OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Oct 17, 2019
To: "Logan Williams" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1743

RE: Manuscript Number ONG-19-1743

A randomized trial comparing pain perception using topical EMLA versus lidocaine injection for vulvar biopsy

Dear Dr. Williams:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Nov 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a well written and timely paper. I have only a few questions:

1) The the authors first describe the 30 minutes required for the EMLA application was too disruptive to clinic flow, they should at least stay therefore we modified that application time before biopsy. One has to read down several paragraphs before finding out what they actually did.

2) Please discuss the you changed the recommended wait time and why you chose 10 minutes instead of 30.

Reviewer #2: This is a randomized trial performed at a single institution comparing pain scores after application of topical EMLA cream or injected lidocaine prior to vulvar biopsy. This is a well-designed and well-conducted study with presumably good external validity to both benign and oncologic GYN populations. This study would be of interest to the readers of the Green Journal. The sample size for the study is very small and the study was concluded prior to targeted accrual in anticipation of a resident-research day as interim analysis of the primary end-point reached statistical significance.

My concerns with the paper are that the citations referenced throughout the manuscript often do not support the statements made by the study authors. I also feel the study authors are too far-reaching with their conclusions. This study suggests that 1) lidocaine injections are painful 2) maximal pain scores are less with topical analgesia than with injectables, likely because injections are painful 3) patients prefer topical anesthetics to injected anesthetics. The findings do NOT support the conclusion that EMLA performed better than lidocaine as an anesthetic as there were no significant differences in pain from biopsy between the two groups. Given that one of only 19 patients in the EMLA arm had to receive an emergency injection of lidocaine for insufficient analgesia, I don't believe that the authors can conclude that "EMLA alone should be considered a standard anesthetic method for vulvar biopsy."

1) Line 65-66: Would remove this last sentence as the authors found NO significant difference between the two arms in terms of analgesia at the biopsy site (Lines 230-232 state that "No statistically significant difference was observed between treatment arms with regard to pain at biopsy p = 0.47).")

2) Line 71-73: The citation cited in support of this statement comes from literature examining outpatient hysteroscopy rather than vulvar biopsy. Furthermore, the publication cited determined that pre-procedural analgesia and type of anesthetic administered during the procedure did NOT influence whether women would attend outpatient hysteroscopy in

the future. Please find a reference that supports the statement: "Very painful or uncomfortable procedures may discourage a patient from returning to clinic or receiving necessary follow-up." It would be helpful to provide literature specific to vulvar biopsy to support the importance of the study being presented.

3) Line 75-79: These statements are anecdotal in nature. Please support these statements with citations from the literature. We perform many gyn related biopsies without anesthesia including cervical, upper vaginal and endometrial biopsies. A discussion of why vulvar biopsy is different should be included (discuss innervation of lower vagina and sensorineural basis for pain of the vagina and vulva from the pudendal nerve).

4) Lines 82: The word "several" is used here, but only two studies are cited. Please remove the word "several." The two references cited are review articles of analgesia in gynecologic procedures that mention colposcopy but do not reference vaginal or vulvar biopsies. Please replace these references with citations that support your sentence.

5) Lines 89-91: The cited references do no support this statement. The first reference is to genital wart removal in men. The second two references relate to esophagoscopy procedures. None of the 3 references relate to the "perceptions of the acceptability or tolerability of vulvar biopsy procedures."

6) Lines 115-117: As this is a randomized trial, please describe thoroughly the random assignment procedure used by REDCap (e.g. simple, blocked, stratified etc). Please clarify at what point the provider was notified of the patient's treatment allocation. As provider awareness of randomization allocation prior to discussion of the office procedure and signing procedural consent, this could potentially bias ascertainment and adjudication of outcomes.

7) Line 143-144: Was there any effort made in the analysis to control for extent of biopsies or multiple biopsies? Recording the highest pain score across all locations seems insufficient if the patient was exposed to multiple or prolonged episodes of pain. If the lidocaine arm included differentially more patients receiving more than one biopsy, they would presumably receive more than one lidocaine infiltration resulting in greater perceived pain scores. Maybe lidocaine is better for single biopsy whereas EMLA would be better for multifocal disease requiring multiple biopsies/infiltrations?

8) Line 189-191: Please clarify that the principal assumptions of linear regression were assessed and validated in this study population to justify the use of linear regression modeling. One such assumption is the normality of the distribution of error in the sample population (I see that non-parametric tests were also performed). Given the very small sample size included and the decision to conclude the study early without meeting targeted accrual, I would recommend careful examination of this analysis by a statistical reviewer.

9) Lines 199-219: Please provide statistical assessments as to whether prior vulvar biopsy, anxiety, chronic use of oral analgesics, punch biopsy, etc. was significant between the two groups rather than providing raw numbers.

10) Lines 203-205: Most patients had prior vulvar biopsies--- was any effort made to ascertain what anesthesia they received during prior biopsies?

11) Line 249-250: I would remove this sentence as it is too definitive. Even in this study, one patient who received EMLA cream had to receive an emergency injection of lidocaine. At the most, I believe the authors could conclude that "the decision to use EMLA cream instead of lidocaine injection should be individualized after informed discussion between patients and providers."

12) Line 265-266: I am unable to read this citation in French, however the abstract asserts that pre-procedural analgesia and type of anesthetic administered during the procedure did NOT influence whether women would attend outpatient hysteroscopy in the future… please clarify.

13) Line 269: Please change the wording to "there was an insignificant trend towards improved subject acceptability with EMLA relative to lidocaine."

14) Line 285-288: This sentence is confusing--- cervical biopsy forceps such as Tischlers are usually uniformly sized and do not allow for tailoring of biopsy size whereas punch biopsy devices are available in a number of different sizes.

15) Line 289: If there was no controlling for extent of biopsy or multiple biopsies in the study analysis, this needs to be included in the limitations section.

16) The discussion lacks information about 1) Cost- is EMLA more expensive than injectable lidocaine and does the improved experience for patients justify the cost? 2) There is no discussion about why there was no difference in provider perception of subject tolerance, especially when a patient in the EMLA arm had to receive a rescue injection. 3) 10 minutes make a big difference in clinic workflow- there is no discussion about why there is no difference in provider satisfaction between the two arms.

Reviewer #3:

General Comments: This study reports the results of a randomized control trial of lidocaine injection versus topical EMLA cream for anesthesia prior to a vulvar biopsy. The primary outcome was comparison of the highest level of pain, whenever it occurred during the visit. The results presented are from an interim analysis performed out of convenience. The authors conclude based on the interim analysis that primary outcome was determined by the limited data set and that the EM:LA cream provides superior analgesia for a vulvar biopsy. Due to the limited data set, however, none of the secondary study aims could be determined.

Specific Comments:

Line 50 - Since the for primary outcome, the highest pain recorded, includes pain of injection, the study not really comparing pain of injection versus pain of biposy with EMLA cream?

Line 221 - Confused about the results a bit - median highest score in the EMLA group was 20mm, but the median following biopsy in the same group was only 6mm. Can only interpret this as application of the EMLA cream itself caused more discomfort than the biopsy (as is clearly the case for the injection)

Line 234 - To say that patient acceptability "approached statistical significance" is to defeat the whole purpose of statistical analysis. If you have established a cut off of $p < 0.05$, then the patient acceptability did not meet that criterea and to suggest otherwise is inaccurate.

Line 263 - while this may be novel, i am not convinced that it is a very significant concern or issue. The provider's primary concern should be obtaining an adequate biopsy for analysis with minimum patient discomfort. In my mind the perception of the tolerability for the patient is irrelevant.

Line 270 - the term "borderline significance" has no statistical significance and should be removed.

Line 286-7 - The size of the sample obtained (measurement and or weight) should be part of a standard pathology report and could be used to address this concern.

Table 1 - Why is the Total column included and why are p values not included to demonstrate equivalency of randomized groups?

Table 2 - Again, why is the Total column included? The comparison is between the groups so do not see the reason for including this data.

Figure 1 - This should be included as an appendix.

Figure 3 - The time between pain of anesthesia and pain of procedure is very restricted in the injection group. How does this effect the results and interpretation of this data? It is not really correct to have Time on the X-axis here when the times represented in the two data sets are different.

Reviewer #4: Review of Manuscript ONG-19-1743 "A randomized trial comparing pain perception using topical EMLA versus lidocaine injection for vulvar biopsy"

Williams and colleagues report their results from a single center RCT in women undergoing planned vulvar biopsy which evaluated 2 anesthetic approaches - topical EMLA versus injection lidocaine and the authors have included the CONSORT checklist. Somewhat interestingly, perhaps, the authors measured pain at 3 distinct time points - baseline and both following anesthesia as well as after biopsy. As noted in the abstract, the planned sample size was 106 patients although analysis occurred with only 38 enrolled/randomized patients with 37 being evaluated. I have the following comments/questions.

Title - No comments.

Précis - Acceptable

Abstract - If space allows, note informed consent obtained. Any other data like age, parity, prior lacerations, etc. that can be included?

Introduction - Good summary

Methods - Well described how the study was designed and what was going to be measured. Were thoughts given initially to perform an interim analysis rather than having to do those for slower than predicted accrual? What was the initial predicted accrual time? Was thought given to analyzing results based on biopsy type - punch vs. other - or to limit to one

type or another? Were thoughts given to exclude patients with prior biopsies to exclude the issue of possible anticipatory pain with the biopsy?

Results - Logical presentation of provided data. Line 211-2 was the difference statistically significant in terms of anxiety/pre-procedure nervousness? If so could this have driven some of your findings in terms of favoring EMLA against lidocaine?

Discussion - Would note that the application must be in place for at least 10 minutes.

Tables - Consider removing the right most column of summary data from table 1, not sure that it adds much.

Figure - Interestingly the figures are in reverse order in the PDF. For figure 3 was thought give to provide the measured outcomes since this was the primary outcome in the study?

