Date: Aug 17, 2018
To: "Hannah B Anastasio" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1406

RE: Manuscript Number ONG-18-1406

Avoiding NSAIDs postpartum for hypertensive disorders: a premature decision?

Dear Dr. Anastasio:

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 07, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This topic is clinically important to those of us working on Labor and Delivery and wanting to optimize blood pressure control during the postpartum period. The authors seek to answer important questions with their study: does NSAID use increase blood pressures postpartum and does use of NSAIDs postpartum affect opioid pain medication use. I think that the study is well-done and I appreciate that it includes patients affected by all manner of hypertensive diseases of pregnancy.

Comments and Questions
1) Your blood pressure data is all reported with respect to MAP, however, clinically we typically use the absolute systolic or diastolic blood pressure for clinical decision making. Were there any differences in the number of patients who had SBP or DBP over the thresholds we typically base treatment on (i.e. SBP >160 mmHg)?

2) As this was a retrospective study design, my interpretation is that the choice of postpartum medications prescribed and intervals (i.e. scheduled or prn dosing) would be based on provider discretion. In Table 3, you show the cumulative opioid dose and this is the basis for your conclusion about opioid use. My concern is that this could have been influenced by prescribing practices. Can you comment on the standard practice at your institution during the study period for postpartum ordering of NSAIDs and opioids for both vaginal and cesarean deliveries? Was there a standard order set used, were narcotic medications prn or scheduled as a default? Other studies with post-operative opioids have shown less patient use with prn orders versus scheduled, so more knowledge about the standard of care at your institution would help to put these data into context. Along the same lines, did you look at if the decrease in opioid equivalents had any relationship to mode of delivery, vaginal versus cesarean?

Reviewer #2:

Overall Comment:

The authors present data from a retrospective cohort study in women with hypertensive disorders of pregnancy. The patients were analyzed in two cohorts as to whether they received non-steroidal anti-inflammatory drugs postpartum. They wished to evaluate whether the administration of NSAID medications postpartum to women with hypertensive disorders was associated with worsening hypertension. Rather than looking at changes in systolic and diastolic pressure, they powered the study to look at change of mean arterial pressure during the postpartum period. As a secondary aim,

they were looking at the cumulative dose of opioid medication in women receiving NSAIDs compared to those not receiving NSAIDs.

While a very important clinical question, a larger study was published in Obstetrics and Gynecology in October, 2017. A reference was made to the 2013 ACOG recommendation regarding the use of non-steroidal anti-inflammatory medications in postpartum women with hypertensive disorders; however, there have been subsequent reports stating the need for a randomized controlled trial. Although interesting, this report has a small N, is not powered to look at the difference between groups in diastolic and systolic pressures, reflects bias by the nature of the retrospective study, and the issue of opioid use is somewhat a secondary aim in this report and really does not add to the literature.

Specific Comments:

Title: Instead of a question, would consider The Effective NSAIDS Postpartum in Women with Hypertensive Disorders.

Abstract: The background section is not a part of the structured abstract.

Introduction: Should supply a hypothesis.

Materials and Methods: Please clarify why a look at mean arterial pressure was performed instead of looking at change in systolic and diastolic pressures specifically. Is there a MID for a change in the mean arterial pressure? If so, please put this information in the methods.
Results: Were there any difference in outcomes in women that delivered vaginally versus by C-section? Could the authors please also provide the baseline and follow-up systolic and diastolic blood pressure as well as mean arterial pressure in the two groups.

Discussion: It does review the report's findings in the context of the existing literature well.
Tables: I would also provide the mean systolic and diastolic blood pressures baseline as well as postpartum.
References: Reference 8, line 282, the word with is misspelled.

Reviewer #3:

This is a retrospective cohort study conducted on postpartum patients to investigate the effect of NSAIDs on blood pressure in those patients diagnosed with hypertensive disorder during pregnancy.

- In introduction, it's important to mention the mechanism of action of NSAID that leads to increased blood pressure, as well as to reference previous studies conducted on non pregnant populations.

- In materials and methods:
How was the different hypertensive disorders in pregnancy diagnosed, a referrence is needed.
What were the average blood pressures antepartum?
How many patients were on anti-hypertensives? what are the anti-hypertensives used?

- Chronic hypertension and preeclampsia have different pathophysiology so it will be interesting to know what is the MAP difference in chronic hypertension patients receiving NSAID postpartum. Prior studies have shown that NSAID can inhibit the effectiveness of anti-hypertensives and can have a prohypertensive effect in a dose dependent manner.

