid use postop, we should explore it.

11. Line 251
Use of opioids postop. That is debatable depending on what group you belong too. If you implement ERAS correctly, most of patents do not need any opioids during recovery. I do agree with individualized approach.

Reviewer #2: This study was a large undertaking of obtaining records from a large database source to look at the important topic of narcotic use after hysterectomy.

Some comments:
1. This study was obviously difficult to design given the very large database. I know that patients who had previous prescriptions of opioids were not included due to the potential of chronic use. It would have been helpful to keep them as a subset to actually see if hysterectomy actually decreased long term opioid use. Many patients and doctors blame pain on things like fibroids. Most gyne surgeons counsel that hysterectomy doesn't usually improve pain so don't use it as an indication for hysterectomy but would have been clinically relevant to see a decrease in opioid prescriptions after.

2. I think including a very large date range is useful to capture as many patients as possible. However, during that time EMR was implemented at different times for notes and at many institutions for prescriptions. Studies have looked at number of pills prescribed and most often the prescription is equal to the default prompt. Is there a way to separate the data to look at implementation of electronic prescriptions over time? When this study first began, many wrote paper prescriptions for narcotics due to pharmacy requirements for authenticity.

3. I think it's important to comment in the discussion how this information may or may not help a clinician in managing opioid prescriptions post hysterectomy.

Reviewer #3: You have highlighted an important and timely issue that relates to clinical practice. The very large databases used give strength to your bottom-line conclusions that in opioid naïve patients undergoing hysterectomy, very few end up with continuous or prolonged use and therefore very few were at risk for abuse. The use of both "continuous" and "prolonged" use definitions seems especially unique. You have identified several factors that seemed to influence post hysterectomy continuous or prolonged opioid use. Overall, I feel that this is worthy of publication, but there are some reservations. These include:

1. The lack of diagnosis data - although all subjects had "benign" indications for their surgery, clearly some conditions result in most complicated operative procedures, and this could influence the need/use of narcotic analgesics.

2. The lack of more detailed operative data - i.e. was there lysis of adhesions required, was ureteral lysis required, was there any intra-op complications? All again, could influence post-op opioid use.

3. The lack of post-op data - i.e. complications, etc.? All again, could influence post-op opioid use.

4. While the subjects were censored if they needed another "invasive" procedure in the follow-up period, how many subjects was that? Did they have a different opioid use profile prior to the second procedure?

5. Was there a trend in the types of opioid prescribed and continuous or prolonged use?

6. Finally, if your database does not allow you to address the above concerns, I think you should acknowledge them in your discussion of the limitations.

STATISTICAL EDITOR'S COMMENTS:

1. I think the precis tells part of the story. The bad news is that 2-3% of women had another opioid Rx during each of the 12 months following hysterectomy. And by design, this study excluded those with prevalent opioid use, which comprised ~ 30% of the total population.

2. lines 154-156: In this data base, how much loss to follow-up is there and how could that have potentially biased the results?

3. Table 1: Need units for age and age categories.

4. Table 3 by definition, only includes those women who initially had an opioid Rx. Should include the proportion with no fill somewhere in this Table for each surgical group.

5. Table 4: I assume that this Table also only includes those women who had an initial opioid Rx, but that should be made clear.

6. Fig 2: Should explicitly state for the reader which stratum is the referent and should include a column of unadjusted RRs for comparison.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. 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.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

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

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

http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 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.

7. 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.

8. 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.

9. 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.

10. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

11. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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 Journal's Production Editor had the following to say about this manuscript:

"Figures 1–2: Please upload as separate figure files on Editorial Manager (eps, tiff, jpeg, etc.). "

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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*We thank the editor for the opportunity to resubmit this manuscript and are grateful for the comments from both reviewers. We feel strongly that addressing these comments has strengthened this manuscript and look forward to hearing back after additional review.*

**REVIEWER COMMENTS:**

**Reviewer #1:**

**This is a retrospective cohort study. Authors reviewed database records of women who underwent a hysterectomy using a large commercial insurance database in US, using prescription claims to estimate opioid use postop. Aim was to assess for risk of long-term opiod use and to look at what factors results in opiod prescriptions getting filled. Time period was 2005 to 2015. Sample size was large.**