STATISTICAL EDITOR COMMENTS:

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

lines 165-172, 186-187 vs 189-197 and 221-227: While the power analysis/sample size estimation was straightforward, the actual analysis, formatting and citing of the primary outcome was not and the two were inconsistent. The primary was initially cited as a difference between the means of the maximum pain scores for the two cohorts, based on a minimum clinical difference of 16 and an expected SD = 25. The method used then accounted for the difference in baseline scores (vs the maximum scores) and also adjusted for the multiple procedures by individual providers. The method also assumed normal distributions, but based on samples of n = 18 vs n = 19, which would yield inadequate power to establish whether the distributions were in fact normal. Finally, the maximum scores are formatted as median(IQR), rather than as mean(SD), with the primary outcome apparently taken as the adjusted difference in maximum differences (ie, 25.7 with 95% CI -45.1 to -6.3).

The primary should be consistently stated from the initial statement to the stats method and results. It should be clearly separated from the secondary ones.

EDITOR COMMENTS:

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

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

- Do not include your personal address on professional documents like this or your phone number. You should use your professional contact information. Unfortunately, haters are going to hate and you don't want to make it easy for them.

- Do not include your personal address on professional documents like this or your phone number. You should use your professional contact information. Unfortunately, haters are going to hate and you don't want to make it easy for them.

- We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

- If EMLA is a brand name it cannot be used in the precis. If its an abbreviation, it needs to be spelled out. See instructions for autnors about this. You may want to substitute "topical lidocaine 2.5% and prilocaine 2.5% cream....." Brand name, if that is what it is, cannot be in the title either.

- Either spell out "19" or edit sentence to avoid starting it w/ a numeral. Do this for all instances where a numeral starts the sentence.

- This second sentence of your conclusion is essentially a restating of the first sentence. You can either delete it.

- This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMeD, Google Scholar, EMBASE for example), the date ranges searched, and the search terms used. If not done, please edit it out of the paper.

- since EMLA includes lidocaine, for clarity please describe this as "injected lidocaine" throughout your paper.

- were they told a priori what a given provider used? (ie, before they decided to randomize)

- In discussion, please comment whether differences in anxiety score may be related to the possible increasing anxiety while waiting rather than just getting it over with in injected lidocaine group.

- As noted by one reviewer, often > 1 site needs to be biopsied. How did you handle that? If patients had 2 biopsies near each other, one application of EMLA cream might be sufficient but 2 injections needed. This would alter, perhaps, pain sensation and anticipation/anxiety.

- How did you control for provider bias about this? If you had providers who felt that EMLA cream would not be sufficient (ie, did not have equipoise around the study subject) s/he could add injected lidocaine more quickly than one who was convinced it was a great approach (also lacking equipoise). Did you address this possibility with providers at all?

- Was it study or clinical personnel who helped the patient during the procedure to complete the VAS's?

- Here is part of the answer to an above question. My concern is that if the woman had injected lidocaine for lesion #1 and thought it was terribly painful, her anticipation and possibly perceived pain for the 2nd lesion may be increased. Can you do an analysis for the first lesion only for those w/ multiple biopsies? I'm sure this will end up being very small numbers of women and thus high risk of Type 1 error but perhaps look at that and see if that's the case.

- Who entered the data? Was there any validation of the data entry?

- What was the plan around your secondary outcome results?

- P Values vs Effect Size and Confidence Intervals
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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. This is true for the abstract as well as the manuscript.

- Please reference Table 1 sooner in your results than you do.

- 22% is closer to 1/5 than 1/4. Please edit.

- Please note statistical editor's comments re: analysis.

- We do no 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.

- Your first sentence should set up the importance of your paper, perhaps being in parallel with your primary outcomes. Also being the "first" as your lead in to your discussion seems like the most important result is being the first--not the actual results. Leading your discussion off with this sentence does not seem to really do this.

- This is perhaps a leap based on 38 women, restricted to non hair baring areas. Particularly since you did not address the issue of multiple biopsies.

- which procedure was this for?

- perhaps explain why the highest score is more important than the net score.

- subject acceptability was non significantly different. Given the abbreviated study, you were underpowered for some of your secondary outcomes and you cannot make any conclusions re: neg findings for these.

- blind patients, providers or assessors

- Its too bad that you did the GAD after they knew the randomization arm. In future studies, the more proximal to the intervention that you can do the randomization, the less likely there will be 1) patient drop out and 2) contamination of any data by events, feelings, etc that occur between the randomization and the procedure. The best way to have done you randomization in this case would have been in the treatment room just before anesthesia was to be applied.

- please add comment about multiple biopsies, limiting to hair line. Since vulvar skin has a wide variability in hair distribution, this is big limitation as far as generalizability to other patients.

2. You are also receiving a second attachment, which contains the Editor's review of your CONSORT checklist. Please make sure you review the comments in that file prior to submitting your revision.

Most of the areas of concern from the check list I've included in my comments you will receive, but it may be worth comparing my assessment with your own, just for interest. Thank you as well for your data sharing plan. We are finding that some authors don't recognize the importance of making individual patient data available, at the very least for future IPD meta analyses.

3. 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.

4. 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.

5. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

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

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

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

12. 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.

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

14. 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.

15. 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%").

16. Line 245: 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.

17. 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.

18. Figures

Figure 1: Please upload high resolution figure files to Editorial Manager (eps, tiff, jpeg).

Figures 2 and 3 may be resubmitted as-is.

19. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

20. 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 Nov 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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DUKE UNIVERSITY MEDICAL CENTER

Department of Obstetrics and Gynecology
Division of Gynecologic Oncology

Dear Dr. Chescheir,

Thank you for you detailed and thoughtful review of our manuscript. I am pleased to submit revisions to our research entitled “A randomized trial comparing lidocaine-prilocaine cream versus injected lidocaine for vulvar biopsy” for consideration. This research is being submitted exclusively to *Obstetrics and Gynecology.* I, Logan Williams, the lead author of this manuscript, affirm that this 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 deviations from the originally planned study have been explained. I have personally reviewed the instructions to authors document.

Below, please find responses to all reviewers and to the editor. Please note that what was previously referred to as EMLA in the first submission is now referred to as “lidocaine-prilocaine cream.” All line number references in the response document refer to the “tracked changes” version of the manuscript. Both a “tracked changes” version and a “clean” version have been submitted.

We conducted a randomized, controlled trial to evaluate pain perception with two different analgesic modalities during office vulvar biopsy. Our primary outcome was the highest pain score associated with administration of anesthetic and biopsy procedure in the two groups. Further, we surveyed patients’ perception of the acceptability and tolerability of the procedure. We found that subjects in the lidocaine-prilocaine cream group had lower pain scores and better overall experiences compared to the lidocaine injection group, providing an alternative analgesic method for providers to use while performing vulvar biopsy in the clinic.

This study is a single site randomized controlled trial and is registered at www.clinicaltrials.gov (NCT03654417). The Duke University Health System Institutional Review Board approved the study protocol.

Please see below

Best,

Logan Kai Williams

Logan Kai Williams MD
Duke Obstetrics and Gynecology

REVIEWER COMMENTS:

Reviewer #1:

This is a well written and timely paper. I have only a few questions:

1) The authors first describe the 30 minutes required for the EMLA application was too disruptive to clinic flow, they should at least stay therefore we modified that application time before biopsy. One has to read down several paragraphs before finding out what they actually did.

Response: Thank you for this comment. In the tracked-changes manuscript we have now edited the sentence in question, stating that we excluded patients needing a biopsy on a hair bearing surface, into 2 sentences: "Lidocaine-prilocaine cream requires a 30 minute waiting period following application on hair-bearing surfaces, compared to a 10 minute wait on non-hair bearing and mucosal surfaces. Thirty minutes was felt to be time-prohibitive given clinic flow; therefore we enrolled only subjects whose vulvar lesions were on non-hair bearing surfaces (e.g., labia majora, perineum, vulvo-vaginal junction, and peri-clitoral skin (citation in manuscript)".

This edit is intended to clarify that we did not in fact modify a standard wait time, but that we selected only patients needing biopsy on the mucosal surfaces in which the standard, prescribed wait time of 10 minutes could be followed within our clinic flow.

2) Please discuss the you changed the recommended wait time and why you chose 10 minutes instead of 30.

Response:

Please also see our response to Reviewer 1, question 1. Based on FDA recommendations, when lidocaine-prilocaine cream is applied to the genital mucosa, a 10 minute wait time is necessary for therapeutic effect, compared to a 30 minute wait time on the hair bearing surfaces of the skin.

Reviewer #2:

This is a randomized trial performed at a single institution comparing pain scores after application of topical EMLA cream or injected lidocaine prior to vulvar biopsy. This is a well-designed and well-conducted study with presumably good external validity to both benign and oncologic GYN populations. This study would be of interest to the readers of the Green Journal. The sample size for the study is very small and the study was concluded prior to targeted accrual in anticipation of a resident-research day as interim

analysis of the primary end-point reached statistical significance.

1) My concerns with the paper are that the citations referenced throughout the manuscript often do not support the statements made by the study authors I also feel the study authors are too far-reaching with their conclusions. This study suggests that 1) lidocaine injections are painful 2) maximal pain scores are less with topical analgesia than with injectables, likely because injections are painful 3) patients prefer topical anesthetics to injected anesthetics. The findings do NOT support the conclusion that EMLA performed better than lidocaine as an anesthetic as there were no significant differences in pain from biopsy between the two groups. Given that one of only 19 patients in the EMLA arm had to receive an emergency injection of lidocaine for insufficient analgesia, I don't believe that the authors can conclude that "EMLA alone should be considered a standard anesthetic method for vulvar biopsy."

Response: Thank for your comments. When we compared the highest subjective pain score across the three time points of baseline, application, and biopsy, subjects using lidocaine-prilocaine had lower pain scores. The intentional design was an attempt to consider whether injection of anesthesia is more painful than the biopsy itself. Given that subjects in the lidocaine-prilocaine group had statistically significantly lower pain scores and better overall subjective experience scores, we came to the conclusion that in our study lidocaine-prilocaine cream performed better.