STATISTICAL EDITOR COMMENTS:

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

lines 66-67: Should be power = .85, beta = 0.15.

lines 170: Here beta is cited as 0.8. Need to reconcile to a consistent parameter value and again, I hope the meaning is power, not beta = .80. Should include in sample size estimation the SD for ΔMAP used in calculation. (Appears to be ~ 9-10 mm Hg.)

lines 177-179: Perhaps some selection bias in that those with elevated creatinine were not as likely to be given NSAIDs. Any information on the creatinine values for the NSAID cohort before and after receiving NSAIDs?

lines 191-194, Table 2: These measures and outcomes were not part of the primary outcome, most were infrequent and therefore there was low power to have discerned any difference. Cannot generalize the NS findings.

Table 3, lines 202-205: The SD for morphine milliequivalents seems too narrow. Please verify that this was SD, not SE. Same comment re: low power and therefore cannot generalize the NS findings.

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 Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.

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. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). 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://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. 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. 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 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 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.

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 appendixes).

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

8. 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).

9. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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. 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.

***

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 Sep 07, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir
Editor in Chief of Obstetrics & Gynecology

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

[redacted] Floor

September 5, 2018

Dr. Chescheir and Editorial Board
Obstetrics and Gynecology
409 12th Street, SW
Washington, DC 20024

Dear Dr. Chescheir and Editorial Board Members,

Thank you for the opportunity to revise our manuscript for your ongoing consideration for publication. Enclosed please find a revised manuscript (with changes tracked), as well as our response to reviewers comments (below).

We appreciate your consideration, and look forward to your decision.

Sincerely,

Hannah Anastasio, MD
[redacted]

REVIEWER #1:

This topic is clinically important to those of us working on Labor and Delivery and wanting to optimize blood pressure control during the postpartum period. The authors seek to answer important questions with their study: does NSAID use increase blood pressures postpartum and does use of NSAIDs postpartum affect opioid pain medication use. I think that the study is well-done and I appreciate that it includes patients affected by all manner of hypertensive diseases of pregnancy.
Comments and Questions

1) Your blood pressure data is all reported with respect to MAP, however, clinically we typically use the absolute systolic or diastolic blood pressure for clinical decision making. Were there any differences in the number of patients who had SBP or DBP over the thresholds we typically base treatment on (i.e. SBP >160 mmHg)?
Response: Thank you for this suggestion. MAP was chosen because it encompasses both SBP and DBP, both of which (in our opinion) are equally relevant for obstetric patients. We do acknowledge that MAP is used less clinically that SBP or DBP in obstetrics, but felt that we could not choose just one of these parameters as primary outcome. A sentence was added to Materials and Methods to further clarify this choice of primary outcome (lines 184-186). We did analyze SBP and DBP postpartum for both cohorts and found no difference during the postpartum period. Maximum postpartum SBP and DBP were added to Table 2, which did not differ between groups (lines 366-368).

2) As this was a retrospective study design, my interpretation is that the choice of postpartum medications prescribed and intervals (i.e. scheduled or prn dosing) would be based on provider discretion. In Table 3, you show the cumulative opioid dose and this is the basis for your conclusion about opioid use. My concern is that this could have been influenced by prescribing practices. Can you comment on the standard practice at your institution during the study period for postpartum ordering of NSAIDs and opioids for both vaginal and cesarean deliveries? Was there a standard order set used, were narcotic medications prn or scheduled as a default? Other studies with post-operative opioids have shown less patient use with prn orders versus scheduled, so more knowledge about the standard of care at your institution would help to put these data into context. Along the same lines, did you look at if the decrease in opioid equivalents had any relationship to mode of delivery, vaginal versus cesarean?
Response: Thank you for raising this important point. All patients delivered at our institution are under care of the same resident physicians, who have a standard postpartum order-set that includes ibuprofen and oxycodone/acetaminophen, both PRN, unless the attending physician specifically requests otherwise (which is atypical). The percocet is typically ordered with parameters, so patients can take 1-2 tabs as needed. The patient and RN use shared decision making to determine the dose and frequency of medications to control postpartum/postoperative pain. Therefore their use of opioids likely reflects actual need by patients, rather than prescribing practices. However, we

acknowledge that the nurses counseling and suggestions toward patients could influence their medication consumption. We added a statement on prescribing practices at our institution to Materials and Methods (lines 156-164). We also added a sub-analysis looking at cumulative opioid dose by mode of delivery (Table 4).