**General comment:**

**1. Most MIS hysterectomies if ERAS is followed properly do not need any narcotics. Same can be said about very aggressive ERAS after open cases, but it is more likely that patients took narcotics while in the hospital and did not need them at home. As this paper predates ERAS era, would it be possible to put your work into perspective in the modern era of ERAS?**

This is an important point and we appreciate the Reviewer's comment. It would definitely be interesting to evaluate more recent data as they become available to see if there is a decrease in the proportion of women filling an opioid prescription after a hysterectomy, as ERAS becomes integrated and more widely used for hysterectomy procedures. We have added the following the discussion section of our paper to acknowledge the potential impact of ERAS.

Line 328:

*Another factor that may impact opioid use after hysterectomy is the integration of enhanced recovery after surgery (ERAS) protocols.(1) As ERAS protocols become further utilized for hysterectomies, the use of postoperative opioids may decrease.(2) As more recent data become available, further research evaluating the impact of ERAS protocols on opioid prescribing habits and prolonged opioid use would be an important contribution to the field.*

**Methods:**

**2. Thank you for detailed description of the database you used and for putting it into perspective. Why was it chosen over other insurance databases?**

Marketscan is a validated and reliable data source that includes inpatient and outpatient claims as well as pharmacy claims. Furthermore, it includes a substantial number of individuals and is one of the largest and longest-running health claims databases in the United States. It has been widely used for health services research, having been used in more than 1,800 peer-reviewed articles. Researchers and programmers at UNC have more than a decade of experience using these data. While other sources of insurance claims data exist, these data include a wider range of patient ages than, for example, Medicare claims; wider geographic representation than, for example, commercial insurance from a single state; and are similar in terms of data quality and the overall number of lives covered to other data sources that include the desired breadth of age and geography (e.g. Optum).

**3. Why was the period of 2004-2015 chosen as a convenience sample?**

The most recent year of data available at UNC at the time we conducted the analyses was 2015. Because diagnosis coding in the United States transitioned from ICD-9 CM to ICD-10 CM in October of 2015, we limited the sample to those who underwent surgery between January 1, 2005 and September 31, 2015. This period covers an important time in opioid prescribing in the US – including the peak in the national prescribing rate in 2012 (CDC published estimates).

**4. One of the major strengths of the database is that it is not just inpatient, but also outpatient hysterectomies (which is majority of them in current era).**

Thank you for recognizing the importance of this fact and providing this feedback.

**5 Lines 134-136**

**Women with prevalent opioid use were excluded. One of the definitions was filling opioid prescriptions within 180-30 days preop. Some surgeons give their patients medications to fill for post-op use at pre-op visits, and some of these preop visits happen before 30 days to allow patients to plan their lives and work ahead of time. What was 30-day assumption based on? Is this standard of care in opioid research?**

We agree that a preop visit could happen prior to 30 days. We based this on the sense that some clinical labs need to be obtained within 30 days to be valid (ie. type & screen). Clinically, it would seem that a preop visit too far in advance prior to surgery (ie. 3 months in advance) would be too far from the date of surgery. Given that we were interested in studying opioid naïve women, we decided to err on the side of caution limiting the preop visit time window to 30 days. While excluding women who filled an opioid more than 30 days prior to hysterectomy results in excluding women with preop visits more than 30 days prior to surgery, it also minimizes inclusion of women who are prevalent opioid users. Using a window longer than 30 days for preop visits would result in including more women who were prevalent opioid users. Misclassifying prevalent opioid users as newly initiating opioid users would introduce bias into the study.

While there is not a standard in opioid research for defining the pre-op window, another published study using MarketScan data, Johnson et al. also used a 30-day window prior to surgery to assess perioperative opioid use for hand surgery.