However, after reviewing our conclusions in light of your comments, we have revised the manuscript to more specifically state what we believe readers can accurately take from our study, and that can now be found in lines 97-100 in the conclusion of the abstract: "Lidocaine-prilocaine cream prior to vulvar biopsy resulted in a lower maximum pain score and significantly better patient rating of the biopsy experience when compared to lidocaine injection. Lidocaine-prilocaine cream alone is a reasonable option to use for vulvar biopsy."

The sentence in the Discussion has now been revised to (line 397-399): "Lidocaine-prilocaine cream alone should be considered as an anesthetic method for vulvar biopsy on an individualized basis after an informed discussion between patients and providers."

2) Line 65-66: Would remove this last sentence as the authors found NO significant difference between the two arms in terms of analgesia at the biopsy site (Lines 230-232 state that "No statistically significant difference was observed between treatment arms with regard to pain at biopsy p = 0.47).")

Response: Thank you for this comment. Please note the explanation provided to reviewer #2, question #1. The final sentence has been deleted from the abstract. The final sentence now states lines 97-100 in the conclusion of the abstract: "Lidocaine-prilocaine cream prior to vulvar biopsy resulted in a lower maximum

pain score and significantly better patient rating of the biopsy experience when compared to lidocaine injection. Lidocaine-prilocaine cream alone is a reasonable option to use for vulvar biopsy."

3) Line 71-73: The citation cited in support of this statement comes from literature examining outpatient hysteroscopy rather than vulvar biopsy. Furthermore, the publication cited determined that pre-procedural analgesia and type of anesthetic administered during the procedure did NOT influence whether women would attend outpatient hysteroscopy in the future. Please find a reference that supports the statement: "Very painful or uncomfortable procedures may discourage a patient from returning to clinic or receiving necessary follow-up." It would be helpful to provide literature specific to vulvar biopsy to support the importance of the study being presented.

Response: Thank you for pointing out this discrepancy. Although in the case of in-office hysteroscopy the cited study noted that pre-procedure analgesia or anesthesia did not influence whether women would attend in the future, the pain score using VAS and the difference between anticipated pain and actual pain were the determinants of procedure acceptability. The intention of the citation was to introduce the idea that pain is a factor that may discourage a patient from returning to the clinic. Lines 110-114 now read, "A prior study of patients undergoing in-office hysteroscopy reported that pain score using the visual analog scale (VAS) and the difference between anticipated pain and actual pain were the primary determinants of whether a patient would return to that clinic for the procedure in the future".

4) Line 75-79: These statements are anecdotal in nature. Please support these statements with citations from the literature. We perform many gyn related biopsies without anesthesia including cervical, upper vaginal and endometrial biopsies. A discussion of why vulvar biopsy is different should be included (discuss innervation of lower vagina and sensorineural basis for pain of the vagina and vulva from the pudendal nerve).

Response: Thank you for bringing attention to this issue. The following text with citations has been added to this portion of the introduction, lines 116-127: "Vulvar biopsy can lead to significant discomfort, and some form of anesthesia is recommended[2]. The labia are densely innervated in the superficial layers by the pudendal nerve (S3-S4) somatic innervation resulting in highly sensitive tissue[3]. Conversely the cervix and uterus are innervated by sympathetics (T10-L2) and parasympathetics (S2-S4)[4]; pain results primarily from cervical manipulation as nerve fibers enter deeply, starting in the myometrium in the uterus without nerve endings in the endometrium[5]. For this reason, office hysteroscopy can often be performed successfully without anesthesia while it is standard to use anesthesia for a vulvar biopsy. A current standard in our gynecologic oncology practice is to inject local anesthetic prior to vulvar biopsy. However, the injection procedure is

associated with its own level of pain, and for many, the anticipation of receiving an injection provokes anxiety[6,7,8].”

5) Lines 82: The word "several" is used here, but only two studies are cited. Please remove the word "several." The two references cited are review of analgesia in gynecologic procedures that mention colposcopy but do not reference vaginal or vulvar biopsies. Please replace these references with citations that support your sentence.

Response: Thank you for this correction. In lines 133-134, The word “several” has now been removed. It now reads, “Previous studies have examined the use of topical anesthetics in the place of or in addition to injected anesthesia[9,10]”. The citation has now been updated to reflect a review article that includes a vulvar biopsy and use of lidocaine-prilocaine and/or lidocaine injection and a study that compared lidocaine-prilocaine cream to lidocaine injection for genital wart procedures in men.

6) Lines 89-91: The cited references do no support this statement. The first reference is to genital wart removal in men. The second two references relate to esophagoscopy procedures. None of the 3 references relate to the "perceptions of the acceptability or tolerability of vulvar biopsy procedures."

Response: Thank you for the comment. The citations have now been relocated to appropriate locations as noted above and the citation concerning esophagoscopy has been removed. This citation was initially reviewed while determining evidence-based questions for acceptability and tolerability for procedures.

7) Lines 115-117: As this is a randomized trial, please describe thoroughly the random assignment procedure used by REDCap (e.g. simple, blocked, stratified etc). Please clarify at what point the provider was notified of the patient's treatment allocation. As provider awareness of randomization allocation prior to discussion of the office procedure and signing procedural consent, this could potentially bias ascertainment and adjudication of outcomes.

Response: Thank you for the clarifying question. The randomization was stratified by clinic site, as our Gynecologic Oncology clinic is in two locations. The randomization model was created and downloaded to REDcap such that clinic coordinators after entering a subject and their initial information could randomize the subject on their tablet before proceeding. Lines 187-193 in the materials and methods now state “Randomization was stratified by clinic location to ensure equal allocation of treatment arms at both sites. An independent biostatistician created the randomization schedule and loaded the assignments into REDCap to use random number generation within the database. Clinical research coordinators exclusively had the ability to then generate the randomization assignment after informed consent was performed.”

The general workflow functioned such that the provider evaluated the patient, and once noting that a vulvar biopsy was indicated, consented the patient for the biopsy procedure and inquired whether she would be interested in study participation. If the patient agreed, the research team would be notified, informed consent for the study would be completed, the subject would be randomized, and the provider then notified of the group to which the subject was assigned. As stated in the materials and methods, lines 177-180, potential subjects were notified that if they did not participate in the study, standard anesthesia (usually, lidocaine injection) would be used for their vulvar biopsy, per their provider's preference: "Patients meeting inclusion criteria were approached initially by a gynecologic oncology provider; those expressing interest in participation then met with a clinical study coordinator and were given the options of enrollment in the study or proceeding to biopsy using their provider's standard method of vulvar anesthesia."

8) Line 143-144: Was there any effort made in the analysis to control for extent of biopsies or multiple biopsies? Recording the highest pain score across all locations seems insufficient if the patient was exposed to multiple or prolonged episodes of pain. If the lidocaine arm included differentially more patients receiving more than one biopsy, they would presumably receive more than one lidocaine infiltration resulting in greater perceived pain scores. Maybe lidocaine is better for single biopsy whereas EMLA would be better for multifocal disease requiring multiple biopsies/infiltrations?

Response: Thank you for the insightful question. Given that the subjects recruited were those clinically needing vulvar biopsy, we did not control the number of biopsies that were permitted for study participation. Six subjects required more than 1 biopsy: 3 in the lidocaine-prilocaine group and 3 in the lidocaine group. In 2 of the 3 lidocaine-prilocaine cases, only one of the intended biopsy sites was on a non-hair bearing service of the vulva; therefore, the complete study protocol procedures, including pain scores, were performed prior to the second biopsy being completed. In the third lidocaine-prilocaine case, cream was applied once for 2 different unilateral biopsy sites. In 2 of the 3 lidocaine injection cases, 2 unilateral biopsies were collected but one lidocaine injection was performed as anesthesia for both biopsies. In the third lidocaine case, lidocaine was injected twice for two contralateral biopsies.

Thus, there was one subject in each group whose responses may have been biased by having multiple anesthesia applications and multiple biopsies. Only one collective pain score was collected from these subjects; one for pain at time of application of anesthesia and one for pain at time of biopsy given that anesthesia was administered immediately one after the other and the biopsies were performed consecutively as well.

To address the issue of multiple biopsies in a sensitivity analysis, we refit our linear regression model excluding the three lidocaine injection cases with two

biopsies and the one lidocaine-prilocaine case with two biopsies on the same side of the vulva. The two lidocaine-prilocaine cases in whom the study protocol was completed prior to the second biopsy were retained. For the sensitivity analysis, there are 15 lidocaine injection and 18 lidocaine-prilocaine patients in this subset of the data. The new beta, 95% confidence interval, and p value are -24.3, (-45.6, -3.03), and 0.03, respectively. In contrast, the results we reported in the manuscript using all patients were β = -25.7 with a 95% confidence interval of (-45.1, -6.3) and p value of 0.009. In other words, our point estimate only shifted by 1.4 mm towards no difference between lidocaine and lidocaine-prilocaine, but our confidence widened slightly due to the decrease in sample size. Therefore, the results were similar after narrowing our study population down to the patients that only had one study biopsy taken.

In lines 308-329, subjects with multiple biopsies are now addressed in the Results sections of the manuscript: " The patient was analyzed under the lidocaine-prilocaine cream arm. There were a total of 6 subjects who required two vulvar biopsies, and these were distributed equally between the treatment groups as follows. In 2 of the lidocaine-prilocaine cases, only one biopsy was on the hair bearing surface of the vulva and included in the study, this biopsy and all study procedures were completed first. In 2 of the lidocaine cases, 2 biopsies were collected, but lidocaine was only injected one time. In one case in the lidocaine injection arm, lidocaine was injected twice at separate locations and two biopsies were performed, and in one case in the lidocaine-prilocaine arm the same occurred." Sensitivity analysis results were also added in lines 342-361 "To address the issue of subjects requiring more than one vulvar biopsies in a sensitivity analysis, the linear regression model was refit excluding the three lidocaine injection cases with two biopsies and the one lidocaine-prilocaine case with two biopsies on the same side of the vulva. The two lidocaine-prilocaine cases where the study protocol was completed prior to the second biopsy were retained. Therefore, for the sensitivity analysis, there were 15 lidocaine injection and 18 lidocaine-prilocaine subjects. The significant difference in highest pain score favoring the lidocaine-prilocaine group persisted ($\boldsymbol{\beta = -24.3}$, $\boldsymbol{(-45.6, -3.03)}$, $\boldsymbol{p = 0.03}$). "

In the discussion of limitations, the statement has now been added in lines 468-472, "Our primary analysis did not control for the 3 subjects in each group who received more than one vulvar biopsy during the study; subjects receiving two biopsies may have had altered pain scores due to this. However, our sensitivity analysis, in which the 4 subjects receiving multiple biopsies were excluded confirmed our primary findings with statistical significance."