REVIEWER #2:

Overall Comment: The authors present data from a retrospective cohort study in women with hypertensive disorders of pregnancy. The patients were analyzed in two cohorts as to whether they received non-steroidal anti-inflammatory drugs postpartum. They wished to evaluate whether the administration of NSAID medications postpartum to women with hypertensive disorders was associated with worsening hypertension. Rather than looking at changes in systolic and diastolic pressure, they powered the study to look at change of mean arterial pressure during the postpartum period. As a secondary aim, they were looking at the cumulative dose of opioid medication in women receiving NSAIDs compared to those not receiving NSAIDs.

While a very important clinical question, a larger study was published in Obstetrics and Gynecology in October, 2017. A reference was made to the 2013 ACOG recommendation regarding the use of non-steroidal anti-inflammatory medications in postpartum women with hypertensive disorders; however, there have been subsequent reports stating the need for a randomized controlled trial. Although interesting, this report has a small N, is not powered to look at the difference between groups in diastolic and systolic pressures, reflects bias by the nature of the retrospective study, and the issue of opioid use is somewhat a secondary aim in this report and really does not add to the literature.
Specific Comments:

1) Title: Instead of a question, would consider The Effective NSAIDS Postpartum in Women with Hypertensive Disorders.
Response: Thank you for the suggestion, we changed the title.

2) Abstract: The background section is not a part of the structured abstract.
Response: Background section was now removed from abstract.

3) Introduction: Should supply a hypothesis.
Response: Thank you for this suggestion, a hypothesis was now added for the primary outcome (lines 113-115).

4) Materials and Methods: Please clarify why a look at mean arterial pressure was performed instead of looking at change in systolic and diastolic pressures specifically. Is there a MID for a change in the mean arterial pressure? If so, please put this information in the methods.

Response: Thank you for this comment. Please see response to Reviewer 1 comment 1 which addresses this choice of primary outcome. We chose to look at *change* in postpartum blood pressure rather than absolute blood pressure as a primary outcome, both to account for any potential baseline differences in blood pressure between cohorts, as well as to evaluate any potential effect of NSAID administration on blood pressure after initiation of NSAIDs postpartum. We added change in postpartum Systolic and Diastolic blood pressure to Table 2, which also did not significantly differ between groups. These findings were added to the results discussion as well.

5) Results: Were there any difference in outcomes in women that delivered vaginally versus by C-section? Could the authors please also provide the baseline and follow-up systolic and diastolic blood pressure as well as mean arterial pressure in the two groups.
Response: Thank you for this comment, also raised by Reviewer 1 comment 2. Please see response to comment regarding differences by mode of delivery above. Unfortunately we do not have access to patients' outpatient blood pressure data at this time, as our hospital has changed medical records and data from this cohort has since been archived.

6) Discussion: It does review the report's findings in the context of the existing literature well.
Response: Thank you for this comment.

7) Tables: I would also provide the mean systolic and diastolic blood pressures baseline as well as postpartum.
Response: Thank you for this suggestion. We added change in SBP and DBP, as well as maximum SBP and DBP to Table 2, none of which differed significantly between cohorts.

8) References: Reference 8, line 282, the word with is misspelled.
Response: Thank you for this feedback, the spelling was now corrected.

REVIEWER #3: This is a retrospective cohort study conducted on postpartum patients to investigate the effect of NSAIDs on blood pressure in those patients diagnosed with hypertensive disorder during pregnancy.

1) In introduction, it's important to mention the mechanism of action of NSAID that leads to increased blood pressure, as well as to reference previous studies conducted on non pregnant populations.
Response: Thank you for this suggestion. This information was added to the introduction, with accompanying references (lines 96-100).

2) In materials and methods: **How was the different hypertensive disorders in pregnancy diagnosed, a reference is needed**.

Response: Hypertensive disorders of pregnancy were defined according to 2013 Hypertension in Pregnancy Task Force definitions. Patient charts were reviewed for blood pressure, laboratory findings and patient symptoms, and 2013 Task Force Definitions were applied. We comment on these definitions in the last sentence of paragraph 2 of Materials and Methods (lines 127-128).

3) What were the average blood pressures antepartum?
Response: Unfortunately we do not have access to this information because the previous electronic medical record used to collect data has been archived.