We have clarified the language in the methods, Line 142:

*We focused on opioid naïve patients undergoing hysterectomy, and excluded women with prevalent opioid use. Prevalent opioid use was defined as an opioid prescription filled between 180 to 30 days prior to hysterectomy (Figure 1).*

**It seems a bit high that 31% of women were excluded because of prevalent opioid use. That seems much higher than what I am seeing in practice as a high volume benign gyn surgeon. What can explain this?**

We appreciate your comment and insight. We, too, find that this statistic is somewhat alarming, but it has been consistent across analyses of various surgical interventions.(3-6)

One factor that may explain the relatively high rate of prevalent opioid use relative to an individual provider's experience is the fact that this is based on the patient's prescriptions from all sources – not only the provider (or practice) where the patient is being treated for her benign gynecologic condition. This may include musculoskeletal injuries, dental pain, etc. In addition, there may be regional

differences in opioid use such that your area of practice may have less opioid use than other areas of the country.

Finally, we acknowledge that our definition of prevalent use (any prescription fill in the 180-30 days prior to surgery) may unnecessarily exclude some women whose prior pain has resolved. However, we would rather be more conservative and exclude more women to ensure that the study population was opioid naïve in order to focus on long term use that is related to hysterectomy rather than a pre-existing condition. This approach is less extreme than other studies which have excluded any individual with a prescription in the prior year (3, 7, 8).

**6. Your definitions of prevalent opioid use includes one use in 30-180 days prior to surgery. If patient filled >2 fills in 30 days they were also excluded. What is this based on? Is that a standard in opioid research? Lines 158-161 do explain how prolonged opioid use is used in other publications, which was very helpful.**

While we acknowledge that a patient may fill an opioid prescription after a preoperative visit, it would be unlikely for them to fill 2 or more opioid prescriptions if the purpose of the opioid prescription was for postoperative use. This is the rationale for excluding individuals with 2 fills in 30 days prior to surgery.

This has been stated in the manuscript, line 146:

*While we assumed that one prescription within 30-days prior to surgery represented opioids prescribed in a preoperative visit for use for postoperative pain, evidence of two or more opioid prescriptions was indicative of potential prevalent use for nonsurgical related pain.*

**Results**

**7. Route**

**Lines 164-173 were very helpful to highlight trend in route.**

Thank you for this feedback.

**8. Descriptive findings were very interesting. Thank you for including.**

**Line 182, 192-194: it is very interesting that factors like age made a difference in terms of filling the prescription but route of surgery did not. While that was the case, out of those who did fill opioid prescriptions, more patients in abdominal group were more likely to use more narcotics for longer. This is interesting to explore in more depth in discussion.**

**Most MIS hysterectomies if ERAS is followed properly do not need any narcotics. Same can be said about very aggressive ERAS after open cases, but it is more likely that patients took narcotics while in the hospital and did not need them at home. Also this paper predates ERAS era.**

Thank you for this comment. We added to the following text discussing differences in postoperative opioid use by route.

We agree that ERAS can certainly impact postoperative narcotic use (please see our response to Comment #1 above). In this era of minimally invasive surgery, hysterectomies performed abdominally may have indications that result in more postoperative pain, otherwise it is likely that the hysterectomy would have been done laparoscopically or vaginally.

Lines 276:

*We saw differences by surgical route when examining postoperative opioid use, with patients undergoing abdominal surgery being more likely to have continued opioid use. This is consistent with expectations, as abdominal hysterectomies are associated with long recovery times compared to minimally invasive (laparoscopic, vaginal) routes.(9, 10) When clinically possible, minimally invasive routes are preferred, however abdominal surgery may be performed in patients who have complicated clinical cases. These patients may also have indications that result in more postoperative pain.(9)*

**9. Lines 211-220**

**Time periods mostly pre-dates ERAS era. Now we do not use narcotics after hysterectomies and rely on non-narcotic meds and multimodal pain therapies. How would this practice change affect these findings? Even though surgery shifted to MIS route, unless you aggressively implement ERAS policies, surgeons will keep prescribing narcotics post-op. I think this is important to note, and that might be why reference 13 did not see decrease in narcotic prescription with increase in MIS routes. May be your findings are telling us that we should stop worrying about addiction and focus on patient satisfaction and cost savings?**

Thank you for these comments. We also agree that ERAS protocols may impact opioid prescribing, and analyses of more recent and future years of data after more integration of ERAS will be interesting to conduct. In the meantime, we want to ensure that we continue to do our part to prescribe opioids as safely as possible, and that patient pain is adequately managed during recovery. We must also continue to evaluate and research clinical practice to assist in any way that we can regarding the opioid crisis. We believe that our study presents important pharmacoepidemiologic data regarding different methods to assess long-term, persistent opioid use during this time as clinical practice continues to shift and evolve.