The information concerning the number of biopsies collected has been added to Table 1.

9) Line 189-191: Please clarify that the principal assumptions of linear regression were assessed and validated in this study population to justify the use of linear regression modeling. One such assumption is the normality of the distribution of error in the sample population (I see that non-parametric tests were also performed). Given the very small sample size included and the decision to conclude the study early without meeting targeted accrual, I would recommend careful examination of this analysis by a statistical reviewer.

Response: Thank you for the question. The assumptions of the linear regression model for the primary outcome were checked by the statistical team. The residuals were approximately normally distributed with mean 0 and constant variance. We have added into the manuscript (lines 335-336) that these assumptions were checked and verified: "The distribution of the residuals from the linear regression model were approximately normally distributed with mean 0 and a constant variance." The linear regression model results for the secondary outcome pain at biopsy have been removed and replaced with results from a non-parametric test due to non-normality of the residuals and the small sample size, but the conclusion did not change.

10) Lines 199-219: Please provide statistical assessments as to whether prior vulvar biopsy, anxiety, chronic use of oral analgesics, punch biopsy, etc. was significant between the two groups rather than providing raw numbers.

Response: Thank you for the question. While we appreciate the reviewer's concerns regarding potential imbalance of participant characteristics across randomization arms, we respectfully disagree that p values should be presented in Table 1. There is an overwhelming consensus against performing and reporting baseline comparisons of characteristics by study arm in randomized trials [1-10]. These statistical tests assess the likelihood that the difference occurred by chance – but it is already known that any significant differences that do occur are caused by chance when randomization is properly implemented, as in our study. They also do not measure similarity across the groups, thus researchers describe these comparisons as illogical/absurd [3, 5-6, 8], superfluous/unnecessary/not useful [6-10], "misleading" [1, 4-6, 8], and "inappropriate" [1, 3, 5]. Further, in all hypothesis testing there is a small probability that a true null hypothesis will be incorrectly rejected. We note that adjustment for covariates based solely on statistically significant baseline differences is also erroneous [1, 6-7].

Consensus holds that the clinical magnitude of the differences and the prognostic strengths of the variables that appear imbalanced is important [6]. We did not note any clinically meaningful differences in our baseline characteristics to warrant concern, and feel comfortable assuming that there were no flaws in our randomization. Given that pre-procedural anxiety is not a pre-randomization

variable, but a subject reported outcome, it has been removed from Table 1, but the comments about our findings remain the same in the manuscript in lines 302-304, "The groups differed in acute anxiety/pre-procedural nervousness, with a median score of 19.0 mm for lidocaine-prilocaine cream vs. 31.5 mm for lidocaine injection, respectively (Table 1)."

The references below support our preference not to present significance testing in Table 1:

1. **Assmann SF, Pocock SJ, Enos LE, and Kasten LE (2000), Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet, 355, 1064-1069.**
2. **Altman DG and Doré CJ (1990), Randomisation and baseline comparisons in clinical trials, Lancet, 335, 149-153.**
3. **Austin PC, Manca A, Zwarenstein M, Juurlink DN, and Stanbrook MB (2010), A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals, Journal of Clinical Epidemiology, 63, 142-153.**
4. **de Boer MR, Waterlander WE, Kuijper LD, Steenhuis IH, and Twisk JW (2015), Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate, International Journal of Behavioral Nutrition and Physical Activity, 12:4.**
5. **Gruijters SL (2016), Baseline comparisons and covariate fishing: Bad statistical habits we should have broken yesterday, The European Health Psychologist, 18, 205-209.**
6. **Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. (2010), CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. Journal of Clinical Epidemiology, 2010(63), e1-37.**
7. **Pocock SJ, Assmann SE, Enos LE, and Kasten LE (2002), Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems, Statistics in Medicine, 21, 2917-2930.**
8. **Senn S (1994) Testing for baseline balance in clinical trials, Statistics in Medicine, 13, 1715-1726.**
9. **Senn S (2004). Controversies concerning randomization and additivity in clinical trials, Statistics in Medicine, 23, 3729-2753.**
10. **Schulz KF, Chalmers I, Grimes DA, and Altman DG (1994), Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals, JAMA, 272, 125-128.**

11) Lines 203-205: Most patients had prior vulvar biopsies--- was any effort made to ascertain what anesthesia they received during prior biopsies?

Response: Thank you for bringing our attention to this. Given that most of the patients had prior vulvar biopsies in the same clinic, and that the previous standard was to use injected lidocaine, subjects were not asked what was used previously. To address this, we have added the following to the limitations portion of the discussion (lines 451-453): "Second, most of the subjects had prior experience with vulvar biopsy, possibly predisposing them to bias; data concerning the anesthesia used in previous biopsies was not recorded."

12) Line 249-250: I would remove this sentence as it is too definitive. Even in this study, one patient who received EMLA cream had to receive an emergency injection of lidocaine. At the most, I believe the authors could conclude that "the decision to use EMLA cream instead of lidocaine injection should be individualized after informed discussion between patients and providers."

Response: Thank you for the suggestion. The sentence in the discussion has now been revised to (line 397-399): "Lidocaine-prilocaine cream alone should be considered as an anesthetic method for vulvar biopsy on an individualized basis after an informed discussion between patients and providers."

13) Line 265-266: I am unable to read this citation in French, however the abstract asserts that pre-procedural analgesia and type of anesthetic administered during the procedure did NOT influence whether women would attend outpatient hysteroscopy in the future… please clarify.

Response: Thank you for pointing out this discrepancy. Please see our response to Reviewer #2, Question 3 as below:

Although in the case of in-office hysteroscopy the cited study noted that pre-procedure analgesia or anesthesia did not influence whether women would attend in the future, the pain score using VAS and the difference between anticipated pain and actual pain were the determinants of procedure acceptability. The intention of the citation was to introduce the idea that pain is a factor that may discourage a patient from returning to the clinic. Lines 110-114 now read: "A prior study of patients undergoing in-office hysteroscopy reported that pain score using the visual analog scale (VAS) and the difference between anticipated pain and actual pain were the primary determinants of whether a patient would return to that clinic for the procedure in the future".

14) Line 269: Please change the wording to "there was an insignificant trend towards improved subject acceptability with EMLA relative to lidocaine."

Response: Thank you for the suggested edit. The wording has been revised in line 368-373 to "Patient acceptability demonstrated a non-significant difference

favoring the use of lidocaine-prilocaine cream (median (IQR) VAS score 0 (0, 18) mm vs. 10.5 (1, 33) mm for lidocaine injection; p = 0.06). Comparing lidocaine-prilocaine to lidocaine injection, no difference was observed for provider satisfaction score (β = 8.2; 95% confidence interval = [-9.0, 25.4]; p = 0.35), or provider's perception of subject tolerance (β = -2.9; 95% confidence interval = [-15.5, 9.7]; p = 0.65) (Table 2)."

15) Line 285-288: This sentence is confusing--- cervical biopsy forceps such as Tischlers are usually uniformly sized and do not allow for tailoring of biopsy size whereas punch biopsy devices are available in a number of different sizes.

Response: Thank you for suggesting this clarification. In our experience, punch biopsies generally result in a fuller thickness skin sample, often extending into the subcutaneous fat. This depth biopsy is not often needed in a vulvar biopsy, but may be more painful. We often use an Eppendorfer forceps, whose "jaws" can be closed down somewhat prior to initiation of the biopsy procedure to achieve a tailored size or depth of the specimen. We feel that one can affect the depth of sample with cervical biopsy forceps compared to a punch biopsy. However, we understand that others may have a different experience or approach with these biopsy methods. We have revised the sentence to read, Line 473-475:

"Further, at least 26 of 37 (70.3%) of biopsies in this study were performed using cervical biopsy forceps; only 5 of 37 (13.5%) of subjects underwent a punch biopsy."

16) Line 289: If there was no controlling for extent of biopsy or multiple biopsies in the study analysis, this needs to be included in the limitations section.

Response: Thank you for this suggestion. Please see our extensive response to reviewer #2, response # 8 including the description of the sensitivity analysis performed that has also been added to the Results section:

In the discussion of limitations, the statement has now been added in lines 468-472, "Our primary analysis did not control for the 3 subjects in each group who received more than one vulvar biopsy during the study; subjects receiving two biopsies may have had altered pain scores due to this. However, our sensitivity analysis, in which the 4 subjects receiving multiple biopsies were excluded confirmed our primary findings with statistical significance."

The information concerning the number of biopsies collected has been added to Table 1.

17) The discussion lacks information about 1) Cost- is EMLA more expensive than injectable lidocaine and does the improved experience for patients justify the cost? 2) There is no discussion about why there was no difference in provider perception of

subject tolerance, especially when a patient in the EMLA arm had to receive a rescue injection. 3) 10 minutes make a big difference in clinic workflow- there is no discussion about why there is no difference in provider satisfaction between the two arms.

Response: Thank you for noting the omission of cost considerations. We did not do a formal cost analysis, but we did research the cost difference between the two medications for purposes of our research study budget. Based on a pharmacy acquisition request at our institution, two milliliters of 1% lidocaine costs $0.99, while 5g EMLA topical cream costs $7.36, for a difference of $6.37. On an individual basis, given that both treatment options are of relatively low cost, we feel that it would be reasonable to use either.