4) How many patients were on anti-hypertensives? What are the anti-hypertensives used?
Response: 80 of 267 patients were on antepartum antihypertensive agent(s). The most commonly used agent was labetalol, followed by nifedipine XL. There were significantly *more* women on antihypertensive therapy in the group receiving NSAIDs than the group not receiving NSAIDs. Table 1 as well as Results section of manuscript were updated with this information. Specifically, we now added a row ‘’On antihypertensive medication at admission’’ in Table 1 as suggested.

4) Chronic hypertension and preeclampsia have different pathophysiology so it will be interesting to know what is the MAP difference in chronic hypertension patients receiving NSAID postpartum. Prior studies have shown that NSAID can inhibit the effectiveness of anti-hypertensives and can have a prohypertensive effect in a dose dependent manner.
Response: Thank you for this comment. We performed a sub-analysis according to presence or absence of chronic hypertension, and found no differences in outcomes (Table 5).

STATISTICAL EDITOR COMMENTS

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

1) lines 66-67: Should be power = .85, beta = 0.15.
Response: Thank you for pointing out this error in terminology. We removed this statement from abstract, but have corrected it in the remainder of the manuscript.

2) lines 170: Here beta is cited as 0.8. Need to reconcile to a consistent parameter value and again, I hope the meaning is power, not beta = .80. Should include in sample size estimation the SD for ΔMAP used in calculation. (Appears to be ~ 9-10 mm Hg.)
Response: Thank you for pointing out this error. Beta was 0.15, Power 0.85, we have corrected this error throughout the manuscript, and added SD used from Wasden paper, of 7.9mmHg to materials/methods (line 189).

3) lines 177-179: Perhaps some selection bias in that those with elevated creatinine were not as likely to be given NSAIDs. Any information on the creatinine values for the NSAID cohort before and after receiving NSAIDs?
Response: We agree there is a potential selection bias with regard to this difference between groups, which is a limitation of the study. We do not routinely check creatinine values on all patients postpartum, and decision to monitor labs serially is dictated by individual patient circumstances as well as physician discretion. Creatinine values after NSAID administration are not available for most of our study subjects.

4) lines 191-194, Table 2: These measures and outcomes were not part of the primary outcome, most were infrequent and therefore there was low power to have discerned any difference. Cannot generalize the NS findings.
Response: Thank you for your comment. We agree, and did address this limitation in the discussion (lines 283-286). We also added a comment to Results section acknowledging this limitation (lines 224-225).

5) Table 3, lines 202-205: The SD for morphine milliequivalents seems too narrow. Please verify that this was SD, not SE. Same comment re: low power and therefore cannot generalize the NS findings.
Response: Thank you for noticing this error. It was a typo that we now corrected in Table 3.

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 Katie McDermott and she will send it by email – kmcdermott@greenjournal.org.*****
Response: Responses to Editors Comments are as follows:

1. **Please read the instructions for authors (always a good idea). The word count of the abstract significantly exceeds the limit. Your abstract does not have the appropriate headings in it--again in IFA. We don't use background information in the abstract and we ask that the objective be a simple "To" statement**
   Response: Apologies for this oversight. Background was removed from abstract. Abstract has been edited down to 302 words. Objected was changed as advised.

2. **You could state your objective as "To determine whether NSAIDs.....and secondarily to determine the association..."**
   Response: Done
3. **If they were diagnosed w/ hypertensive disorder of pregnancy only post partum were they excluded?**
   Response: Postpartum diagnoses were not excluded.
4. **In the abstract, please provide absolute numbers as well as which ever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. 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)**
   Response: Completed.
5. **Do not begin a sentence with a numeral. Either reorganize your sentence to not start with a number OR write out the number in words.**
   Response: Completed.
6. **Did you include only women delivered vaginally or also by cesarean? Could you match by route of delivery as this is particularly relevant for your narcotic use? Are the groups similar with respect to route of delivery?**
   Response: Both modes of delivery were included. No statistically significant difference was observed regarding mode of delivery (Table 1), but there is a trend toward higher rate of cesarean delivery among women who received NSAIDs, compared with those who did not (42 vs 33%, p=.06). We performed a sub-analysis by mode of delivery as suggested (Table 4).
7. **May lead? how about leads?**
   Response: Removed the word “may.”
8. **Please do a subanalysis matching by route of delivery.**
   Response: Completed (Table 4).
9. **which is it? receipt or avoidance that your are measuring? And who would be avoiding it? The patient or provider (Or nurse?)**
   Response: Edited to “receipt.”
10. **Provide the ICD-9 codes used as supplemental digital content.**
    Response: Completed.
11. **Who did the abstraction? Was there a check done on a portion of the abstractions for accuracy? REDcap is spelled as indicated in this note.**
    Response: Maternal demographic information as well as clinical data were abstracted by authors SM and AB. Training on data abstraction was provided by Maternal-Fetal Medicine physicians (HA and AR), and data abstraction was initially overseen until accurate independent abstraction was achieved. Data abstraction questions or inconsistencies were resolved by a physician on review of medical record. Materials and Methods was updated with these details. Capitalization error was corrected in the text.
12. **Define "baseline"**
    Response: Baseline refers to prior to 20 weeks gestation. The word “baseline” was removed from the text, and “prior to 20 weeks gestation” was inserted.