We have added the following text to the discussion, Line 328:

*Another factor that may impact opioid use after hysterectomy is the integration of enhanced recovery after surgery (ERAS) protocols.(1) As ERAS protocols become further utilized for hysterectomies, the use of postoperative opioids may decrease.(2) As more recent data become available, further research evaluating the impact of ERAS protocols on opioid prescribing habits and prolonged opioid use would be an important contribution to the field.*

Line 338:

*This study provides important pharmacoepidemiologic data regarding different methods to asses prolonged opioid use. The current findings describe the postoperative opioid prescriptions in a ten-year period during which the US opioid prescribing rate peaked and will be able to serve as a benchmark for future work as the clinical landscape changes, with advances in surgical techniques and implementation of ERAs protocols.*

**10. Line 216: I am wondering if this needs to be expanded on. Age is very interesting. Is there something about those age groups that makes them less likely to receive narcotics? If we are trying to reduce opioid use postop, we should explore it.**

Thank you for this comment. We have added more context pulling from other published literature regarding age and its association with postop opioid use.

Line 251:

*This is consistent with other studies that have found that older age is associated with less opioid use in patients undergoing hysterectomies for benign indications as well as with other surgeries including breast cancer and orthopedic procedures.(11-14)*

**11. Line 251 Use of opioids postop. That is debatable depending on what group you belong too. If you implement ERAS correctly, most of patents do not need any opioids during recovery. I do agree with individualized approach.**

Thank you for this comment. We agree with the reviewer and have changed the wording to say the following, Line 303:

*Opioids are an important part of the healthcare system and evidence supports their efficacy in managing short-term or acute pain.(15)*

**Reviewer #2: This study was a large undertaking of obtaining records from a large database source to look at the important topic of narcotic use after hysterectomy.**

Thank you for this feedback.

**Some comments:**

**1. This study was obviously difficult to design given the very large database. I know that patients who had previous prescriptions of opioids were not included due to the potential of chronic use. It would have been helpful to keep them as a subset to actually see if hysterectomy actually decreased long term opioid use. Many patients and doctors blame pain on things like fibroids. Most gyne surgeons counsel that hysterectomy doesn't usually improve pain so don't use it as an indication for hysterectomy but would have been clinically relevant to see a decrease in opioid prescriptions after.**

This is certainly an interesting area to explore; however, because our data source is based on insurance claims only, we do not know the indication for opioid prescriptions. It is possible that they are using opioids prior to surgery for chronic back pain for example. To address the question posed, it would be more meaningful to evaluate a cohort of patients using opioids for pelvic pain and then assess if their differences in opioid use between patients who undergo hysterectomy compared to those who did not have hysterectomy. While this is a very interesting question, this would require a different study design to properly assess and we regret that it is beyond the scope of the current analyses.

**2. I think including a very large date range is useful to capture as many patients as possible. However, during that time EMR was implemented at different times for notes and at many institutions for prescriptions. Studies have looked at number of pills prescribed and most often the prescription is equal to the default prompt. Is there a way to separate the data to look at implementation of electronic prescriptions over time? When this study first began, many wrote paper prescriptions for narcotics due to pharmacy requirements for authenticity.**

Thank you for these comments. Unfortunately, we cannot differentiate between paper and electronic prescriptions in these claims data. These data are based on prescriptions filled, so it is possible that a provider gave a prescription to a patient, but then the patient did not fill the prescription. This data source represents only filled prescriptions.

We agree that there may be differences in prescribing habits between paper and electronic prescriptions; however, anecdotally, it is not likely that providers individualized their opioid prescribing habits when using paper prescriptions as they likely prescribed the same amount based on procedure as part of their routine. If they were someone who tried to individualize prescribing with paper prescriptions, then it's likely that they would continue that practice with electronic prescriptions.