Lines 433-437 of the discussion comment, "When considering the cost difference between the anesthetic options, based on a pharmacy acquisition request at our institution, two milliliters of 1% lidocaine costs $0.99, while 5g EMLA topical cream costs $7.36, for a difference of $6.37. On an individual basis, given that both treatment options are of relatively low cost, it would be reasonable to use either."

18) There is no discussion about why there was no difference in provider perception of subject tolerance, especially when a patient in the EMLA arm had to receive a rescue injection.

Response: Thank you for the comment. Regarding provider perception of subject tolerance, as posed this is not an answerable question. Since only one subject among 18 in the lidocaine-prilocaine cohort required a rescue dose of lidocaine, one would not expect that one experience to affect providers' perceptions overall. In our personal experience, patients tend to experience significant discomfort with lidocaine injection, which is usually more than the discomfort experienced at the time of a small biopsy following application of lidocaine-prilocaine. It may be that providers who perform vulvar biopsies frequently have an expectation that no matter what they do, their patients will have at least a small level of discomfort. It is notable that subjects in the study generally found these procedures to be very tolerable and acceptable; for all subjects in the study, median subject acceptability on the 100mm VAS was 5.0 mm, indicating highly acceptable procedures. Subjects in the lidocaine-prilocaine group reported a procedure tolerability of 3.0 mm on the VAS and subjects in the lidocaine injection group reported a procedure tolerability of 15 mm, both indicating the procedure to be highly tolerable.

19) 10 minutes make a big difference in clinic workflow- there is no discussion about why there is no difference in provider satisfaction between the two arms.

Response: Thank you for the observation. Like many gynecologic oncology clinics, ours is extremely busy, with providers seeing multiple patients at once, usually with assistance from residents, fellows, or advanced practice providers. We have multiple working exam rooms, thus applying lidocaine-prilocaine cream to the appropriate site and seeing another patient in the interim did not prohibit clinic flow. We correctly predicted that a 10 minute wait would not adversely affect flow or affect patient acceptability; the MD was not required to remain in the room during the 10 minutes between lidocaine-prilocaine cream placement and biopsy; the subject was allowed to take her feet out of stirrups and rest comfortably.

Regarding provider satisfaction, because the results were derived from an interim analysis, it is difficult to comment on the clinical implications of non-significant findings of secondary outcomes.

Reviewer #3:

General Comments: This study reports the results of a randomized control trial of lidocaine injection versus topical EMLA cream for anesthesia prior to a vulvar biopsy. The primary outcome was comparison of the highest level of pain, whenever it occurred during the visit. The results presented are from an interim analysis performed out of convenience. The authors conclude based on the interim analysis that primary outcome was determined by the limited data set and that the EM:LA cream provides superior analgesia for a vulvar biopsy. Due to the limited data set, however, none of the secondary study aims could be determined.

Specific Comments:

1) Line 50 - Since the for primary outcome, the highest pain recorded, includes pain of injection, the study not really comparing pain of injection versus pain of biopsy with EMLA cream?

Response: Thank you for the clarifying question. The a priori primary outcome of the study was the highest subjective pain score at any of 3 time points between the two treatment groups because we suspected that even if the pain scores were lower in the lidocaine group at time of biopsy, the pain experienced with lidocaine injection might be greater than pain at biopsy in the lidocaine-prilocaine group. The study team decided that the best way to study this hypothesis was to consider the highest subjective pain score between arms for any of the given timepoints.

2) Line 221 - Confused about the results a bit - median highest score in the EMLA group was 20mm, but the median following biopsy in the same group was only 6mm. Can

only interpret this as application of the EMLA cream itself caused more discomfort than the biopsy (as is clearly the case for the injection)

Response: Thank you for requesting clarification. The highest pain score for the lidocaine-prilocaine group can be broken down as follows: 12/19 had more pain from the biopsy than from anesthesia, 3/19 had the same pain score at biopsy and anesthesia, and 4/19 had more pain from anesthesia than biopsy. In the lidocaine group, 1/18 patients had equal pain between biopsy and anesthesia and 17/18 had more pain from anesthesia than biopsy. To summarize, the highest pain score for the lidocaine group is always the pain score from the anesthesia, but the lidocaine-prilocaine group's highest pain score is a mix. If you examine Figure 3, which shows the pain score at the two time points by treatment arm, you will see that the median pain score during application of lidocaine-prilocaine (0 mm) was lower than at biopsy (6 mm). In other words, it was not the case that the application of the lidocaine-prilocaine cream caused more discomfort than the biopsy. If we need to make any corresponding edits to the manuscript to augment Figure 3 and the Results section, please let us know.

3) Line 234 - To say that patient acceptability "approached statistical significance" is to defeat the whole purpose of statistical analysis. If you have established a cut off of $p < 0.05$, then the patient acceptability did not meet that criteria and to suggest otherwise is inaccurate.

Response: Please see response to reviewer #2, response 14 as below:

The wording has been revised in line 368-373 to "Patient acceptability demonstrated a non-significant difference favoring the use of lidocaine-prilocaine cream (median (IQR) VAS score 0 (0, 18) mm vs. 10.5 (1, 33) mm for lidocaine injection; p = 0.06). Comparing lidocaine-prilocaine to lidocaine injection, no difference was observed for provider satisfaction score (β = 8.2; 95% confidence interval = [-9.0, 25.4]; p = 0.35), or provider's perception of subject tolerance (β = -2.9; 95% confidence interval = [-15.5, 9.7]; p = 0.65) (Table 2)."

4) Line 263 - while this may be novel, i am not convinced that it is a very significant concern or issue. The provider's primary concern should be obtaining an adequate biopsy for analysis with minimum patient discomfort. In my mind the perception of the tolerability for the patient is irrelevant.

Response: Thank you for the comment. We agree with your conclusion. This evaluation was an exploratory outcome. Certainly, it is most important that the patient deems the procedure acceptable and that the provider is able to collect an adequate sample. However, it is interesting to consider whether providers are assessing accurately how the patient tolerates the procedure. To address the reviewer's question, Spearman's correlation between patient acceptability of the

procedure and provider's perception of patient tolerance was estimated to be 0.49 with a 95% confidence interval of (0.20, 0.70). In other words, there was moderate positive monotonic trend between how acceptable the patient found the procedure and how the provider thought the patient tolerated the procedure. The confidence interval is fairly wide due to the small sample size.

5) Line 270 - the term "borderline significance" has no statistical significance and should be removed.

Response: Thank you for the comment. Please also see response to reviewer #2, response 14 and reviewer #3, response 3 as below:

The wording has been revised in line 368-373 to "Patient acceptability demonstrated a non-significant difference favoring the use of lidocaine-prilocaine cream (median (IQR) VAS score 0 (0, 18) mm vs. 10.5 (1, 33) mm for lidocaine injection; p = 0.06). Comparing lidocaine-prilocaine to lidocaine injection, no difference was observed for provider satisfaction score (β = 8.2; 95% confidence interval = [-9.0, 25.4]; p = 0.35), or provider's perception of subject tolerance (β = -2.9; 95% confidence interval = [-15.5, 9.7]; p = 0.65) (Table 2)."

6) Line 286-7 - The size of the sample obtained (measurement and or weight) should be part of a standard pathology report and could be used to address this concern.

Response: Thank you for the comment. Please see response to reviewer #2, response 15 as below:

We find that punch biopsies generally result in a full thickness skin sample and extend into the subcutaneous fat. This depth is not often needed in a vulvar biopsy. We often use an Eppendorfer forceps, whose "jaws" can be closed down somewhat prior to initiation of the biopsy procedure to achieve a desired size or depth of the specimen. One can affect the depth of sample with cervical biopsy forceps compared to a punch biopsy, which is always full thickness.
We have revised the sentence to read, Line 473-475: "Further, at least 26 of 37 (70.3%) of biopsies in this study were performed using cervical biopsy forceps; only 5 of 37 (13.5%) of subjects underwent a punch biopsy."

7) Table 1 - Why is the Total column included and why are p values not included to demonstrate equivalency of randomized groups?

Response: Thank you for the comment. Please see the response to comment #10 from reviewer #2 regarding p values.

While we appreciate the reviewer's concerns regarding potential imbalance of participant characteristics across randomization arms, we respectfully disagree

that p values should be presented in Table 1. There is an overwhelming consensus against performing and reporting baseline comparisons of characteristics by study arm in randomized trials [1-10]. These statistical tests assess the likelihood that the difference occurred by chance – but it is already known that any significant differences that do occur are caused by chance when randomization is properly implemented, as in our study. They also do not measure similarity across the groups, thus researchers describe these comparisons as illogical/absurd [3, 5-6, 8], superfluous/unnecessary/not useful [6-10], "misleading" [1, 4-6, 8], and "inappropriate" [1, 3, 5]. Further, in all hypothesis testing there is a small probability that a true null hypothesis will be incorrectly rejected. We note that adjustment for covariates based solely on statistically significant baseline differences is also erroneous [1, 6-7].

Consensus holds that the clinical magnitude of the differences and the prognostic strengths of the variables that appear imbalanced is important [6]. We did not note any clinically meaningful differences in our baseline characteristics to warrant concern, and feel comfortable assuming that there were no flaws in our randomization.

The references below support our preference not to present significance testing in Table 1:

11. **Assmann SF, Pocock SJ, Enos LE, and Kasten LE (2000), Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet, 355, 1064-1069.**
12. **Altman DG and Doré CJ (1990), Randomisation and baseline comparisons in clinical trials, Lancet, 335, 149-153.**
13. **Austin PC, Manca A, Zwarenstein M, Juurlink DN, and Stanbrook MB (2010), A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals, Journal of Clinical Epidemiology, 63, 142-153.**
14. **de Boer MR, Waterlander WE, Kuijper LD, Steenhuis IH, and Twisk JW (2015), Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate, International Journal of Behavioral Nutrition and Physical Activity, 12:4.**
15. **Gruijters SL (2016), Baseline comparisons and covariate fishing: Bad statistical habits we should have broken yesterday, The European Health Psychologist, 18, 205-209.**
16. **Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. (2010), CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. Journal of Clinical Epidemiology, 2010(63), e1-37.**
17. **Pocock SJ, Assmann SE, Enos LE, and Kasten LE (2002), Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems, Statistics in Medicine, 21, 2917-2930.**

18. **Senn S (1994) Testing for baseline balance in clinical trials, Statistics in Medicine, 13, 1715-1726.**
19. **Senn S (2004). Controversies concerning randomization and additivity in clinical trials, Statistics in Medicine, 23, 3729-2753.**
20. **Schulz KF, Chalmers I, Grimes DA, and Altman DG (1994), Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals, JAMA, 272, 125-128.**

The total column has been removed from Table 1.