13. **This doesn't seem correct. At least at our insitution, the total dose of drug administered by PCA is recorded.**
Response: PCA doses at our institution were not recorded in the Medication Administration Record, they were in a separate anesthesia medical record system that OBGYN physicians do not have access to. This is a limitation of our study. Materials/methods section of the paper was clarified to explain this limitation. (lines 151-154)

14. **Did this include intrathecal narcotic administration?**
Response: Intrathecal narcotic medication was omitted from this calculation, for the same reason as noted in comment 13. Epidural and spinal anesthetic at our institution do contain fentanyl 1.5mcg/mL in infusion, which is run at 14mL/hr (21 mcg/hr of fentanyl). Epidurals are removed in the operating room following cesarean delivery and IV PCA is utilized for less than 24 hours post-operatively, followed by transition to oral opioid. Long acting intrathecal morphine (duramorph) is not used at our institution. These practice patterns were also clarified in Materials and Methods (lines 156-162).

15. **It seems that route of delivery would be a better matching critieria.**
Response: We acknowledge that route of delivery is important. We were unable to match on the basis of delivery due to time constraints for revision, but sub-analysis by mode of delivery was performed. (Table 4)

16. **Please limit p values to 3 decimals.**
Response: Completed.

17. **Since you have only 276 patients, you should probably limit it to 2 decimal points. 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.**
Response: Completed

18. **Did you look at change over time? Not uncommon to see women have a rise in BP around day 3.**
Response: We did not evaluate change over time. The majority of study subjects delivered vaginally and so were discharged postpartum day 2. We agree that the short term follow-up of blood pressure was a limitation, given that blood pressure often peaks again 72 hours postpartum. The majority of our patients have an outpatient blood pressure check 1-2 days postpartum by a nurse, and if elevated, are sent back to triage. By including "readmission for hypertensive disorder" as a secondary outcome, we hoped to address this limitation, although we acknowledge that ideally complete blood pressure data for at least 72 hours postpartum for all study subjects would have been ideal. We acknowledge this limitation (lines 284-286).

19. **Your study was not powered to be able to detect "no difference"s in these outcomes as you note in your discussion section. As such, you cannot state there was "no difference". You can state that your study was underpowered for these outcomes.**
Response: We agree, and did address this in our study limitations. We have also added a comment to the results section of the paper, noting "This study was not

adequately powered to detect changes in these secondary outcomes, however. “ (lines 224-225 and lines 284-286).

20. **This is called a primacy claim (your paper is the first or biggest) and must either be deleted or supported by providing the search terms used, dates, and data bases searched (Medline, Ovid, Pubmed, Google Scholar, etc) in order to substantiate your claim.**
Response: This statement was removed, after noting an error in statistical analysis for opioid use, this finding was no longer statistically significant.

21. **Do you believe this to be true? your study affirms others' studies. If you think other studies are needed, please specificy what other studies. what knowledge gap on your primary, and secondary objectives exist?**
Response: Edited wording as follows: “These findings lead us to question the recommendation against use of NSAIDs postpartum in women with hypertensive disorders of pregnancy. Larger studies, or meta-analysis of existing studies may shed further light on rare adverse outcomes, which individual studies to date have been under-powered to evaluate.” (lines 295-299)

22. **May?**
Response: The word “may” was removed. Please see response to comment 21 for edited wording.

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.

Response: OPT-IN

3. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the August 2014 issue). 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://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.
Response: Done

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.
Response: The corresponding 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.

5. 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), and quality improvement in

health care (ie, SQUIRE 2.0). 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, or SQUIRE 2.0 guidelines, as appropriate.
Response: The manuscript was reported following the STROBE guidelines

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 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.
Response: Done

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 appendixes). Please limit your Introduction to 250 words and your Discussion to 750 words.
Response: Our manuscript is 23 pages, and 3499 words in total. Introduction is 278 words, and Discussion is 531 words.