**3. I think it's important to comment in the discussion how this information may or may not help a clinician in managing opioid prescriptions post hysterectomy.**

Thank you for this feedback as well. This study focuses on population-based data regarding perioperative opioid prescriptions and long-term use. We are unable to assess individual factors such as indication for surgery and other comorbidities/factors that may impact the surgery. Given the lack of clinical detail, it is difficult to make specific recommendations on opioid prescriptions for surgery. We feel that it is important to highlight the fact that only 84% filled a prescription and that it is not 100% of women, and that the long-term continuous use is low so that it is possible that persistent opioid use after hysterectomy may not be as high as has been previously reported.

We have added the following to the discussion Line 376:
*This study focuses on population-based data regarding perioperative opioid prescriptions and long-term use. We are unable to assess individual factors such as indication for surgery and other comorbidities/factors that may impact the surgery. Given the lack of clinical detail, it is difficult to make specific recommendations on opioid prescriptions for surgery. Our findings highlight that only 84% of hysterectomy patients filled an opioid prescription for surgical pain, and that rates of continuous use of opioids was low, suggesting that persistent opioid use following hysterectomy may not be as high as previously reported.*

**Reviewer #3: You have highlighted an important and timely issue that relates to clinical practice. The very large databases used give strength to your bottom-line conclusions that in opioid naïve patients undergoing hysterectomy, very few end up with continuous or prolonged use and therefore very few were at risk for abuse. The use of both "continuous" and "prolonged" use definitions seems especially unique. You have identified several factors that seemed to influence post hysterectomy continuous or prolonged opioid use. Overall, I feel that this is worthy of publication, but there are some reservations. These include:**

1. **The lack of diagnosis data - although all subjects had "benign" indications for their surgery, clearly some conditions result in most complicated operative procedures, and this could influence the need/use of narcotic analgesics.**

   Thank you for your comment. In response to this question, we examined diagnosis codes present in the 30 days prior to the procedure, grouped using Clinical Classification Software diagnosis groups as previously described by Wu et.al.

   We have added the following text to the methods, Line 130:
   *To examine possible indications for hysterectomy, we examined diagnosis codes in the 30 days prior to hysterectomy, using Clinical Classification Software diagnosis groups: 46 – Benign neoplasm of uterus, 168 – Inflammatory disease of female pelvic organs, 169 – Endometriosis, 170 – Prolapse of female genital organs, and 171 – Menstrual disorders).(16)*

   We have added the following text to the results, Line 198:
   *During the month prior to hysterectomy, 60% of all women in the study population were diagnosed with benign neoplasm, 56% had a diagnosis code indicating menstrual disorder, 31% were diagnosed with endometriosis, and 30% were diagnosed with inflammatory pelvic disease (Table 1).*

   Line 206:
   *Those who filled an opioid prescription were younger (46.6±9.2 vs 50.0±11.5), more likely to reside in the South (49.6% vs 44.0%), less likely to reside in the Northeast (9.9% vs 14.4%), had a lower Charlson Comorbidity Index (mean 0.3 vs 0.5), and were more likely to have a diagnosis of menstrual disorder (57.6% vs 48.2%).*

We have also added this information to Table 1 and Figure 2.

**2. The lack of more detailed operative data - i.e. was there lysis of adhesions required, was ureteral lysis required, was there any intra-op complications? All again, could influence post-op opioid use.**

Thank you for this comment. In response, we have conducted additional analyses examining complications both during surgery and in the 60 days following surgery.

We have added the following text to the methods, Line 133:
*Because surgical complications may impact postoperative opioid use, we examined diagnosis and procedure codes indicative of surgical complications (lysis of adhesion, bowel injury, ureteral injury, acute renal failure, urinary tract infection, shock/sepsis, wound disruption, postoperative infection, CPR, unplanned intubation, and prolonged intubation) occurring on the day of surgery and in the 60 days following surgery.*

We have added the following text to the results section, Line 201:
*Bowel injury was the most common intraoperative complication, occurring in 4.2% of surgeries, followed by lysis of adhesion, occurring in 3.8% of surgeries (Appendix Table 1).*

Line 232:
*We also found that those with surgical complications during surgery or in the 60 days post-surgery were more likely to have prolonged opioid use compared to those without complications. (Appendix Table 3).*

Discussion, Line 282:
*In stratified analyses, we also found that patients who received hydrocodone and those with surgical complications were more likely to have prolonged opioid use.*