8) Table 2 - Again, why is the Total column included? The comparison is between the groups so do not see the reason for including this data.

Response: We agree with your comment. The totals column has been removed from table 2.

9) Figure 1 - This should be included as an appendix.

Response: Thank you for the edit. Figure 1 is now included in the manuscript as an appendix and referred to as Appendix 1.

10) Figure 3 - The time between pain of anesthesia and pain of procedure is very restricted in the injection group. How does this effect the results and interpretation of this data? It is not really correct to have Time on the X-axis here when the times represented in the two data sets are different.

Response: The x-axis represents the two time points of application of anesthesia and then biopsy being performed, but is not representative of the actual time passed between the two. In other words, the lines come from connecting the data point for pain during anesthesia and the data point for pain during biopsy; we feel that this may be a useful visual in terms of understanding individual subjects' pain experience. For example, you can see that the lidocaine injection patients tended to start with more pain from the injection, but then reported lower pain at biopsy relative to their pain score at anesthesia. We do not think the time between the two greatly affects our interpretation of the data given that we followed standard protocols for onset of action of both methods of anesthesia, though these time intervals are not the same.

Reviewer #4:

Review of Manuscript ONG-19-1743 "A randomized trial comparing pain perception using topical EMLA versus lidocaine injection for vulvar biopsy"

Williams and colleagues report their results from a single center RCT in women undergoing planned vulvar biopsy which evaluated 2 anesthetic approaches - topical

EMLA versus injection lidocaine and the authors have included the CONSORT checklist. Somewhat interestingly, perhaps, the authors measured pain at 3 distinct time points - baseline and both following anesthesia as well as after biopsy. As noted in the abstract, the planned sample size was 106 patients although analysis occurred with only 38 enrolled/randomized patients with 37 being evaluated. I have the following comments/questions.

Title - No comments.

Précis - Acceptable

1. Abstract - If space allows, note informed consent obtained. Any other data like age, parity, prior lacerations, etc. that can be included?

Response: Thank for you for the comment. We agree, in lines 67-70. The first lines of the Results portion of the abstract states, "From October 2018 through March 2019, 38 subjects completed informed consent and were randomized. Participants were women with mean age of 58 years. Most characteristics between groups were similar."

Introduction - Good summary

Methods - Well described how the study was designed and what was going to be measured.

2. Were thoughts given initially to perform an interim analysis rather than having to do those for slower than predicted accrual?

Response: Thank you for the thoughtful question. We did consider the possibility of an interim analysis at the planning stage. We initially had a predicted accrual time of around one year, but the time available for accrual was reduced to approximately 6 months because there was a prolonged approval time within the institution. After discussion with the statistical analysis team and limited time frame for accrual, we decided to proceed without it. The interim analysis then arose out of necessity from our Research Day deadlines; at that time, we discussed several possibilities with our statistical team before ultimately settling on a plan that would require re-accrual of study subjects from zero if we did not observe significance of the primary outcome.

3. What was the initial predicted accrual time?

Response: Based on our initial prediction, we estimated around 125-150 vulvar biopsies per year and an estimated accrual of 75%. We planned for approximately one year of accrual time prior to Research Day deadlines with the potential for increasing the accrual time if indicated beyond research day requirements.

4. Was thought given to analyzing results based on biopsy type - punch vs. other - or to limit to one type or another?

Response: Thank you for the interesting question. We discussed both limiting the type of biopsy to be performed in the study and stratifying, but at an open departmental review of the research plan, several faculty members voiced that the study would be more generalizable if it included both cervical biopsy forceps and punch biopsy. We suspected based on prior experience in our clinic that the punch biopsy numbers would be too low to analyze these separately.

5. Were thoughts given to exclude patients with prior biopsies to exclude the issue of possible anticipatory pain with the biopsy?

Response: Thank you for the question. We did not consider excluding subjects with prior biopsy. Based on the number of patients we follow with a history of vulvar cancer and severe dysplasia, we anticipated having a large number of subjects with prior biopsies. Excluding these individuals would have further reduced the feasibility of timely accrual.

6. Results - Logical presentation of provided data. Line 211-2 was the difference statistically significant in terms of anxiety/pre-procedure nervousness? If so could this have driven some of your findings in terms of favoring EMLA against lidocaine?

Response: Pre-procedural anxiety was not statistically different between the two groups (p = 0.09), but it is possible this is due to a lack of power. Clinically, we suspect that a slightly higher anxiety level in the lidocaine arm (31 mm versus 19 mm on a 100 mm VAS scale) may have been due to administration of the anxiety assessment questionnaire after randomization; the knowledge of lidocaine injection may have had some effect on anxiety level in that arm. To address concerns about whether anxiety drove our findings, we have run an alternative analysis in which we added pre-procedural anxiety as a covariate to our linear regression model and found that the treatment effect did not shift much (difference of 25.7 mm favoring EMLA vs. 23.8 mm favoring EMLA after additionally controlling for pre-procedural anxiety), but the confidence interval became wider due to adding another covariate to the model with our limited sample size (new 95% confidence interval = -44.6 to -3.0; p = 0.03). Therefore, we feel confident that pre-procedural anxiety did not drive our findings.

7. Discussion - Would note that the application must be in place for at least 10 minutes.

Response: Thank you for the suggestion. The first sentence of the Discussion in lines 394-397 states, "In the current study, we found that application of lidocaine-prilocaine cream alone for a minimum of 10 minutes prior to vulvar biopsy on a non-hair bearing surface results in a significantly lower maximum pain score and

a significantly better patient rating of the biopsy experience when compared to lidocaine injection."

8. Tables - Consider removing the right most column of summary data from table 1, not sure that it adds much.

Response: Thank you for the suggestion. See response to reviewer #3, responses 8 and 9 as below:

We agree. The totals columns have been removed from tables 1 and 2.

9. Figure - Interestingly the figures are in reverse order in the PDF. For figure 3 was thought give to provide the measured outcomes since this was the primary outcome in the study?

Response: Thank you for the comment. Initially there was a table with this information, but given that it is directly stated in the results section, we decided to present the information in the form of the spaghetti plot.

STATISTICAL EDITOR COMMENTS:

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

lines 165-172, 186-187 vs 189-197 and 221-227: While the power analysis/sample size estimation was straightforward, the actual analysis, formatting and citing of the primary outcome was not and the two were inconsistent. The primary was initially cited as a difference between the means of the maximum pain scores for the two cohorts, based on a minimum clinical difference of 16 and an expected SD = 25. The method used then accounted for the difference in baseline scores (vs the maximum scores) and also adjusted for the multiple procedures by individual providers. The method also assumed normal distributions, but based on samples of n = 18 vs n = 19, which would yield inadequate power to establish whether the distributions were in fact normal. Finally, the maximum scores are formatted as median(IQR), rather than as mean(SD), with the primary outcome apparently taken as the adjusted difference in maximum differences (ie, 25.7 with 95% CI -45.1 to -6.3).

The primary should be consistently stated from the initial statement to the stats method and results. It should be clearly separated from the secondary ones.

Response: Thank you for your comment. Our primary outcome was the highest pain score recorded (i.e. the maximum between pain at anesthesia and pain at biopsy) for each patient. A linear regression model was fit to compare the treatments while controlling for the pain score measured before the procedure. We decided to report summary statistics for the primary outcome in median (IQR)

due to the small sample size and non-normality of the outcome. However, we felt comfortable fitting a parametric model as the assumptions of both fitting and making inference from a linear regression model were met. That is, while the outcome was not normally distributed, the residuals were normally distributed.

We have added some text to more clearly separate the primary from the secondary outcomes by paragraph (Lines 333-373).

EDITOR COMMENTS:

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

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

1. Do not include your personal address on professional documents like this or your phone number. You should
use your professional contact information. Unfortunately, haters are going to hate and you don't want to
make it easy for them.

Response: Thank you for the kind suggestion. It has been edited in the title page of the manuscript

2. We no longer require that authors adhere to the Green Journal format with the first submission of their papers.
However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Response: Thank for you the suggestion, the guidelines have been closely adhered to in the submission of our revised manuscript.

3. If EMLA is a brand name it cannot be used in the precis. If its an abbreviation, it needs to be spelled out. See
instructions for authors about this. You may want to substitute "topical lidocaine 2.5%

and prilocaine 2.5% cream....." Brand name, if that is what it is, cannot be in the title either.
Response: Thank you for noting this. EMLA has been replaced with "lidocaine-prilocaine cream" throughout the manuscript, to be consistent with prior literature discussing this medication in the Green journal.

4. Either spell out "19" or edit sentence to avoid starting it w/ a numeral. Do this for all instances where a numeral starts the sentence.

Response: Thank you for the correction. Nineteen is now spelled out, and it has been corrected throughout the manuscript.

5. This second sentence of your conclusion is essentially a restating of the first sentence. You can either delete it.

Response: Thank you for noting the redundancy. Please also see response to reviewer #2, question 1 as below:

In lines 97-100 of the abstract, the conclusion states "Lidocaine-prilocaine cream prior to vulvar biopsy resulted in a lower maximum pain score and significantly better patient rating of the biopsy experience when compared to lidocaine injection. Lidocaine-prilocaine cream alone is a reasonable option to use for vulvar biopsy."

6. This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMeD, Google Scholar, EMBASE for example), the date ranges searched, and the search terms used. If not done, please edit it out of the paper.