8. 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).**

Response: Done. No funding was received for this study. The authors report no conflict of interest as declared in the cover letter and in the manuscript. Data from this study was presented as an Oral Concurrent at 38th Annual SMFM Meeting in Dallas TX on February 2nd, 2018.

9. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."
Response: Done. See Page 2. Precis: Administration of NSAIDs postpartum to women with hypertensive disorders is not associated with increased blood pressure

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.
Response: Done.

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.
Response: Done.

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.
Response: Done.

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.
Response: Done.

From: [redacted]
To: Randi Zung
Subject: Re: Your Revised Manuscript 18-1406R1
Date: Tuesday, September 18, 2018 4:07:06 PM

Good afternoon,

All changes are fine, and I agree with edits made.

Sincerely,

Hannah Anastasio

On Tue, Sep 18, 2018 at 3:24 PM Randi Zung <RZung@greenjournal.org> wrote:

> Dear Dr. Anastasio:
>
> The Editors have reviewed the latest version of your manuscript. They have some additional edits for you to review. In the attached manuscript, the new queries are highlighted in blue.
>
> They are:
>
> 1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.
> 2. Precis: Please note the edit to the Precis. Do you approve?
> 3. Line 264: The Editors are requesting that you move Tables 4 and 5 to Supplemental Digital Content. I have cited Appendix 1 and Appendix 2 here, and renamed the tables at the end of the file. If you would prefer to cite Appendix 1 and Appendix 2 somewhere else, please make sure they stay in order of appearance. The Manuscript Editor will add the final links and move the tables to SDC when she completes her final review. Is this okay?
>
> If you do not have any changes to v5, please let me know. If you would like to send back an updated file, please try to return it to me by September 21 at 12 PM (Eastern).
>
> Thank you,
>
> Randi
>
> **From:** Hannah Anastasio [redacted]
> **Sent:** Friday, September 14, 2018 11:08 AM
> **To:** Randi Zung <RZung@greenjournal.org>
> **Subject:** Re: Your Revised Manuscript 18-1406R1

Good morning,

Thank you for the opportunity to make these corrections. Updated manuscript and STROBE checklist are attached. Dr. Cruz will submit an updated authorship form to me today and I will forward as soon as I have it. I confirmed she has no conflict of interest.

Sincerely,

Hannah Anastasio

On Thu, Sep 13, 2018 at 9:40 AM Randi Zung <RZung@greenjournal.org> wrote:

> Dear Dr. Anastasio:
>
> 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. Please submit an Author Agreement form for Dr. Cruz with **both** the "Disclosure of Potential Conflicts of Interest" and "Authorship" sections completed.
>
> Should the last name "Carreno" be added after "Cruz"?
>
> 3. Please submit a completed STROBE checklist. The checklist is available at http://www.editorialmanager.com/ong/default.aspx.
>
> 4. Line 72: 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.

5. Line 81: Please expand “MAP.”

6. Line 87: We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms “trend” or “tendency” or “marginally different”) or “lower doses” unless there is a statistical difference. Please edit here and throughout. Also, your adverse outcomes were underpowered to be able to say there was no difference. For the Abstract-Results, please begin by stating that you were underpowered to be able to confirm that there was no difference in acute renal insufficiency, postpartum transfusion or morphine milliequivalents…

Please also make the related edits throughout your manuscripts as needed.

7. Line 177: Can you elaborate on this? Is there something formal done for “shared decision making” other than the patient reporting a need for pain relief and the nurse administering the drug matching that need? This is the same thing we’ve always done, isn’t it? If you do something formally for “shared decision making” please explain.

8. Line 200: Did you do your power analysis before or after you selected your patients?

9. Line 230: We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms “trend” or “tendency” or “marginally different”) unless there is a statistical difference. Please edit here and throughout.

10. Line 257: We do not allow authors to describe variables or outcomes in terms that imply a difference (such us of the terms “trend” or “tendency” or “marginally different”) unless there is a statistical difference. Please edit here and throughout.

To facilitate the review process, we would appreciate receiving a response by September 17.

Best,

Randi Zung

– –

Randi Zung (Ms.)

Editorial Administrator | *Obstetrics & Gynecology*

American College of Obstetricians and Gynecologists

409 12th Street, SW

Washington, DC 20024-2188

T: 202-314-2341 | F: 202-479-0830

http://www.greenjournal.org

--

Hannah B. Anastasio

--
Hannah B. Anastasio