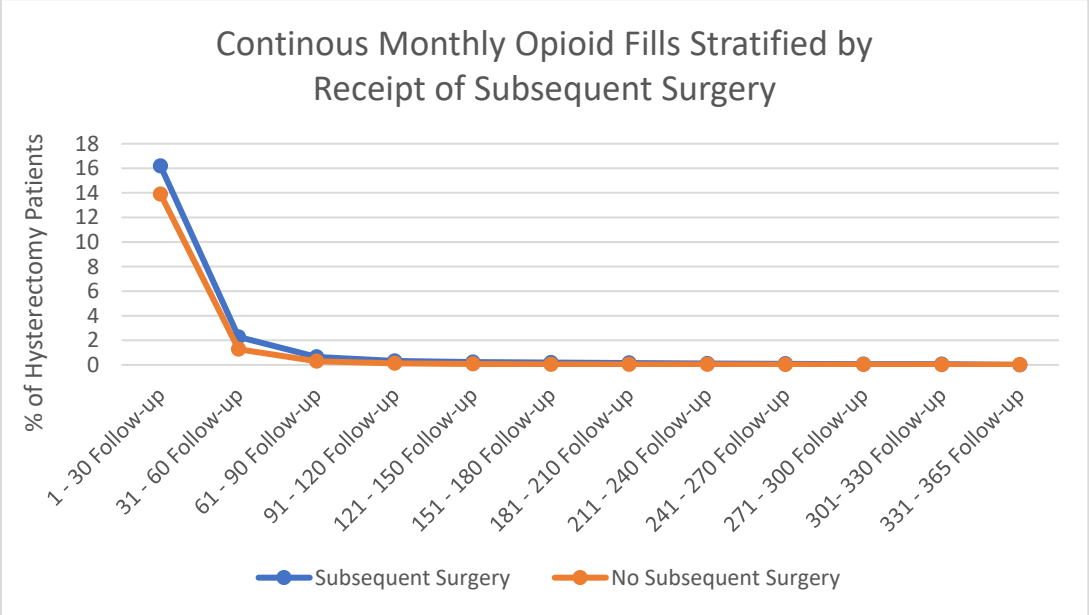
**3. The lack of post-op data - i.e. complications, etc.? All again, could influence post-op opioid use.**

Again, thank you for this comment. Please refer to our response to comment # 2 directly above. Results for both intraoperative and postoperative complications are summarized in Appendix Tables 1 and 3.

**4. While the subjects were censored if they needed another "invasive" procedure in the follow-up period, how many subjects was that? Did they have a different opioid use profile prior to the second procedure?**

Overall, 15% of patients had another invasive procedure in the year following hysterectomy. These patients were included in the analysis and contributed to the reported results until the time of the second procedure, thus any opioid use prior to the second procedure is included in the analysis.

To examine the opioid use profiles of those who had a subsequent procedure, we have plotted the proportion with continuous monthly fills, stratified by receipt of subsequent surgery. We do observe that those with a surgery during follow-up had slightly higher rates of opioid prescriptions after hysterectomy (and prior to the subsequent surgery), however differences were negligible after 90 days of follow-up. In general, these results have limited clinical utility given that at the time of initial surgery, clinicians cannot know whether a patient will have a subsequent surgery.




**5. Was there a trend in the types of opioid prescribed and continuous or prolonged use?**

Thank you for this comment. We examined trends in prolonged use stratified by the most common opioids prescribed in our study population.

We have added the following to the methods, Line 183: *We conducted stratified analyses of continued monthly use stratified by the initial opioid prescribed.*

And the following to the results, Line 230:
*In our stratified analyses, we found that patients whose initial postoperative prescription was for oxycodone had lower proportions with prolonged use compared to those initiating on hydrocodone (Appendix Table 2).*

And the following to the discussion, Line 282:
*In stratified analyses, we also found that patients who received hydrocodone and those with surgical complications were more likely to have prolonged opioid use. The increased proportion with prolonged use among patients receiving hydrocodone may be due to varying factors, such as changes in hydrocodone scheduling and temporal prescribing trends which were not accounted for in the current analysis.*

**6. Finally, if your database does not allow you to address the above concerns, I think you should acknowledge them in your discussion of the limitations.**

We have added analyses including information on hysterectomy indications, and surgical complications during the intraoperative period and in the 60 days post-surgery. The indications and complications are defined using diagnosis and procedure codes, and without clinical notes the level of detail is limited, however we feel that these additions add to the strength of the research findings – thank you for the comments and suggestions to strengthen this work.