Response: Thank you for the kind instruction. Lines 141-145 of the introduction now read, "Additionally, consideration of either the subjects' or providers' perceptions of the acceptability or tolerability of vulvar biopsy procedure is a unique quality of the study allowing for exploration of the perceived overall experience of the subject and provider beyond gross pain scores."

7. since EMLA includes lidocaine, for clarity please describe this as "injected lidocaine" throughout your paper.

Response: Thank you for noting this to aid in clarification. It has been edited in the manuscript accordingly throughout.

8. were they told a priori what a given provider used? (ie, before they decided to randomize)
Response: Thank you for the question. Lines 176-180 of the materials and methods state: "Patients meeting inclusion criteria were approached initially by a

gynecologic oncology provider; those expressing interest in participation then met with a clinical study coordinator and were given the options of enrollment in the study or proceeding to biopsy using their provider's standard method of vulvar anesthesia."

The subjects were told what a given provider used before deciding to randomize, which in the vast majority of cases was injected lidocaine.

9. In discussion, please comment whether differences in anxiety score may be related to the possible increasing anxiety while waiting rather than just getting it over with in injected lidocaine group.

Response: Thank you for the insightful comment. Our results do not seem to be consistent with the effect you suggested. In fact, and pre-procedure anxiety scores were higher for injected lidocaine treatment (less wait time) than lidocaine-prilocaine cream (more wait time).

10. As noted by one reviewer, often > 1 site needs to be biopsied. How did you handle that? If patients had 2
biopsies near each other, one application of EMLA cream might be sufficient but 2 injections needed. This would alter, perhaps, pain sensation and anticipation/anxiety.

Response: Thank you for pointing out this issue. Please see also our response to reviewer #2 response 8 as below: Given that the subjects recruited were those clinically needing vulvar biopsy, we did not control the number of biopsies that were permitted for study participation. Six subjects required more than 1 biopsy: 3 in the lidocaine-prilocaine group and 3 in the lidocaine group. In 2 of the 3 lidocaine-prilocaine cases, only one of the intended biopsy sites was on a non-hair bearing service of the vulva; therefore, the complete study protocol procedures, including pain scores, were performed prior to the second biopsy being completed. In the third lidocaine-prilocaine case, cream was applied once for 2 different unilateral biopsy sites. In 2 of the 3 lidocaine injection cases, 2 unilateral biopsies were collected but one lidocaine injection was performed as anesthesia for both biopsies. In the third lidocaine case, lidocaine was injected twice for two contralateral biopsies.

Thus, there was one subject in each group whose responses may have been biased by having multiple anesthesia applications and multiple biopsies. Only one collective pain score was collected from these subjects; one for pain at time of application of anesthesia and one for pain at time of biopsy given that anesthesia was administered immediately one after the other and the biopsies were performed consecutively as well.

To address the issue of multiple biopsies in a sensitivity analysis, we refit our linear regression model excluding the three lidocaine injection cases with two biopsies and the one lidocaine-prilocaine case with two biopsies on the same

side of the vulva. The two lidocaine-prilocaine cases in whom the study protocol was completed prior to the second biopsy were retained. For the sensitivity analysis, there are 15 lidocaine injection and 18 lidocaine-prilocaine patients in this subset of the data. The new beta, 95% confidence interval, and p value are -24.3, (-45.6, -3.03), and 0.03, respectively. In contrast, the results we reported in the manuscript using all patients were β = -25.7 with a 95% confidence interval of (-45.1, -6.3) and p value of 0.009. In other words, our point estimate only shifted by 1.4 mm towards no difference between lidocaine and lidocaine-prilocaine, but our confidence widened slightly due to the decrease in sample size. Therefore, the results were similar after narrowing our study population down to the patients that only had one study biopsy taken.

In lines 308-329, subjects with multiple biopsies are now addressed in the Results sections of the manuscript: " The patient was analyzed under the lidocaine-prilocaine cream arm. There were a total of 6 subjects who required two vulvar biopsies, and these were distributed equally between the treatment groups as follows. In 2 of the lidocaine-prilocaine cases, only one biopsy was on the hair bearing surface of the vulva and included in the study, this biopsy and all study procedures were completed first. In 2 of the lidocaine cases, 2 biopsies were collected, but lidocaine was only injected one time. In one case in the lidocaine injection arm, lidocaine was injected twice at separate locations and two biopsies were performed, and in one case in the lidocaine-prilocaine arm the same occurred." Sensitivity analysis results were also added in lines 342-361 "To address the issue of subjects requiring more than one vulvar biopsies in a sensitivity analysis, the linear regression model was refit excluding the three lidocaine injection cases with two biopsies and the one lidocaine-prilocaine case with two biopsies on the same side of the vulva. The two lidocaine-prilocaine cases where the study protocol was completed prior to the second biopsy were retained. Therefore, for the sensitivity analysis, there were 15 lidocaine injection and 18 lidocaine-prilocaine subjects. The significant difference in highest pain score favoring the lidocaine-prilocaine group persisted ($\boldsymbol{\beta = -24.3}$, $\boldsymbol{(-45.6, -3.03)}$, $\boldsymbol{p = 0.03}$)."

In the discussion of limitations, the statement has now been added in lines 468-472, "Our primary analysis did not control for the 3 subjects in each group who received more than one vulvar biopsy during the study; subjects receiving two biopsies may have had altered pain scores due to this. However, our sensitivity analysis, in which the 4 subjects receiving multiple biopsies were excluded confirmed our primary findings with statistical significance."

The information concerning the number of biopsies collected has been added to Table 1.

11. How did you control for provider bias about this? If you had providers who felt that EMLA cream would not be sufficient (ie, did not have equipoise around the study

subject) s/he could add injected lidocaine more quickly than one who was convinced it was a great approach (also lacking equipoise). Did you address this possibility with providers at all?

Response: Our senior investigator, who sees a high number of patients with vulvar pathology and who previously solely used injected lidocaine, piloted FDA-approved application of lidocaine-prilocaine cream alone in her clinic for several months with highly encouraging results during our protocol writing period. This afforded the study team significant comfort in recommending the trial to the entire clinical division. We next performed a study initiation meeting with providers at both sites from which patients were recruited and presented them with our literature review and reviewed procedures for both anesthetic methods in detail. The rescue lidocaine provision was put in place for both provider and patient "comfort". It is possible that individual providers introduced bias, but their bias may have changed as they performed more biopsies. Since only one subject received rescue lidocaine, we don't feel that bias against lidocaine-prilocaine cream was a major factor.

12. Was it study or clinical personnel who helped the patient during the procedure to complete the VAS's?

Response: Study personnel, not providers or clinic personnel, aided the patient in completing the VAS on the provided tablet during and after the procedure.

13. Here is part of the answer to an above question. My concern is that if the woman had injected lidocaine for lesion #1 and thought it was terribly painful, her anticipation and possibly perceived pain for the 2nd lesion may be increased. Can you do an analysis for the first lesion only for those w/ multiple biopsies? I'm sure this will end up being very small numbers of women and thus high risk of Type 1 error but perhaps look at that and see if that's the case.

Response: Please see the prior response to the Reviewer #2, response 8 and the main editor, question 10. As noted above, there was only 1 subject in each arm who had 2 anesthesia applications and 2 biopsies. Note in the response above that we have now performed a sensitivity analysis around the issue of multiple biopsies, which did not change the overall results.

14. Who entered the data? Was there any validation of the data entry?

Response: The data was entered by study personnel or by subjects themselves directly into Redcap using electronic entry on tablets in the examination room. After the subject performed informed consent on the tablet and their subject identifiers were confirmed, the subject entered all of the rest of the information themselves. There was no transfer or re-entry of data. Given that the information is survey data, it would not be possible to validate it further. This information was noted in the methods section in lines 195-196, "Subjects used a tablet to

enter their own responses directly into REDCap including pain scores with the visual analog scale."

15. What was the plan around your secondary outcome results?

Response: We discussed plans including restarting accrual to evaluate the secondary outcomes, but given there were significant findings with the primary outcome, we made the decision not to recruit further.

16. P Values vs Effect Size and Confidence Intervals
While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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. This is true for the abstract as well as the manuscript.

Response: Thank you for your comment. We agree that p values alone provide little information about the strength of the association, and that confidence intervals are more appropriate to report. We have revised the text in both the abstract and the paper to report an effect size and confidence interval for all parametrically tested outcomes.

17. Please reference Table 1 sooner in your results than you do.

Response: Thank you for the suggestion, it is now referenced in line 296.

18. 22% is closer to 1/5 than 1/4. Please edit.

Response: In line 297, one fourth was edited to one fifth.

19. Please note statistical editor's comments re: analysis.

Response: Please see response to statistical editor's comments as below:

Our primary outcome was the highest pain score recorded (i.e. the maximum between pain at anesthesia and pain at biopsy) for each patient. A linear regression model was fit to compare the treatments while controlling for the pain score measured before the procedure. We decided to report summary statistics for the primary outcome in median (IQR) due to the small sample size and non-normality of the outcome. However, we felt comfortable fitting a parametric model as the assumptions of both fitting and making inference from a linear regression

model were met. That is, while the outcome was not normally distributed, the residuals were normally distributed.

We have added some text to more clearly separate the primary from the secondary outcomes by paragraph (Lines 271-285).

20. We do no 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.

Response: Thank you for this correction. Please see responses to Reviewer #2, response 14 and reviewer #3, responses 3 and 5 as below.

In the results lines 368-373 state, “Patient acceptability demonstrated a non-significant difference favoring the use of lidocaine-prilocaine cream (median (IQR) VAS score 0 (0, 18) mm vs. 10.5 (1, 33) mm for lidocaine injection; p = 0.06). Comparing lidocaine-prilocaine to lidocaine injection, no difference was observed for provider satisfaction score (β = 8.2; 95% confidence interval = [-9.0, 25.4]; p = 0.35), or provider’s perception of subject tolerance (β = -2.9; 95% confidence interval = [-15.5, 9.7]; p = 0.65) (Table 2).”