**STATISTICAL EDITOR'S COMMENTS:**

1. **I think the precis tells part of the story. The bad news is that 2-3% of women had another opioid Rx during each of the 12 months following hysterectomy. And by design, this study excluded those with prevalent opioid use, which comprised ~ 30% of the total population.**

   We have updated the precis to clarify that this study was conducted among opioid-naïve patients. In the precis limited to 25 words, we focused on our main analysis, continuing monthly fills, which we feel has more clinical relevance. The 2-3% result may be misleading as these fills may be occurring after long periods without opioid use and may be unrelated to the iatrogenic effects of hysterectomy.

2. **lines 154-156: In this data base, how much loss to follow-up is there and how could that have potentially biased the results?**

   Thank you for this comment. We examined opioid use for the year after hysterectomy. Overall, the mean follow-up time was 273.6 days, and 56% of patients had follow-up for the entire year. While 24.3% of patients disenroll from the database during the first year of follow-up, most of these patients (58%) disenroll at the end of the calendar year (December 31$^{st}$), suggesting that this disenrollment may be indicative of routine administrative changes in insurance companies, and unrelated to patient health status. We have summarized the reasons for end of follow-up in the table below.

| **End of Follow-Up** | **% of Hysterectomy Patients** |
|---|---|
| 1 Year Follow-Up | 56.1% |
| Disenrollment from MarketScan | 24.3% |
| Subsequent surgery | 14.9% |
| End of Study Data (Dec 31, 2015) | 4.7% |

   Overall, the majority of patients were followed for the whole study period, and we assume that disenrollment and reaching the end of the study period are administrative, noninformative losses to follow-up. We do not have reasons to believe that those who are lost to follow-up due to disenrollment or reaching the end of the study period have differences in the likelihood to have prolonged opioid use, and thus do not expect that the loss to follow-up biases our conclusions.
   As described earlier, 15% of patients were censored within the 1$^{st}$ year due to having a subsequent surgery. Because opioid prescriptions obtained after the second surgery may be unrelated to the hysterectomy procedure, we censored these patients at the time of the second surgery.

   We have added the following to the results, Line 190:
   *Among the 393,097 remaining women in our study population, the average follow-up time was 273.6 days.*

3. **Table 1: Need units for age and age categories.**

   We have added units to the label in Table 1.

4. **Table 3 by definition, only includes those women who initially had an opioid Rx. Should include the proportion with no fill somewhere in this Table for each surgical group.**

   Thank you for this comment. We have updated this table accordingly.

5. **Table 4: I assume that this Table also only includes those women who had an initial opioid Rx, but that should be made clear.**

   Correct. We have updated this table to make this more clear.

6. **Fig 2: Should explicitly state for the reader which stratum is the referent and should include a column of unadjusted RRs for comparison.**

   We have added a column displaying unadjusted RRs, and labels to explicitly state which stratum is the referent.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. 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:

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

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

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

The following text appears on the Methods section of the manuscript beginning on Line 99:

*For this retrospective cohort study, we used the 2004 to 2015 MarketScan® Commercial Claims and Encounters database and Medicare Supplemental and Coordination of Benefits databases (copyright © 2015 IBM Watson Health. All rights reserved).(17, 18) These data have been validated by IBM*

*Watson Health and are population-based and de-identified healthcare claims drawing from approximately 150 payors in the U.S., representing employees, dependents, and retirees with employer-based insurance in the U.S. These databases include longitudinal inpatient and outpatient healthcare claims allowing researchers to observe dates of service, patient-level diagnosis codes and procedure codes, and all reimbursed outpatient prescription medications. Unique individuals can be followed over time using encrypted identification numbers, and detailed enrollment data were used to ensure that only individuals who could generate a claim were included in the population at risk at any given time.*

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

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

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 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.

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Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

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