21. Your first sentence should set up the importance of your paper, perhaps being in parallel with your primary
outcomes. Also being the "first" as your lead in to your discussion seems like the most important result is
being the first--not the actual results. Leading your discussion off with this sentence does not seem to really
do this.

Response: Thank you for noting this. In lines 394-397, the first sentence of the discussion now reads, “In the current study, we found that application of lidocaine-prilocaine cream alone for a minimum of 10 minutes prior to vulvar biopsy on a non-hair bearing surface results in a significantly lower maximum pain score and a significantly better patient rating of the biopsy experience when compared to lidocaine injection.”

22. This is perhaps a leap based on 38 women, restricted to non-hair baring areas. Particularly since you did not address the issue of multiple biopsies.

Response: Thank you for the comment. Please also see response to reviewer #2, responses 1 and 12 as below:

We agree, and to make our conclusions for the study more appropriate given the limitations, it now reads, (line 397-399): “Lidocaine-prilocaine cream alone should

be considered as an anesthetic method for vulvar biopsy on an individualized basis after an informed discussion between patients and providers."

23. which procedure was this for?

Response: Line 401: This study was looking at vulvar biopsy.

24. perhaps explain why the highest score is more important than the net score.

Response: Thank you for the suggestion for clarification. The following sentence was added in lines 411-413, " Comparing the highest score allows us to consider the possibility that the pain of anesthesia application may be greater than the pain of any other portion of the biopsy procedure."

25. subject acceptability was non-significantly different. Given the abbreviated study, you were underpowered for some of your secondary outcomes and you cannot make any conclusions re: neg findings for these.

Response: Thank you for the correction. Please see responses to Reviewer #2, response 14 and reviewer #3, responses 3 and 5, and response #20 to the editor.

In the results lines 368-373 state, "Patient acceptability demonstrated a non-significant difference favoring the use of lidocaine-prilocaine cream (median (IQR) VAS score 0 (0, 18) mm vs. 10.5 (1, 33) mm for lidocaine injection; p = 0.06). Comparing lidocaine-prilocaine to lidocaine injection, no difference was observed for provider satisfaction score (β = 8.2; 95% confidence interval = [-9.0, 25.4]; p = 0.35), or provider's perception of subject tolerance (β = -2.9; 95% confidence interval = [-15.5, 9.7]; p = 0.65) (Table 2)."

26. blind patients, providers or assessors

Response: Lines 450-451, We were limited in our ability to blind patients and providers given the interventions, we did not attempt to blind statistical assessors of the data.

27. Its too bad that you did the GAD after they knew the randomization arm. In future studies, the more proximal to the intervention that you can do the randomization, the less likely there will be 1) patient drop out and 2) contamination of any data by events, feelings, etc that occur between the randomization and the procedure. The best way to have done you randomization in this case would have been in the treatment room just before anesthesia was to be applied.

Response: Thank you for the suggestion. Please also see response to reviewer #4, response 6 as below:

Pre-procedural anxiety was not statistically different between the two groups (*p* = 0.09), but it is possible this is due to a lack of power. Clinically, we suspect that a slightly higher anxiety level in the lidocaine arm (31 mm versus 19 mm on a 100 mm VAS scale) may have been due to administration of the anxiety assessment questionnaire after randomization; the knowledge of lidocaine injection may have had some effect on anxiety level in that arm. To address concerns about whether anxiety drove our findings, we have run an alternative analysis in which we added pre-procedural anxiety as a covariate to our linear regression model and found that the treatment effect did not shift much (difference of 25.7 mm favoring EMLA vs. 23.8 mm favoring EMLA after additionally controlling for pre-procedural anxiety), but the confidence interval became wider due to adding another covariate to the model with our limited sample size (new 95% confidence interval = -44.6 to -3.0; *p* = 0.03). Therefore, we feel confident that pre-procedural anxiety did not drive our findings.

We were fortunate that we only had one subject who was withdrawn after randomization occurred, and the reason was that it was subsequently determined by the provider that she did not need a biopsy that day. However, we agree that ideally, the GAD-7 to assess for long term anxiety and the pre-procedural nervousness questions should have been completed prior to their knowledge of randomization.

28. please add comment about multiple biopsies, limiting to hair line. Since vulvar skin has a wide variability in hair distribution, this is big limitation as far as generalizability to other patients.

Response: Thank you for allowing us to provide transparency. Please also see response to the Editor, question 10 as below: In the discussion of limitations, the statement has now been added in lines 468-472, "Our primary analysis did not control for the 3 subjects in each group who received more than one vulvar biopsy during the study; subjects receiving two biopsies may have had altered pain scores due to this. However, our sensitivity analysis, in which the 4 subjects receiving multiple biopsies were excluded confirmed our primary findings with statistical significance."

We agree that the lack of applicability to hair-bearing vulvar lesions is a limitation. The following has been added to the discussion in lines 508-510: "The generalizability of our results is also limited by our enrollment of subjects requiring biopsy of non-hair-bearing surfaces".

B. You are also receiving a second attachment, which contains the Editor's review of your CONSORT checklist. Please make sure you review the comments in that file prior to submitting your revision.

Most of the areas of concern from the check list I've included in my comments you will

receive, but it may be worth comparing my assessment with your own, just forsinterest. Thank you as well for your data sharing plan. We are finding that some authors don't recognize the importance of making individual patient data available, at the very least for future IPD meta analyses.

Response: Thank you for your review of the CONSORT checklist. An edited CONSORT checklist has been submitted with our revisions.

C. 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.

Response: Thank you for the opportunity for transparency. We will OPT-IN.

D. 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.

Response: Thank you for the notice. The coauthors with submission of revisions have confirmed accuracy of disclosures.

E. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

Response: As noted in the manuscript. Please see our data sharing plan here:

Data Sharing Statement Table	
Will individual participant data be available?	Yes
What data will be shared?	Individual participant data collected during the trial, after deidentification
What other documents will be available?	none
When will data be available?	Upon request
With whom?	Investigators at academic institutions who make written requests will be eligible for data sharing if the primary, senior, and primary statistical authors agree
For what types of analyses?	Any
By what mechanism will data be available?	By link, upon request

F. 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://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_About-2DACOG_ACOG-2DDepartments_Patient-2DSafety-2Dand-2DQuality-2DImprovement_reVITALize&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=9uzWFyWrrh25cxbadHoYbcgQ7NLTNlyBmS7eEFqj5Rk&e= . If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: Thank you, upon review, there are no apparent issues with stated definitions in revitalize.

G. 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.

Response: Thank you for this information. Excluding the references, the manuscript is exactly 22 pages.

H. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..."

should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

Response: Thank you for the note. The title for the manuscript is, "A randomized trial comparing lidocaine-prilocaine cream versus injected lidocaine for vulvar biopsy." It Is 99 characters including spaces.

I. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

Response: Thank you. All financial support has been acknowledged as well as assistance in manuscript preparation that are not authors.

J. 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: Thank you for the note. The word count for the abstract is 296.

K. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online

here: https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_sampleabstract-5FRCT.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=tBXFTSzSdjlFf4L_6tpFSvdMA5M9HMuyK_C_cKVsT8s&e= . Please edit your abstract as needed.

Response: Thank you for the reference, the model was used to edit the abstract.

L. Only standard abbreviations and acronyms are allowed. A selected list is available online athttps://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=drCDvh5Vc_U8XKQdbEYgL5OUZm4PfXxIILmSQIVhlsQ&e= . 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.

Response: Thank you for the information. Only approved acronyms are used.

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

Response: Thank you for the reminder, this has been edited throughout the manuscript. To be consistent with Green Journal literature in the past and with guidelines, EMLA has been replaced with “lidocaine-prilocaine cream.”

N. 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: Thank you for the comment, this is edited accordingly in the manuscript.

15. 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%").

Response: Thank you for your comment. Please also see response to the Editor, question 16.

We agree that p values alone provide little information about the strength of the association, and that confidence intervals are more appropriate to report. We have revised the text in both the abstract and the paper to report an effect size and confidence interval for all parametrically tested outcomes. All p values and percentages contain the correct amount of decimal places.

O. Line 245: 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.

Response: Thank you for sharing your concern. Please also see our response to the Editor, question #6.

Lines 141-145 of the introduction now read, "Additionally, consideration of either the subjects' or providers' perceptions of the acceptability or tolerability of vulvar biopsy procedure is a unique quality of the study allowing for exploration of the perceived overall experience of the subject and provider beyond gross pain scores."

P. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_table-5Fchecklist.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=RLECudUQy8OceysYDg6--OJ0882FVq_ERuo-hKq3sAw&e= .

Response: Thank you for the reference. It was used to ensure that our tables conform appropriately to the Green Journal style.

Q. Figures

Figure 1: Please upload high resolution figure files to Editorial Manager (eps, tiff, jpeg).

Figures 2 and 3 may be resubmitted as-is.

Response: Figure 1 has been uploaded an a Jpeg.

R. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_LWW-2DES_A48&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=NxGK90_V3TXU8AMkpCLmZv1j9Fqnt6h_2f80-GQaHh4&e= . The cost for publishing an article as open access can be found at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_acd_accounts_ifauth.htm&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=_ke_oPPd7mzDoZQKAWvQHugxxZIjjUiZjPLLJ-h-TyU&e= .

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

S. If you choose to revise your manuscript, please submit your revision through Editorial Manager at https://urldefense.proofpoint.com/v2/url?u=http-3A__ong.editorialmanager.com&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=IJknHFCI_2A-2bpplK-whlW_Djm9A23bSEuC-kNaPOE&e= . 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 (https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_authors.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsiEgHoG1i6YHLR0Sj_gZ4adc&r=eH8FIKiGXHoTZgO0SdbSapXup-3P87pZ3va3A9oNCXg&m=C4HKUpty1jcODIzel_ZrDm_kcQ2TjX2VuZ_GJysNE_U&s=wxh3jaqDVasWZx6I7KjH7rMj8dYk-MbSbgaLza_zN58&e=), 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.